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Determinants of menopause-related symptoms in women during the transition to menopause and the postmenopausal period – A systematic literature review

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ABSTRACT

Introduction: Menopause is a complex physiological, self-perceived health condition caused by the reduction and termination of ovarian function, a process that results in a range of both psychological and physiological symptoms. The aim of this literature review was to synthesize the results of published studies on factors associated with menopausal symptoms in women during the transition to menopause and the postmenopausal period.

Methods: This systematic review was carried out according to the PRISMA statement. Primary studies published between 2007 and 2017 were identified through the following databases: PUBMED, SCOPUS, and CINAHL. In total, 3301 studies were identified and 279 were screened in full text. Of these, 54 studies were included for quality assessment using checklists from the Norwegian Institute for Public Health. A total of 22 studies were ultimately selected for inclusion in the results. These were thematically reviewed.

Results: A wide range of determinants was sorted as socio-demographic predictors, reproductive factors, clinical characteristics, behavioral, and lifestyle characteristics, and their association with the following outcomes was examined: The prevalence and severity of menopausal symptoms; sexual functioning; health indicators and health behaviors; health-related quality of life; physical performance; cognitive changes and attitudes; and the prevalence and age of natural menopause.

Conclusions: The current state of knowledge regarding menopause indicates that a wide array of instruments and variables have been employed and assessed to further understanding about menopause-related symptoms. This systematic review provides information on factors that should be considered in the treatment of menopause-related changes that may be bothersome for menopausal women.

Keywords: Determinants; menopause; psychological health; physical health; sexual health; symptoms

INTRODUCTION

Menopause is a complex physiological process during which ovarian function and the production of sex hormones slowly diminish (1). Projections indicate that, by 2030, women aged 50 and older

will number 1.2 billion; of these, 76% will be living in developing countries (1,2). More than 50% of middle-aged women experience frequent menopause-related symptoms (3). These physiological changes result in a complex clinical picture and the experience of highly subjective symptoms. Because the symptoms are subjective, there is a risk that they may be underdiagnosed or undertreated (4). The increase of average life expectancy in the developed world is evident (5), and many social norms are under re-examination, such as the sphere of menopausal women's health and sexual health in older age. A national sample of 3005 adults between 57 and 85 years of age in the United States found that many older adults are sexually active (6), including women who experience an increase in menopause-related sexual difficulties (7-9).

The elderly population will expand between 2000 and 2050 (10). With an aging population, the number of women seeking help for menopause-related issues will increase (11). The menopausal transition is associated with sexual dysfunction for many women (12). Attitudes toward menopause range from negative to positive, and reflect the role of culture, attitude on the ageing process and the general life context of women (13).

Women's sexuality in welfare countries is in the midst of a transition away from gender norms, creating a new cultural scenario where women's sexual function after 40 is a way to see them as visible sexual beings (14). A study by Sayakhot et al. (2012) shows the differences in perceptions and experiences of menopause between women from Laos and Australia. Australian women more commonly reported menopause-related symptoms (psychological symptoms, sexual dysfunction, and vasomotor symptoms); similarities between groups included deficiencies in understanding with regard to menopausal therapies (15). Menopause is associated with a high risk of abnormalities of lipids and lipoproteins, insulin resistance and the development of cardiovascular diseases. Treatment with hormone replacement provides benefits against cardiovascular diseases but is dependent on the exact prescription, which is still being researched (16).

In a Brazilian population study, it was shown that 53.5% of menopausal women perceived their sex

life as being good (17); in contrast, it was shown in a study from Spain that sexual satisfaction declines progressively after age 45 (18).

Menopause occurs, on average, at the age of 50 (11,19,20), and results from a loss of ovarian function; as a result of this process, a woman's final menstruation marks that the period of fertility is over (provided there is no proven pathological condition) (2). Menopause is divided into perimenopause and postmenopause. Perimenopause is the result of a gradual loss of ovarian function over 5-10 years (19). Symptoms that occur during this period are menstruation irregularity, night sweats and hot flushes (21), genitourinary syndrome, and metabolic disorders; osteoporosis (19,20). Chou et al.'s (2014) study in Macau, China showed that menopausal symptoms affect the quality of life in about 57.2% of women (22). Barlow et al. (1997) found that genitourinary syndrome caused by decreased production of estrogen affects about 48.8% of women (23), and manifests as itching, pain, dryness, vulvovaginal atrophy, and urinary retention.

