

CLINICAL ARTICLE

Gynecology

Sharing the multidisciplinary clinical approach to peri- and postmenopausal women: A Delphi consensus among Italian gynecologists, endocrinologists, and cardiologists for an integrated and optimal approach to clinical practice

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Abstract

Objective: The critical phase of perimenopausal period is marked by a reduction in estrogen levels, leading to various clinical issues (vasomotor and neurodegenerative symptoms, increased osteoporosis risk and cardiovascular risk). These complex clinical scenarios pose challenges to clinicians in providing the right support for diagnosis and treatment. A group of Italian cardiologists, endocrinologists, and gynecologists conducted a survey among expert colleagues to assess consensus on controversial issues and best practices for screening and treating peri- and postmenopausal women. **Methods:** The Delphi methodology was used to analyze responses from a qualitative expert panel comprising 25 cardiologists, 25 endocrinologists, and 25 gynecologists, selected nationwide. Two consecutive questionnaires were proposed between February and May 2023. Agreement among experts was assessed following the Delphi method as developed by the RAND Corporation.

Results: The results of this Delphi Consensus have been shared by the leading scientific societies: Italian Society of Cardiology, Italian Society of Endocrinology, Italian Society of Gynecology and Obstetrics, and Italian Hospital Obstetricians Gynecologists Association.

Conclusions: The experts highlighted comorbidities and hormone deprivation as crucial clinical problems to be evaluated in perimenopausal women, requiring investigation from cardiovascular and endocrinologic perspectives to assess cardiovascular risk, involving the use of BMI, standard blood samples, endocrine-metabolic tests, and lifestyle assessment, particularly in women with higher cardiovascular and metabolic risks candidates for hormone replacement therapy (HRT). The experts also agreed

The Delphi Consensus scientific results have been shared by the leading scientific societies: SIC—Italian Society of Cardiology, SIE—Italian Society of Endocrinology, SIGO—Italian Society of Gynecology and Obstetrics, and AOGOI—Italian Hospital Obstetricians Gynecologists Association.

All authors contributed equally to the study.

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on the benefits of HRT in improving lipid metabolism and reducing insulin resistance, thereby mitigating the metabolic risks associated with menopause. However, this therapy should be tailored considering individual women's comorbidities and thrombotic risk.

KEYWORDS

comorbidities, Delphi consensus, intersociety consensus, menopause, perimenopause, postmenopause

1 | INTRODUCTION

The menopausal transition and the postmenopause represent pivotal phases in a woman's life, marked by significant changes that encompass physical alterations affecting various organs and systems, as well as emotional adjustments within the socio-emotional sphere.¹

Clinically, menopause is defined as the permanent cessation of menstruation, typically diagnosed retrospectively after 12 consecutive months without a menstrual period in a previously menstruating woman. It reflects the complete or nearly complete loss of ovarian function and fertility.² These changes are accompanied by various clinical manifestations due to estrogen deficiency, impacting different organs and systems. Short-term effects include vasomotor symptoms, vaginal dryness, and urogenital symptoms, while long-term consequences encompass osteoporosis and increased cardiovascular risk.³ This risk for women is a complex issue influenced not only by hormonal factors, such as estrogen, but also by the woman's awareness of her own risk, the recognition of risk factors by healthcare providers, and the aggressiveness of the management strategies implemented.⁴ Specifically, estrogen is associated with a lower incidence of cardiovascular events and exerts a positive influence on vascular function and tone. Thus, cardiovascular diseases emerge as the primary cause of mortality and morbidity in postmenopausal women, placing them at a similar risk level as men.⁵ Accordingly, effective management of menopause necessitates consideration of various factors, including medical history, current health status, family history, age and menopausal status, severity of symptoms, personal preferences, bone health, psychological well-being and lifestyle factors. The decision to start HRT is highly individualized, and the potential benefits and risks should be thoroughly discussed with a healthcare provider. Regular follow-ups are typically recommended to monitor the ongoing appropriateness of HRT based on individual health status and any changes in risk factors.

Unfortunately, fragmented knowledge and variability in the clinical practices of physicians can hinder the support available to many peri- and postmenopausal patients in preventing, diagnosing, and promptly treating cardiovascular and metabolic diseases. Consequently, women consulting cardiologists or endocrinologists may not be carefully counseled on gynecologic problems and sexual experiences. Moreover, the Women's Health Initiative (WHI) data

from the past has led to confusion among different specialists in this field, causing perplexity about the indications and usefulness of hormone therapy (HT) and its potential oncologic or cardiovascular risk, resulting in a drastic decline in its use.^{6,7}

During the menopausal transition and postmenopause, women commonly refer to the gynecologist, but due to the associated cardiovascular risks and endocrinological changes, cardiologists and endocrinologists are also frequently consulted. Reanalysis of WHI data, innovative studies, and the availability of new molecules and formulation for HT led gynecologic, cardiovascular and endocrinologic scientific societies to reassess the relevance of different risks in peri- and postmenopause and the role of HT.⁸⁻¹⁰ They have collaborated on a shared document outlining diagnostic approaches and management strategies for oncological risk and cardiovascular health during menopausal transition and hormone replacement therapy (HRT) use.¹¹

However, within clinical practice, different opinions and heterogeneous behaviors persist among professionals regarding the implementation, intensification, reduction, or cessation of screening for these conditions. Additionally, debates arise regarding the selection of one preventive treatment strategy over another, or the decision to start HT. Often, the ultimate strategy is determined by a personal decision.¹²

In light of this, it is strategic for women's health to evaluate potential variations in the management of peri- and postmenopausal women regarding different risks and the use of HRT, depending on the specialist involved (cardiologist, endocrinologist, gynecologist). Identifying common actions among the different specialists can serve as the foundation for a multidisciplinary approach to patient management. In such a model, each physician participating in the diagnostic and therapeutic process gains a comprehensive understanding of the issue and, subsequently, can delve deeper into it based on their area of expertise. This integration of knowledge aims not only to streamline the resolution of specific patient issues, but also to benefit physicians and the scientific community as a whole. In an era of ultra-specialization and disintegration of knowledge, this approach enables the amalgamation of strategies and parallel diagnostic methodologies in a single, simplified and easily accessible model.