Additional psychological symptoms that can occur are insomnia, nervousness, irritability, or depression. The period of menopause is characterized as a transition period during which there is often increased fear of diseases such as cancer, anxiety, poorer physiological health, and concern for obesity, and loss of attractiveness (19). Symptomatic vulvovaginal atrophy is common in approximately 50% of postmenopausal women and can significantly impair their quality of life (24). A study by Hughes et al. (2015) showed that vaginal dryness as a sexual problem was typical for the majority of the study population (25). Another study confirmed these outcomes, also reporting that 67% of 49.5-year-old women reported sexual dysfunction (26).

Menopause-related changes affect women's sexual health and may lead to sexual dysfunction (27). Yang et al. (2015) found that menopause-related physical changes can make sexual interaction difficult (28). Robak-Cholubek et al.'s (2014) study showed that degree of difficulty during the menopausal transition is associated with a level of adaptation to the changes – women who adapted to the changes had less frequently reported adverse

experiences in their sexual interactions (29). A study by Cabral et al. (2014) showed that 94.5% of postmenopausal women respondents reported decreased sexual desire (30). A British National Survey confirmed that menopause-related symptoms were associated with low sexual function (31). In an Australian study that focused on the use of effective therapies for menopausal symptoms, it was shown that vaginal estrogen therapy is under-prescribed and under-treated (32). The occurrence and combination of different symptoms affect women's quality of life and are linked to their experience of health, sexuality, and the aging process. We developed our aims for this study in line with guidelines for literature reviews [27]. This systematic review aimed to synthesize the results of published studies on determinants associated with menopause-related symptoms in women during the transition to menopause and the postmenopausal period.

METHODS

This systematic review was carried out according to the PRISMA statement (33) and through use of Covidence, an online Cochrane technology platform for literature reviews (34). The search included studies published between 2007 and 2017. Only articles in English were included in the study. This review considered studies that included any outcome measure related directly or indirectly to menopause-related changes in women's health and women's experience of menopause. Inclusion criteria were primary studies that focused on the physiological menopause processes, and whose title and keywords included a type or types of menopause symptoms (e.g., "sexual dysfunction") or the terms "postmenopausal," "menopause," "women," "quality of life," "endocrine transition," and "menopausal transition." Peer-reviewed original research studies were included in the study, as well as a range of study designs. Studies were included that enrolled women with natural or surgical menopause, used validated or non-validated tools, and were conducted in either community or hospital/clinic settings. Studies including men and women were included in the study, with a focus on results concerning menopausal women. Exclusion criteria consisted of studies that did not include the target population that did not constitute

primary research; were review articles, books or book chapters that focused on diseases or infections (such as HIV or Sexually Transmitted Diseases), cancer, sexual minorities, mental health, pregnancy, tumors, incontinence, intimate partner violence, religiosity, blood pressure, systemic sclerosis, herpes, anxiety, distress, cytostatic treatment, hysterectomy, oophorectomy, pain, depression, partner violence, diabetes, premenstrual, youth, pregnancy, violence, or reproduction. Reports, abstracts, study protocols, conference proceedings, and case reports were excluded, as were reviews and studies employing a qualitative design. A systematic literature search was conducted in PUBMED, SCOPUS, and CINAHL in autumn 2017 to identify studies. The search strategy included the use of Medical Subject Headings terms related to each database. Table 1 shows an example of the search strategy used for the CINAHL database.

The records from the databases were imported into Endnote and then into XML formats and finally into Covidence (34). The review process had the following steps, all of which were conducted by both authors. Step one consisted of screening titles: The coauthors, one midwife, and one psychologist screened titles for relevance together using Covidence. In total, 3301 titles were included in the screening process. Both coauthors discussed each title and agreed on which titles to include and exclude. If there was disagreement on a particular article, the consensus was reached by discussion. Based on the inclusion/exclusion criteria, 3021 titles were excluded from

TABLE 1. Example of search strategy in the CINAHL database

Search ID	Search terms	Results
S1	(MH "Climacteric") OR "climacteric"	387
S2	(MH "Menopause") OR "MENOPAUSE"	3.458
S3	"Menopause treatment"	4
S4	"Menopause symptoms"	75
S5	(MH "Menopause") OR (MH "Women") OR "menopausal women"	9.496
S6	"Menopausia"	13
S7	S1 AND S2	199
S8	S1 OR S2	3.458
S9	S1 OR S4	453
S10	S2 OR S5	10.609
S11	S2 AND S5	2.157
S12	S3 OR S4	78

the study. In step two, the coauthors read abstracts of 279 titles separately. They then discussed these and agreed on the exclusion of 223 titles. In the final step, 54 full-text articles were read in their entirety, and quality assessment was achieved through the use of checklists for the evaluation of research from the Norwegian Institute for Public Health (35); a checklist for evaluation of cross-sectional studies based on the EBMH Notebook; guidelines for evaluating prevalence studies (36); and a checklist for cohort, longitudinal and RCT studies based on Guyatt et al. (2015) (37) and Singh (2013) (38). Finally, only papers that were assessed as being of medium or high quality were included in the study (Figure 1 and Tables 2-5).

Data extraction and synthesis

Because of the marked heterogeneity of the included studies, all were narratively reviewed. The following data were extracted: General information (i.e., author, title, year, and country of origin); study characteristics (i.e., design and setting, and inclusion and exclusion criteria of the participants); characteristics of participants (number, age range, or mean age); assessment of exposure factors and covariates; assessment of outcomes; and main results. Studies based on data from larger follow-up studies were classified as cross-sectional if they included only data from a single follow-up assessment. Most studies included in this review were correlational, and in some cases, the outcome variables of interest – as well as all independent
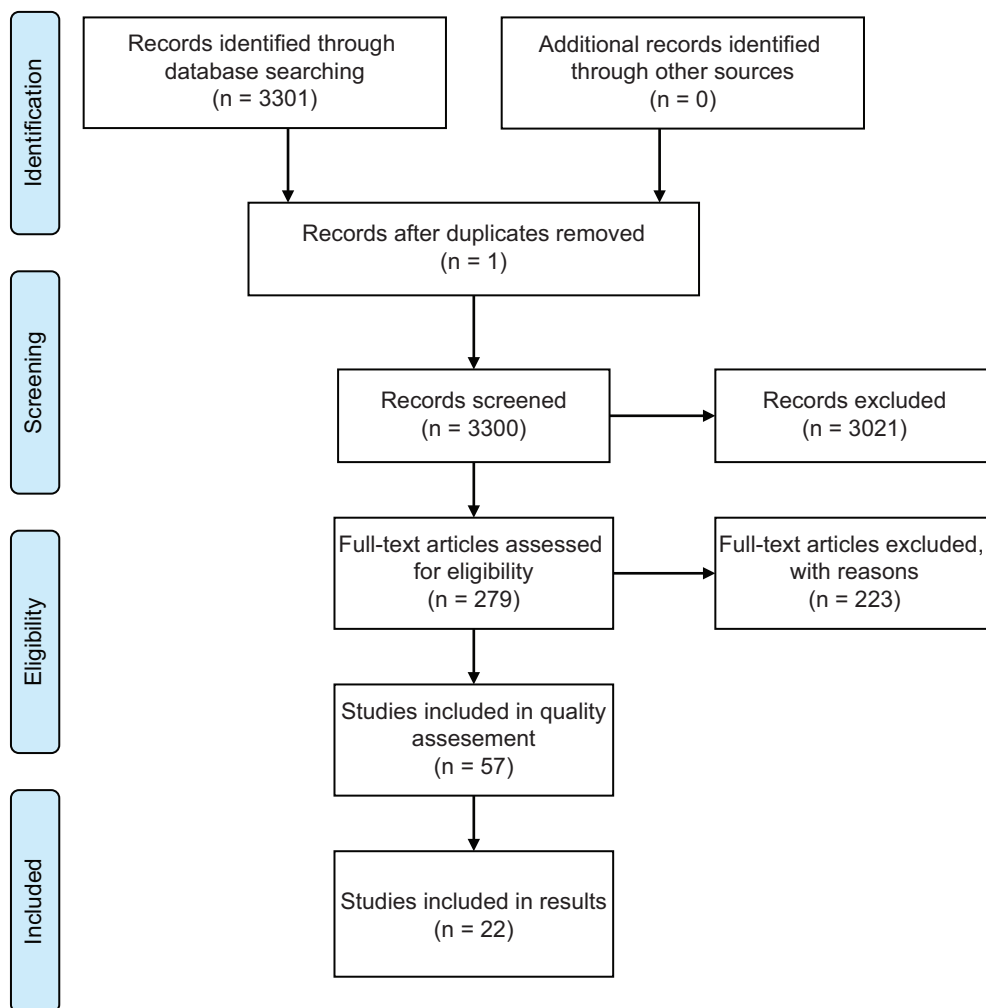

FIGURE 1. Flowchart of a selection of studies for the review.