Thus, taking into account the widening of the postmenopausal population, considering the broad elderly population of European countries that can be treated, and the increase in the number of

individuals with concomitant diseases and treatments (and consequently the possibility of encountering situations of peri- and postmenopausal women in clinical practice that are not precisely regulated by guidelines and recommendations), a team of Italian cardiologists, endocrinologists, and gynecologists promoted a Delphi survey among expert colleagues to assess the level of consensus regarding controversial issues and the best practice to apply on when and how to screen and treat peri- and postmenopausal women. The degree of agreement among participants and the conclusions were drawn using the Delphi methodology.

2 | MATERIALS AND METHODS

This study, conducted between February and May 2023, was spearheaded by authors renowned for their expertise in specialized fields. They designed a Delphi survey, comprising two consecutive questionnaires (Data S1—Questionnaires). These questionnaires were developed following a comprehensive literature review and were subsequently presented to a panel of responding clinicians. Data on physicians' demographics, facility types, geographic locations, and years of experience were collected. Some of this information was utilized as covariates, including respondents' age, years of involvement in managing pathology within their therapeutic area of specialization, and scope of their work. Furthermore, the participating centers were categorized based on their distinctive characteristics.

The first questionnaire (Q1) comprised questions with various structures, organized into four sections (C: cardiovascular, E: endocrinologic, G: gynecologic, T: transversal) covering different areas: (1) approach to gynecologic risks, (2) approach to cardiovascular risk, (3) approach to metabolic risk, (4) approach to symptomatic healthy patient, and (5) approach to HRT including indications, timing, and duration of HRT.

The majority of questions used a scale from 1 (indicating maximum disagreement) to 9 (indicating maximum agreement). However, only a minority of questions employed multiple-choice answers or ranked the proposed items.

The Advisory Board convened to discuss the results of the Q1 survey and subsequently formulated a second questionnaire (Q2) to address unclear aspects from Q1, and to thoroughly evaluate the appropriateness of certain diagnostic, therapeutic and management procedures.

Both questionnaires underwent qualitative validation for content and face validity. Content validity was assessed internally by the Advisory Board, while face validity was qualitatively evaluated by colleagues of Advisory Board members. Their feedback regarding the clarity and potential ambiguities of the questionnaires was considered before finalizing the questionnaire versions.

Q1 and Q2, created as computerized questionnaires, were delivered via a software platform (Sawtooth Software Inc., CBC ADM KIT SUB Lighthouse Studio). Initially, these questionnaires were distributed to a qualitative expert panel (EP) consisting of

25 cardiologists, 25 endocrinologists and 25 gynecologists, who were selected by the Advisory Board and strategically located throughout the country. Q1 was distributed to the EP in February 2023, and the statistical analysis was carried out on the responses received from 62 participants. Subsequently, in May 2023, Q2 was sent out to further refine topics that had generated ambiguous responses in Q1, with responses collected in the same month. The data were analyzed using Microsoft Office Excel, incorporating specific and tailored functions designed for the objectives of this study (as detailed in the next paragraph). Statistical analyses were conducted on the respondents for both Q1 and Q2 (Data S2—Contributors).

Expert agreement was evaluated using the Delphi method, developed by the RAND Corporation.¹³ This method, widely acknowledged and validated, facilitates consensus-building and group decision-making across diverse fields.^{14–17} Rooted in the fundamental principles of anonymity, controlled feedback, and statistical group response, the Delphi method is commonly employed in health research and clinical challenges.¹⁸ The method involves employing a scale ranging from one (indicating maximal disagreement) to nine (indicating maximal agreement), with five denoting a neutral opinion on any given item. Expert scores were subjected to statistical processing to calculate a consensus index. Interpercentile range adjusted for symmetry (IPRAS) scores, a metric of score dispersion adjusted for panel symmetry, were utilized according to the guidelines outlined in the RAND/UCLA Appropriateness Method User's Manual. This approach was used to determine the level of agreement for each item. The rationale behind this approach is that in cases where ratings exhibit symmetry, the interpercentile range (IPR) required to categorize a situation as indicating disagreement is smaller compared to cases with asymmetric ratings. Asymmetry, in this context, is defined as "the distance between the central point of the IPR and the central point of the 1–9 scale, that is, 5". As the degree of asymmetry in ratings increases, the required IPR for establishing disagreement also grows. To address this, the following mathematical function was devised: $IPRAS = IPRr + (AI \times CFA)$, where IPRr represents the IPR needed for disagreement under perfect symmetry; AI is the asymmetry index; CFA is the correction factor for asymmetry. A statement or indication is considered as indicating disagreement when $IPRi > IPRASi$. Using the computation of IPR and IPRAS, each statement can be classified on the appropriateness of a given diagnostic/therapeutic strategy into the following categories: appropriate (panel median of 7–9 without disagreement); uncertain (panel median of 4–6 or any median with disagreement); inappropriate (panel median of 1–3 without disagreement).

According to Italian Law, surveys carried out on healthcare workers do not require approval by Ethical Committees. Participants who filled out the questionnaire also explicitly expressed their consent to collaborate in the study.

Statistical analysis was performed by means of SPSS 27.0 (IBM, Armonk, NY, USA). When appropriate, the significance threshold was set at 0.05.

3 | RESULTS

A total of 75 experts were invited to participate in the project. Thirteen did not respond within the given timeframe. Consequently, statistical analysis was conducted based on data provided by 62 participants (82% of the initial panel) for Q1 and by 47 participants (76% of Q1 respondents) for Q2. The characteristics of the respondents are detailed in Table 1.

Experts were asked to define the criteria and to share ways of defining the best diagnostic and clinical approach that each physician, regardless of their specialty (whether cardiology, endocrinology, or gynecology), should provide for the peri- and postmenopausal patient.

The results of the two rounds of Delphi questionnaires, Q1 and Q2, are summarized in Figure 1. Figure 2 shows items for which consensus was reached among all specialists involved (cardiologists, endocrinologists, and gynecologists), highlighting any necessary and appropriate measures or actions for visits with peri- or postmenopausal women.

3.1 | Approach to the patients in relation to the gynecologic risk

All experts concur that the primary objective of managing and treating a postmenopausal woman is to address her physical, emotional, and sexual well-being, along with implementing preventive programs targeting urogynecologic, osteoporotic and oncologic risks, as well as metabolic and cardiovascular diseases (T5). Gynecologists and endocrinologists, but not cardiologists, agree that factors such as urogenital syndrome and endometrial thickness should be evaluated in the initial approach (G3–G7).