TABLE 2. Quality assessment of the included studies with a cross-sectional design

Main author, year, country, title	1	2	3	4	5	6	7	8	9	10	11	12	Total assessment quality
Alquaiz et al., 2014, Saudi Arabia, Determinants of the severity of menopausal symptoms among Saudi women in Riyadh city	Y	Y	U	U	N	U	Y	Y	Y	Y	U	Y	Medium
Cabral et al., 2013, Brasil, Determinants of sexual dysfunction among middle-aged women	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	U	Y	High quality
Da Câmara et al., 2015, Brasil, Menopausal status and physical performance in middle-aged women: A cross-sectional community-based study in Northeast Brazil	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	U	Y	High Quality
DiBonaventura, et al., 2015, US And Western Europe, The association between Vulvovaginal atrophy symptoms and quality of life among postmenopausal women in the United States and Western Europe	Y	Y	Y	U	N	U	Y	Y	Y	Y	Y	Y	Medium
Field et al., 2013, UK, Associations between health and sexual lifestyles in Britain: Findings from the third National Survey of Sexual Attitudes and Lifestyles (Natsal-3)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	High quality
Gartoulla et al., 2015, Austria, Moderate to severe vasomotor and sexual symptoms remain problematic for women aged 60-65 y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	High quality
Ghazanfarpour et al., 2015, Iran, The relationship between women's attitude towards menopause and menopausal symptoms among postmenopausal women	U	Y	Y	Y	N	U	Y	Y	Y	U	Y	Y	Medium
Hunter et al., 2016, US, Predictors of impact of vaginal symptoms in postmenopausal women	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	High quality
Jacobs et al., 2016, US, Impact of sex and menopausal status on episodic memory circuitry in early midlife	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	High quality
Jaspers et al., 2016, The Netherlands, Sex steroids, sex hormone-binding globulin, and cardiovascular health in men and postmenopausal women: The Rotterdam study	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	U	Y	High quality
Javadivala et al., 2013, Iran, Modeling the relationship between physical activity and quality of life in menopausal-aged women: A cross-sectional study	Y	Y	Y	U	N	U	Y	Y	Y	U	Y	Y	Medium
Jonusiene et al., 2013, Lithuania, Sexual function, mood, and menopause symptoms in Lithuanian postmenopausal women	Y	Y	U	U	Y	Y	Y	U	U	Y	Y	Y	Medium
Li et al., 2012, China, Factors associated with the age of natural menopause and menopausal symptoms in Chinese women	Y	Y	Y	Y	N	Y	U	Y	Y	Y	Y	Y	High quality
Lo et al., 2015, China, Bone health status of postmenopausal Chinese women	Y	Y	Y	N	N	U	Y	Y	Y	Y	Y	Y	High quality
Ornat et al., 2013, Spain, Sexual function, satisfaction with life and menopausal symptoms in middle-aged women	U	Y	Y	U	U	Y	Y	Y	Y	Y	U	Y	Medium

TABLE 2. (*Continued*)

Main author, year, country, title	1	2	3	4	5	6	7	8	9	10	11	12	Total assessment quality
Pallikadavath et al., 2016, India, Natural menopause among women below 50 y in India: A population-based study	Y	Y	Y	U	Y	U	Y	Y	Y	Y	U	Y	Medium
Prairie et al., 2015, US, Symptoms of depressed mood, disturbed sleep, and sexual problems in midlife women: Cross-sectional data from the study of women's health across the nation	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	High quality
Som et al., 2014, India, Menopause-specific quality of life of a group of urban women, West Bengal, India	U	Y	Y	Y	N	U	U	Y	Y	Y	Y	Y	Medium
Yim et al., 2015, Korea, Prevalence and severity of menopause symptoms and associated factors across menopause status in Korean women	Y	Y	Y	Y	N	Y	U	Y	Y	Y	Y	Y	High quality

Checklist for cross-sectional studies based on Boyle MH: Guidelines for evaluating prevalence studies. Evidence-Based Mental Health 1998, 1(2):37-39. (1) Is the problem of the study formulated? (2) Is a prevalence study a suitable design to answer the issue/research question? (3) Is the population from which the sample is taken clearly defined? (4) Was the selection included in the study in a satisfactory manner? (5) Has it been clarified whether the respondents differ from those who have not responded? (6) Is the response rate high enough? (7) Does the study use measurement methods that are reliable (valid) for what you want to measure? (8) Is data collection standardized? 9) Is data analysis standardized? (10) What is the result of this study? (11) Can the results be transferred to practice? (12) Do the results of this study fit with the results of other available studies? (Answers Yes: Y; No: N; Unclear: U)

TABLE 3. Overview criteria met and the quality of the study

Criteria met	The quality of the study
All/almost all criteria met. Any weaknesses cannot change the conclusion of the study	High quality
Used if any of the criteria from the checklist are not met or if the criteria are not satisfactorily described. It is assumed, however, that there is little chance that the weaknesses could have changed the study's conclusion	Medium quality
They are used if few or no criteria from the checklist are met or are not satisfactorily described. The weaknesses may mean that the conclusion of the study is wrong	Inadequate/low
No criteria met	Excluded

variables and covariates – were not clearly stated in the text of the article. In such cases, variables were classified by carefully examining the study aims, data analyses, and tables in the article's results section.