TABLE 1 Characteristics of the study population.

	n = 62
Age, years (median, min–max)	F 59, 31–70 M 57, 28–80
Overall working experience, years (median, min–max)	F 27, 0–41 M 28, 0–51
Field of prevalent activity	
Cardiology (n)	18
Endocrinology (n)	22
Gynecology (n)	22
Geographical area	
North (n)	19
Center (n)	20
South/Islands (n)	23

3.2 | Approach to the patients in relation to the cardiovascular risk

Cardiologists, endocrinologists, and gynecologists concur (C1–C5, C8) that perimenopausal transition signifies a cardiovascular risk condition. They align on key factors to evaluate in such patients, including lifestyle, prior cardiovascular diseases, thrombophilia genetic factors, obstetric and gynecologic history, familial predisposition to cardiovascular events at a young age, lifestyle habits, and presence of cardiovascular diseases. Additionally, they agree on essential assessment tools such as cardiovascular risk charts, measurement of waist-to-hip ratio and body mass index (BMI, calculated as weight in kilograms divided by the square of height in meters), standard hematological and endocrine-metabolic tests, as well as lifestyle evaluation.

Specialists differ in their approaches to good practices for asymptomatic peri- and postmenopausal patients without cardiovascular risk. Cardiologists and endocrinologists concur on the importance of evaluating blood glucose and lipidemia, conducting electrocardiograms, and screening for thrombophilia, particularly in cases of familial thrombotic predisposition. Conversely, gynecologists consider these measures as not initially necessary for all patients but recommend them for individuals deemed “at-risk”, who are identified and referred for cardiological consultation (C9).

There is consensus to prioritize HRT as the initial intervention for symptomatic women, offering short-term effectiveness on symptomatology and middle-long term action for prevention of cardiovascular disease, such as nutrition and exercise (C12).

Furthermore, experts concur that hot flashes should be regarded as a cardiovascular risk factor (C7), necessitating hormonal and cardiometabolic investigations and possible therapy (G2).

3.3 | Approach to the patients in relation to the metabolic risk

There is consensus among several specialists (E1, E2, E4, E6, E7) on different points: the menopause is an independent metabolic risk factor that accelerates the development of metabolic diseases; the age of menopause and the type of menopause do not influence the metabolic risk in a diabetic patient; the healthy peri- and postmenopausal patient with a history of polycystic ovary syndrome should undergo thorough diagnostic investigations of glycid and lipid metabolism; anthropometric parameters (body mass index, waist circumference) are integral part of assessment to be performed in all peri- and postmenopausal women by all the specialists who see the patient; healthy peri- and postmenopausal patient with a history of obstetrical pathology should undergo evaluation of the thrombophilic panel and/or glucose metabolism. Furthermore, consensus among specialists is observed regarding questions E9–E12 concerning thyroid function, although specific data is not provided.

Question n.		QUESTIONNAIRE 1			QUESTIONNAIRE 2		
		Cardiologists	Endocrinologists	Gynecologists	Cardiologists	Endocrinologists	Gynecologists
Q01_a	The transition phase from pre- to peri- to post-menopause represents a cardiovascular risk condition.	appropriate	appropriate	appropriate			
Q02	What factors do you consider to be a priority in defining a peri- and postmenopausal patient's cardiovascular risk?	appropriate	appropriate	appropriate			
Q03_a	Lifestyle factors	appropriate	appropriate	appropriate			
Q03_b	Previous cardiovascular disease	appropriate	appropriate	appropriate			
Q03_c	Obstetric factors	uncertain	uncertain	uncertain			
Q03_d	Gynecological factors	uncertain	uncertain	uncertain			
Q03_e	Endocrinological factors	appropriate	appropriate	uncertain			
Q03_f	Thrombotic genetic factors	appropriate	appropriate	uncertain			
Q04_1	In clinical practice, for the purpose of defining cardiovascular risk in peri- and postmenopause, it is necessary to investigate the woman's obstetrical history (fetal endometrial death, polyabortion, preeclampsia, gestational diabetes).	appropriate	appropriate	appropriate			
Q05_1	In clinical practice, for the purpose of defining cardiovascular risk in peri- and postmenopause, it is necessary to investigate the woman's gynecological history (functional ovarian syndrome, endometriosis, hypogonadotropic hypogonadism, primary ovarian failure).	appropriate	appropriate	appropriate			
Q06_1	In clinical practice, for the purpose of defining cardiovascular risk in peri- and post-menopause, it is necessary to investigate family history for cardiovascular events at a young age, lifestyle (smoking, diet, exercise), presence of cardiovascular disease.	appropriate	appropriate	appropriate			
Q07_1	Hot flashes are experienced by 80-90% of women in menopausal transition, and while they are a disturbing feature, they cannot be considered a cardiovascular risk factor per se.	uncertain	uncertain	uncertain			
Q08	In clinical practice for cardiovascular risk assessment of peri- and postmenopausal women, it is essential to use:						
Q08_a	The cardiovascular risk chart	appropriate	appropriate	appropriate			
Q08_b	The measurement of the waist-to-hip ratio and Body Mass Index	appropriate	appropriate	appropriate			
Q08_c	The Coughlin index	uncertain	uncertain	uncertain			
Q08_d	The standard hematological and endocrine metabolic tests	appropriate	appropriate	appropriate			
Q08_e	The thyroid panel hormone assay	appropriate	uncertain	uncertain			
Q08_f	The lifestyle assessment (sedentary lifestyle, smoking habit, caffeine and alcohol consumption)	appropriate	appropriate	appropriate			
Q09	In asymptomatic peri- and postmenopausal women, in the absence of cardiovascular risk factors, it is good practice to:						
Q09_a	Do not require any examination	inappropriate	appropriate	uncertain	inappropriate	inappropriate	uncertain
Q09_b	Assess blood glucose and lipids	appropriate	appropriate	appropriate	appropriate	appropriate	uncertain
Q09_c	Request an electrocardiogram	uncertain	uncertain	uncertain	uncertain	uncertain	inappropriate
Q09_d	Request blood chemistry tests and an electrocardiogram	uncertain	uncertain	uncertain	uncertain	uncertain	inappropriate
Q09_e	Require in specific cases (family history for thrombotic events) thrombotic genetic assessment of hormone therapy	appropriate	uncertain	inappropriate	appropriate	appropriate	uncertain
Q10	In women with a higher cardiovascular risk profile in whom the decision is made to do replacement therapy, it is necessary to request:						
Q10_a	Cardiology consultation	appropriate	appropriate	appropriate	appropriate	appropriate	appropriate
Q10_b	Routine blood chemistry tests	appropriate	appropriate	appropriate	appropriate	appropriate	appropriate
Q10_c	Thrombotic screening	appropriate	appropriate	uncertain	appropriate	uncertain	uncertain
Q10_d	Endocrinological tests	appropriate	appropriate	uncertain	appropriate	uncertain	uncertain
Q10_e	Electrocardiogram	uncertain	uncertain	uncertain	uncertain	uncertain	inappropriate
Q10_f	Echocardiogram	uncertain	uncertain	inappropriate	appropriate	uncertain	inappropriate
Q10_g	CAC-CT (Coronary Artery Calcium score)	uncertain	uncertain	inappropriate	appropriate	uncertain	inappropriate
Q11	The first level of preventive prevention of cardiovascular disease in healthy postmenopausal women includes:						
Q11_a	Nutrition and exercise	appropriate	appropriate	appropriate			
Q11_b	Prescription of specialized examinations	appropriate	appropriate	uncertain			
Q11_c	Hormone replacement therapy in symptomatic women for postmenopausal	appropriate	appropriate	appropriate			
Q13_a	Hormone replacement therapy started early is a valuable tool for prevention of cardiovascular disease in postmenopausal women.	uncertain	appropriate	appropriate	appropriate	appropriate	appropriate
Q14	In women 100 years old with recent hysterectomy and no cardiovascular risk, initiation of hormone replacement therapy with estrogen alone:						
Q14_a	reduces all-cause mortality	uncertain	appropriate	appropriate	uncertain	appropriate	appropriate
Q14_b	reduces mortality from cardiovascular disease	uncertain	appropriate	appropriate	uncertain	appropriate	appropriate
Q14_c	reduces the risk of osteoporotic fractures	appropriate	appropriate	appropriate	appropriate	appropriate	appropriate
Q14_d	reduces the risk of cognitive decline	uncertain	uncertain	uncertain	appropriate	uncertain	uncertain
Q14_e	reduces the risk of colorectal cancers	uncertain	uncertain	uncertain	uncertain	uncertain	uncertain
Q14_f	The risk of cardiovascular events increases by initiation of hormone replacement therapy after 60	appropriate	appropriate	appropriate			
Q15_a	Menopause is an independent metabolic risk factor that accelerates the development of metabolic disease.	appropriate	appropriate	appropriate			
Q15_b	Signs of menopause in perimenopause do not affect metabolic risk in a patient already with diabetes.	appropriate	appropriate	appropriate			
Q15_c	Hot flashes are a marker of metabolic vulnerability, and women who suffer from them should be considered at risk of developing cardiovascular disease.	uncertain	appropriate	appropriate			
Q16_a	The healthy peri- and postmenopausal patient with a history of polycystic ovary syndrome should undergo in-depth diagnostic investigation of lipid and lipid metabolism.	appropriate	appropriate	appropriate			
Q16_b	Female sexual dysfunction is an indicator of metabolic risk.	uncertain	appropriate	uncertain			
Q16_c	Assessment of anthropometric parameters (body mass index, waist circumference) is an integral part of cardiovascular risk assessment of peri- and postmenopausal women.	appropriate	appropriate	appropriate			
Q17	The healthy peri- and postmenopausal patient with a history of obstetrical pathology (fetal endometrial death, polyabortion, preeclampsia, gestational diabetes) should undergo evaluation of the thrombotic genetic panel and/or glucose metabolism.	appropriate	appropriate	appropriate			
Q18	The use of hormone replacement therapy brings from a metabolic point of view:						
Q18_a	A worsening of glucose metabolism	inappropriate	inappropriate	inappropriate	inappropriate	inappropriate	inappropriate
Q18_b	A dyslipidemia	inappropriate	inappropriate	inappropriate	inappropriate	inappropriate	inappropriate
Q18_c	An improvement in lipid metabolism	appropriate	appropriate	appropriate	appropriate	appropriate	appropriate
Q18_d	A reduction in insulin resistance	appropriate	appropriate	appropriate	appropriate	appropriate	appropriate
Q18_e	A benefit on blood pressure	uncertain	uncertain	uncertain	uncertain	uncertain	uncertain
Q18_f	A general reduction of body fat	uncertain	uncertain	uncertain	uncertain	uncertain	uncertain
Q19	In obese patients, hormone replacement therapy may increase:						
Q19_a	The overall metabolic risk	uncertain	uncertain	uncertain			
Q19_b	The global cardiovascular risk	uncertain	uncertain	uncertain			
Q19_c	The risk of breast cancer	uncertain	uncertain	uncertain			
Q19_d	The risk of endometrial cancer	uncertain	uncertain	uncertain			
Q19_e	The risk of liver cancer	uncertain	inappropriate	inappropriate			
Q19_f	For the initial screening of a peri-/postmenopausal patient, it is critical that lumbar spine + femur CBM be performed at an appropriate timing	appropriate	appropriate	appropriate			
Q20	For a peri- and postmenopausal patient with intense neurovegetative symptoms and in the absence of relevant comorbidities, it is necessary to require:						
Q20_a	No further examination	appropriate	appropriate	appropriate	inappropriate	inappropriate	inappropriate
Q20_b	Hormone assays	appropriate	appropriate	appropriate	appropriate	appropriate	appropriate
Q20_c	Electrocardiogram	uncertain	appropriate	uncertain	uncertain	uncertain	uncertain
Q20_d	Routine hematological examinations	appropriate	appropriate	appropriate	appropriate	appropriate	appropriate
Q20_e	Pressure diary	appropriate	appropriate	appropriate	appropriate	appropriate	appropriate
Q20_f	Hot flash diary	uncertain	uncertain	uncertain	uncertain	uncertain	uncertain
Q20_g	Hot flash electrocardiogram	uncertain	uncertain	uncertain	uncertain	uncertain	uncertain
Q21	A woman presenting with hot flashes requires:						
Q21_a	Follow-up only	inappropriate	inappropriate	inappropriate			
Q21_b	Hormonal and cardiomaternal investigations and possible therapy	appropriate	appropriate	uncertain	appropriate	appropriate	uncertain
Q21_c	Hormonal investigations only and possible therapy	uncertain	appropriate	uncertain			
Q21_d	No initial investigation but supplementation with phytoestrogens	appropriate	appropriate	inappropriate			
Q21_e	Vaginal dryness is a parameter that should always be evaluated in the first approach to the postmenopausal woman.	uncertain	appropriate	appropriate			
Q21_f	Uterine contractions is a parameter that always evaluate in the first approach to the postmenopausal woman.	uncertain	appropriate	appropriate			
Q21_g	Endometrial thickness is a parameter that changes the therapeutic approach to the postmenopausal patient.	uncertain	appropriate	appropriate			
Q22	Hormone replacement therapy in natural menopause should be prescribed:						
Q22_a	Early in asymptomatic patients	inappropriate	uncertain	inappropriate	inappropriate	uncertain	inappropriate
Q22_b	Preocclusally only in symptomatic patients	appropriate	appropriate	appropriate	appropriate	appropriate	appropriate
Q22_c	For a period not exceeding 5 years	uncertain	uncertain	uncertain	uncertain	uncertain	uncertain
Q22_d	Even beyond the age of 60 years	uncertain	uncertain	uncertain	uncertain	uncertain	uncertain
Q23	Hormone replacement therapy in surgical menopause should be prescribed:						
Q23_a	Early in asymptomatic patients	uncertain	appropriate	uncertain	uncertain	uncertain	appropriate
Q23_b	Preocclusally only in symptomatic patients (eg, hot flashes, profuse sweating, palpitations, tachycardia, blood pressure changes, sleep disturbances, etc.)	uncertain	uncertain	uncertain	appropriate	uncertain	uncertain
Q23_c	For a period not exceeding 5 years	uncertain	uncertain	inappropriate	uncertain	uncertain	uncertain
Q23_d	Even beyond the age of 60 years	uncertain	uncertain	uncertain	appropriate	uncertain	uncertain
Q24	Hormone replacement therapy in early menopause should be prescribed:						
Q24_a	Early in asymptomatic patients	uncertain	appropriate	appropriate	uncertain	appropriate	appropriate
Q24_b	Preocclusally only in symptomatic patients (eg, hot flashes, profuse sweating, palpitations, tachycardia, blood pressure changes, sleep disturbances, etc.)	appropriate	uncertain	uncertain	appropriate	uncertain	uncertain
Q24_c	For a period not exceeding 5 years	uncertain	uncertain	inappropriate	uncertain	uncertain	inappropriate
Q24_d	Even beyond the age of 50 years	inappropriate	uncertain	uncertain	uncertain	uncertain	uncertain
Q25	In perimenopause, the use of an estrogenic is indicated for:						
Q25_a	Contraception purposes	uncertain	appropriate	uncertain			
Q25_b	Prevention of bone mass	appropriate	appropriate	appropriate			
Q25_c	Reduction of cardiovascular risk	uncertain	uncertain	uncertain			
Q25_d	Regulation of the cycle	appropriate	appropriate	appropriate			
Q25_e	Therapy of neurovegetative symptomatology	appropriate	appropriate	appropriate			
Q26	In perimenopause, the prescription of hormonal contraception is contraindicated by:						
Q26_a	Presence of hot flashes	inappropriate	inappropriate	inappropriate			
Q26_b	Smoking habit	uncertain	appropriate	appropriate	appropriate	appropriate	appropriate
Q26_c	Previous cardiovascular disease	uncertain	uncertain	uncertain	uncertain	uncertain	uncertain
Q26_d	Thyropathy	uncertain	inappropriate	inappropriate			
Q26_e	Previous cervical cancer	uncertain	uncertain	uncertain	uncertain	uncertain	uncertain
Q27	For the prescription of hormone replacement therapy in postmenopausal women in a healthy women, it is necessary to preliminarily prescribe:						
Q27_a	Routine blood chemistry tests	appropriate	appropriate	appropriate			
Q27_b	Thyroid hormone assays	appropriate	appropriate	uncertain			
Q27_c	Mammography	appropriate	appropriate	appropriate			
Q27_d	Electrocardiogram	uncertain	uncertain	uncertain			
Q27_e	Hemocoagulability assay	uncertain	uncertain	uncertain			
Q27_f	Transvaginal ultrasound	appropriate	appropriate	uncertain			
Q27_g	Coagulation screening	uncertain	uncertain	uncertain			
Q27_h	No examination	inappropriate	inappropriate	inappropriate			
Q28	Vaginal estrogens:						
Q28_a	Have no contraindications	inappropriate	uncertain	appropriate	uncertain	inappropriate	uncertain
Q28_b	Are contraindicated in advanced postmenopausal women	uncertain	uncertain	inappropriate	inappropriate	uncertain	inappropriate
Q28_c	They are contraindicated in breast cancer	uncertain	uncertain	inappropriate	uncertain	uncertain	uncertain
Q28_d	They have the same contraindications as HRT	uncertain	uncertain	inappropriate	uncertain	uncertain	inappropriate
Q29	The priority target of the management of a woman with menopause should include:						
Q29_a	The prevention of breast cancer pathology	appropriate	appropriate	appropriate			
Q29_b	The prevention of oncological pathology of the genital sphere	appropriate	appropriate	appropriate			
Q29_c	The prevention of metabolic and cardiovascular disorders	appropriate	appropriate	appropriate			
Q29_d	The prevention of thyroid disorders	uncertain	appropriate	uncertain			

FIGURE 1 Appropriateness of responses to Questionnaires 1 and 2 evaluated according to the RAND/UCLA method, by clinical specialty of respondents.

3.4 | Approach to symptomatic health patients

In cases involving highly symptomatic patients, unanimous agreement among all specialists exists regarding the necessity for conducting additional investigations and implementing pressure diaries. However, gynecologists do not find it necessary to prescribe hormone assays and electrocardiogram (G1).

3.5 | Approach to HRT

While there is consensus among experts regarding the early prescription of HRT for symptomatic patients, extending beyond the age of 60 years old (G9) in spontaneous menopause, differences emerge for women experiencing surgical or early menopause (G10, G11). In fact, only gynecologists deem it appropriate to prescribe HRT early and beyond the age of 60 in asymptomatic patients, both in surgical and, together with endocrinologists, in early menopause. On the other hand, cardiologists agree solely on prescribing HRT in symptomatic patients.

Regarding cardiovascular implications, specialists align on the fundamental examinations (C10a, C10b) preceding HRT in women with high cardiovascular risk. Notably, only gynecologists consider thrombophilic screening (C10c) unnecessary, and similarly, endocrinologists, unlike cardiologists, do not advocate for electrocardiograms (C10d). Additionally, there is general consensus regarding HRT as a risk reduction strategy in asymptomatic early menopausal patients (C14) and those undergoing surgical menopause (C15).

As regards metabolic implications, there is a substantial agreement on metabolic advantage of HRT (E14), but not in obese women (E15).

There is general consensus on indications and contraindications of estroprogestins in perimenopause (G12, G13).

4 | DISCUSSION

The current Delphi project was designed with the specific purpose to develop a multidisciplinary model endorsed by three different specialized figures. The study highlights a different approach to managing menopausal women, depending on the specialist overseeing their care. Cardiologists and endocrinologists often tend to underestimate all the changes related to sexual and relational experiences and the gynecologic oncologic risk. Conversely, while acknowledging an increased cardiovascular risk in such women, gynecologists may not consistently initiate discussions on preventive measures.

The data clearly demonstrate a unanimous agreement (Table 2) among the different specialists regarding the primary goal of managing and treating peri- and postmenopausal women: the prevention of metabolic and cardiovascular diseases. This transitional phase represents a cardiometabolic risk condition. There is a general consensus on the relevance of the anamnestic risk factors to be evaluated (generic, cardiovascular, obstetric, gynecologic, hot flashes), on the

Question n.	QUESTIONNAIRE 1			QUESTIONNAIRE 2		
	Cardiologists	Endocrinologists	Gynecologists	Cardiologists	Endocrinologists	Gynecologists
C01_a	The transition phase from pre- to peri- to post-menopause represents a cardiovascular risk condition.					
C03	What factors do you consider to be a priority in defining a peri- and post-menopausal patient's cardiovascular risk?					
C03 a	appropriate	appropriate	appropriate			
C03 b	appropriate	appropriate	appropriate			
C03 f	appropriate	appropriate	appropriate			
C04_r1	In clinical practice, for the purpose of defining cardiovascular risk in peri- and postmenopause, it is necessary to investigate the woman's obstetrical history (fetal endouterine death, polyabortion, preeclampsia, gestational diabetes).					
C05_r1	In clinical practice, for the purpose of defining cardiovascular risk in peri- and postmenopause, it is necessary to investigate the woman's gynecological history (polycystic ovary syndrome, endometriosis, hypogonadotropic hypogonadism, primary ovarian failure).					
C06_r1	In clinical practice, for the purpose of defining cardiovascular risk in peri- and post-menopause, it is necessary to investigate familiarity for cardiovascular events at a young age, lifestyle (smoking, diet, exercise), presence of cardiovascular disease.					
C08	In clinical practice for cardiovascular risk assessment of peri- and postmenopausal women, it is essential to use:					
C08 a	appropriate	appropriate	appropriate			
C08 b	appropriate	appropriate	appropriate			
C08 d	appropriate	appropriate	appropriate			
C08 f	appropriate	appropriate	appropriate			
C09	In asymptomatic peri- and postmenopausal women, in the absence of cardiovascular risk factors, it is good practice to:					
C09 b	appropriate	appropriate	appropriate	appropriate	appropriate	uncertain
C10	In women with a higher cardiovascular risk profile in whom the decision is made to do replacement therapy, it is necessary to request:					
C10 a	appropriate	appropriate	appropriate	appropriate	appropriate	appropriate
C10 b	appropriate	appropriate	appropriate	appropriate	appropriate	appropriate
C12	The first level of intervention for prevention of cardiovascular disease in healthy postmenopausal women includes:					
C12 a	appropriate	appropriate	appropriate			
C12 c	appropriate	appropriate	appropriate			
C14_a	uncertain	appropriate	appropriate	appropriate	appropriate	appropriate
C15	In women <60 years old with recent hysterectomy and no cardiovascular risk, initiation of hormone replacement therapy with estrogen alone:					
C15 b	uncertain	appropriate	appropriate	appropriate	appropriate	appropriate
C15 c	appropriate	appropriate	appropriate	appropriate	appropriate	appropriate
C15 d	uncertain	appropriate	appropriate	appropriate	appropriate	appropriate
C16_a	The risk of cardiovascular events increases by initiation of hormone replacement therapy after age 65.					
E01_a	Menopause is an independent metabolic risk factor that accelerates the development of metabolic disease.					
E02_a	Age at menopause and type of menopause do not affect metabolic risk in a patient already with diabetes.					
E04_a	The healthy peri- and postmenopausal patient with a history of polycystic ovary syndrome should undergo in-depth diagnostic investigation of glycid and lipid metabolism.					
E06_a	Assessment of anthropometric parameters (body mass index, waist circumference) is an integral part of cardio-metabolic risk assessment of peri- and postmenopausal women.					
E07_a	The healthy peri- and postmenopausal patient with a history of obstetrical pathology (fetal endouterine death, polyabortion, preeclampsia, gestational diabetes) should undergo evaluation of the thrombophilic panel and/or glucose metabolism.					
E14	The use of hormone replacement therapy brings from a metabolic point of view:					
E14 c	appropriate	appropriate	appropriate			
E14 d	appropriate	appropriate	appropriate			
E16_a	For the initial screening of a peri-/postmenopausal patient, it is critical that lumbar spine + femur CBM be performed at an appropriate timing.					
G01	For a peri- and postmenopausal patient with intense neurovegetative symptoms and in the absence of relevant comorbidities, it is necessary to require:					
G01 e	appropriate	appropriate	appropriate	appropriate	appropriate	appropriate
G02	A woman presenting with hot flashes requires:					
G02 b	appropriate	appropriate	appropriate			
G09	Hormone replacement therapy in natural menopause should be prescribed:					
G09 b	appropriate	appropriate	appropriate	appropriate	appropriate	appropriate
G09 d	uncertain	uncertain	uncertain	appropriate	appropriate	appropriate
G10	Hormone replacement therapy in surgical menopause should be prescribed:					
G10 d	uncertain	uncertain	uncertain	appropriate	appropriate	appropriate
G12	In perimenopause, the use of an estrogen is indicated for:					
G12 b	appropriate	appropriate	appropriate			
G12 d	appropriate	appropriate	appropriate			
G12 e	appropriate	appropriate	appropriate			
G14	For the prescription of hormone replacement therapy in postmenopausal women in a healthy woman, it is necessary to preliminarily prescribe:					
G14 a	appropriate	appropriate	appropriate			
G14 c	appropriate	appropriate	appropriate			
G14 f	appropriate	appropriate	appropriate			
T05	The priority target of the management of a woman with menopause should include:					
T05 a	appropriate	appropriate	appropriate			
T05 b	appropriate	appropriate	appropriate			
T05 c	appropriate	appropriate	appropriate			

FIGURE 2 Response items that were unanimously agreed upon by the participating specialists.

TABLE 2 Shared diagnostic and screening criteria to assess the peri-/postmenopausal woman.

Cardiovascular risk

Factors to assess cardiovascular risk:

- Lifestyle factors;
- Previous cardiovascular diseases;
- Thrombophilia genetic factor;
- Obstetric history (fetal endouterine death, polyabortion, pre-eclampsia, gestational diabetes);
- Gynecologic history (polycystic ovary syndrome, endometriosis, hypogonadotropic hypogonadism, primary ovarian failure);
- Familiarity for cardiovascular events at a young age, lifestyle (smoking, diet, exercise), presence of cardiovascular diseases.

Measures appropriate for cardiovascular risk assessment:

- Cardiovascular chart risk;
- Measurement of the waist to hip ratio and body mass index;
- Standard hematochemical and endocrine-metabolic;
- Lifestyle assessment (sedentary lifestyle, smoking habit, caffeine and alcohol consumption).

In asymptomatic patients without cardiovascular risk, it is appropriate to assess blood glucose and lipidemia.

In patients with high cardiovascular risk, the prescription of hormone replacement therapy must be preceded by:

- A cardiology consultation;
- Routine blood chemistry tests.

The first medical interventions in the prevention of cardiovascular disease:

- Intervening on diet and exercise;
- Prescribing HRT in symptomatic women.

In asymptomatic, early menopausal patients, HRT should be prescribed to reduce cardiovascular risks.

In women <60 years old with recent hysteradnexectomy and no cardiovascular risk, initiation of HRT with estrogen alone:

- Reduces mortality from cardiovascular disease;
- Reduces the risk of osteoporotic fractures;
- Reduces the risk of cognitive decline.

In women >65 years old the initiation of hormone replacement therapy increases the risk of cardiovascular events.

Metabolism

Menopause is an independent metabolic risk factor that accelerates the development of metabolic diseases.

In a patient with diabetes, the age of menopause and the type of menopause do not influence the metabolic risk.

The healthy peri- and postmenopausal patient with a history of polycystic ovary syndrome should undergo thorough diagnostic investigations of glycid and lipid metabolism.

The assessment of anthropometric parameters (body mass index, waist circumference) is an integral part of cardiometabolic risk assessment.

(Continues)

TABLE 2 (Continued)

The healthy patient with a history of obstetrical pathology (endouterine fetal death, polyabortion, pre-eclampsia, gestational diabetes) should undergo evaluation of the thrombophilic panel and/or glucose metabolism.

Hormone replacement therapy (HRT)

HRT always results in improved lipid metabolism and reduced insulin resistance.

For the initial screening of a peri-/postmenopausal patient, perform lumbar spine and femur CBM at an appropriate timing.

In the peri- and postmenopausal patient with intense neurovegetative symptoms and no other important comorbidities, provide a constant assessment of pressure over time.

In a woman with hot flashes, effect a thorough hormonal and cardiometabolic evaluation, and possibly start a therapy.

Hormone replacement therapy in natural menopause should be started early only in symptomatic patients and can be prescribed to patients >60 years old.

In patients who have undergone surgical treatment, hormone replacement therapy can be prescribed to women >60 years old.

In perimenopause, use of estroprogestin to regularize the cycle and to treat for neurovegetative symptoms.

In healthy postmenopausal women, the prescription of hormone replacement therapy must be preceded preliminarily by a:

- Routine blood chemistry test
- Mammography
- Transvaginal ultrasound

essential instruments to use (cardiovascular chart risk, measurement of the waist to hip ratio and BMI), on the standard hematochemical and metabolic tests both for screening and preliminary to HRT. Moreover, specialists agree to consider HRT as a first level intervention for symptomatic women to relieve symptoms and prevent cardiovascular disease. Moreover, HRT is recognized as a tool to improve the metabolic profile, also in symptomatic women in high-risk condition such as early and surgical menopause beyond the age of 60 years. HRT for menopausal women encompasses testosterone therapy, offering potential benefits for sexual well-being, energy levels, and body composition. Non-pharmacological approaches, such as regular physical activity and cognitive-behavioral therapy, are also recommended for managing menopausal symptoms. Additionally, energy-based devices, such as lasers and radiofrequency devices, could be considered as potential treatments for management of peri- and postmenopause symptoms.¹⁹⁻²⁸ The wide chapter of the most recent studies on alternative non-pharmacological therapies would deserve a separate Delphi survey, and for this reason the study design, which was not intended to evaluate every aspect of currently available therapies, focused the topics submitted to the EP to those on which clinicians could express their opinion with a view to a multidisciplinary approach.

Some differences arise in the approach to the patient depending on the referring specialist. Generally, gynecologists are inclined to

prescribe less first level examinations and second level cardiovascular/thrombophilic diagnostic tests in healthy asymptomatic and symptomatic peri- and postmenopausal patients without cardiovascular risk. They also refrain from requesting further cardiovascular and thrombophilic diagnostic investigations when prescribing HRT in cases where cardiovascular risk factors are present, a practice also observed among endocrinologists.

Once more, differences emerge in the indications for HRT across three conditions: natural, surgical, and premature menopause. Cardiologists favor the symptomatology aspect when recommending HRT, while gynecologists prescribe ERT early even in the absence of symptoms for women in surgical menopause and (as well as endocrinologists) for those with premature menopause, suggesting a greater perspective of prevention and long-term general well-being.

The results of the present study challenge the conventional notion of menopause as an abrupt, binary event and instead emphasize the concept of the menopausal transition—a dynamic period characterized by a range of changes in a woman's life. This period is classified according to the Stages of Reproductive Aging Workshop²⁹ staging system, which delineates three distinct phases (reproductive, transition, and postmenopause). Each stage is defined by its typical duration, menstrual cycle characteristics, hormone levels, antral follicle count, and associated symptoms. The paper also delves into the clinical manifestations of menopause, which are categorized as short-, medium-, and long-term symptoms. These include vasomotor symptoms, neurovegetative symptoms, psychological and genitourinary alterations, osteoporosis, increased cardiovascular risk, and cognitive decline. To address these multifaceted comorbidities, the paper advocates for a comprehensive therapeutic approach that encompasses behavioral measures, lifestyle changes, and the subsequent introduction of specific medical therapies.

HRT is recognized as the gold standard treatment for managing menopausal symptoms.³⁰⁻³⁴ Tailored HRT therapies are designed to align hormone levels more closely with natural physiological patterns. The Italian Menopause Society¹⁰ recommends HRT for symptomatic women, preferably under the age of 60 or within 10 years of menopause, excluding contraindications such as abnormal uterine bleeding, breast cancer, and venous thromboembolism. Additional considerations include using the lowest effective doses for the shortest duration to mitigate breast cancer risk. The benefits of HRT are substantial, reducing all-cause mortality, cardiovascular disease, and osteoporotic fractures. However, the procoagulant effect of estrogen-progestogen therapy necessitates caution in patients at high-risk for thrombophilia and in those with risk factors such as cancer or smoking.³⁵ Moreover, the oncogenic potential of HRT, which was originally misinterpreted from the Women's Health Initiative Study, has undergone a reevaluation. It is now categorized based on its effects on tumor recurrence, which can be classified as advantageous, neutral, relatively contraindicated, or disadvantageous depending on the specific cancer type.³⁶ This comprehensive scientific understanding aims to dispel unfounded fears and guide evidence-based decision-making for both healthcare providers and menopausal women considering hormone replacement therapy.³⁷

TABLE 3 Main topics on which there was consensus among the participating experts.

Treating menopausal patients with comorbidities and comedications requires a particular multidisciplinary approach.
Early diagnosis of illness related to hormone deprivation in menopausal women requires a careful consideration of the available diagnostic tools.
In patients with surgical or early menopause, treatment with hormone replacement therapy can be useful to reduce symptoms and cardiovascular risk.
Careful risk/benefit balance between thrombotic and cardiovascular risk should be performed before the starting of treatment with hormone replacement therapy.

The Delphi method facilitated consensus among experts, underscoring the importance of not underestimating the symptoms and consequences of hormonal deprivation in peri- and postmenopausal women. This consensus challenges the conventional “on demand” clinical scheme and advocates for a proactive screening approach, which involves favoring aggressive screening of comorbidities and an early treatment with hormonal replacement therapy. This stance differs from experiences reported in real-world clinical practice.^{38,39} In practice, therapeutic inertia, an “on demand” approach and lack of a clear clinical identity of the peri- and postmenopausal women cohort, suggest a different perception regarding the potential severity of menopause consequences.

In addition, many patients may not receive diagnostics tests or receive them in the wrong time window. The clinical relevance of menopausal mediated symptoms suggests that awareness of hormone deprivation should be increased. Attention should be given to the correct screening and prompt treatment of major comorbidities in menopausal woman and their potential adverse outcomes.

5 | CONCLUSIONS

The Delphi project revealed variations in how experienced Italian cardiologists, endocrinologists, and gynecologists approach the assessment of menopausal women. These differences primarily involve variations in the type and sequence of investigations to be conducted. This evidence implies the need for an integrated training between specialists of different backgrounds to reach a diagnostic-therapeutic protocol shared by all healthcare workers involved in the health of menopausal women. However, all specialists consider cardiometabolic comorbidities and hormone deprivation as a critical clinical problem to be addressed and evaluated in peri- and postmenopausal women.

The Delphi study conducted among Italian expert cardiologists, endocrinologists, and gynecologists revealed a high degree of consensus on several controversial topics and the optimal approaches for managing peri- and postmenopausal women (Tables 2 and 3).

Regarding cardiovascular risk, the panel agrees on defining the perimenopause period as a “vulnerable phase”. Consequently, it is imperative to investigate related cardiovascular, endocrinologic, and

gynecologic factors. Gynecologic risks must be consistently considered and assessed.

Treating menopausal patients with cardiovascular and metabolic risks requires a multidisciplinary approach that involves careful consideration of available diagnostic tools.

The cardiovascular risk in peri- and postmenopausal women should be assessed through the routine clinical use of cardiovascular risk chart, measurement of the waist-to-hip ratio and BMI, standard hematochemical and metabolic tests, and an in-depth lifestyle assessment.

The panel agreed on the definition of menopause as a stage of women's lives in which certain risk factors—both oncologic and cardiometabolic—become predominant. It is recognized as an independent metabolic risk factor that accelerates the development of metabolic and subsequent cardiovascular diseases. Moreover, the panel acknowledged that the use of HRT can potentially ameliorate this risk due to its role in lipid metabolism and reduction of insulin resistance.

In particular, the panel strongly suggests conducting gynecologic, cardiovascular, and endocrinologic evaluations in all women to assess various risks, including cardiovascular and metabolic risk profiles, independently of the need for HRT.

Finally, HRT is regarded as a primary intervention in symptomatic menopausal women, serving as a risk reduction strategy in asymptomatic early menopausal patients and those undergoing surgical menopause. Additionally, it should be prescribed early for the treatment of symptomatic patients experiencing spontaneous early menopause.

AUTHOR CONTRIBUTIONS

Nicola Colacurci, Pasquale Perrone Filardi, Antonio Chiantera, Annamaria Colao, Patrizio Pasqualetti and Andrea Lenzi conceived and designed the Delphi Survey. Patrizio Pasqualetti carried out data acquisition and analysis. Nicola Colacurci, Pasquale Perrone Filardi, Antonio Chiantera, Annamaria Colao, Patrizio Pasqualetti and Andrea Lenzi interpreted the results. Nicola Colacurci, Pasquale Perrone Filardi, Patrizio Pasqualetti and Andrea Lenzi drafted the manuscript. Nicola Colacurci, Pasquale Perrone Filardi, Antonio Chiantera, Annamaria Colao, Patrizio Pasqualetti and Andrea Lenzi revised the manuscript. All authors reviewed, approved, and agreed to be accountable for the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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