The main results concerning the determinants and consequences of menopause-related symptoms in women are summarized in Table 6. The number of participants for a specific study presented in Table 6 corresponds to the number of participants selected for analysis based on the inclusion/exclusion criteria and completed questionnaires (in some articles, the number of participants presented in the abstract includes the initial sample). As the included studies collected data for a broad range of outcomes, descriptive synthesis was organized according to similar outcomes and factors significantly associated with those outcomes.

The primary outcomes of interest in this review were: (1) Menopausal symptoms (39-47); (2) sexual functioning (43,44,48-52); (3) health indicators and health behaviors (41,53-55); and (4) health-related quality of life (41,43,52,56). Secondary outcomes of interest included physical performance and cognitive functioning (57,58); attitudes toward menopause (45,59); and the age and prevalence of natural menopause (42,60).

The classification of exposure or independent variables and potential confounding variables in the included 22 studies is presented in Table 7. All studies examined the effects of women's age as a biological and socio-demographic characteristic. Other frequently examined demographic characteristics were educational level (18 studies); marital/relationship

TABLE 4. Quality assessment of the included studies with cohorts design

Main author, year, country, title	1	2	3	4	5	6	7	8	9	10	11	12	Total assessment quality
Kutob et al., 2017, US, Relationship between marital transitions, health behaviors, and health indicators of postmenopausal women: Results from the women's health initiative	Y	U	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	High quality
Sis Çelik and Pasinlioğlu, 2017, Turkey, Effects of imparting planned health education on hot flush beliefs and quality of life of climacteric women	Y	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	High quality

Checklist for cohorts studies (1) Is the purpose of the study formulated? (2) Were subjects recruited for the cohort satisfactorily? (3) Was the exposure accurately measured? (4) Was the outcome accurately measured? (5) A. Have the authors identified all important confounders in the study's design and analysis? (5) B. Have the authors take into account known, possible confounders in the design and analysis of the study? (6) Were any of the people in the cohort followed up? (7) Were the people followed up long enough? 8) What is the result of this study? (9) Do you trust the results? (10) Can the results be transferred to practice? (11) Do the results of this study fit with the results of other available studies? (12) What are the implications of this study for practice? (answers Yes: Y; No: N; Unclear: U)

1. Guyatt G, Rennie D, Meade M, Cook D. Users' guides to the medical literature: McGraw-Hill Medical:; 2015
2. Magne Nylenna: Slik oppsummerer v forskning. Håndbok for Nasjonalt kunnskapssenter for helsetjenesten. vol. 4: Oslo: Nasjonalt kunnskapssenter for helsetjenesten; 2015; 2006
3. Singh J: Critical appraisal skills programme. Journal of Pharmacology and Pharmacotherapeutics 2013, 4(1):76

TABLE 5. Quality assessment of the included studies with an RCT design

Main author, year, country, title	1	2	3	4	5	6	7	8	9	10	11	Total assessment quality
Tungmunsakulchai et al., 2015 Thailand, The effectiveness of a low dose of testosterone undecanoate to improve sexual function in postmenopausal women	U	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	High quality

Checklist for RCT studies: (1) Is the purpose of the study clearly formulated? (2) Was the assignment to the different groups using a satisfactory randomization procedure? (3) Were all the participants reported at the end of the study? (4) Were participants, health-care providers, and study personnel "blind" to treatment? (5) Were the groups similar at the start of the trial? (6) Aside from the measure being evaluated (experimental intervention), were the groups treated equally? (7) What are the results? (8) How accurate are the results? (9) Can the results be transferred to practice? 10). Were all important outcomes measured in this study? (11) Are the benefits worth the harms and costs? (answers: Yes: Y; No: N; Unclear: U)

status (16 studies); and indicators of socioeconomic status, such as family income (12 studies) and women's occupation or employment (seven studies). Among the independent reproductive variables, the most frequently examined were women's reproductive stage (14 studies) and parity (eight studies). Body mass index (BMI) was the most frequently examined independent variable among clinical characteristics (14 studies), while smoking (ten studies) and physical activity or exercise (ten studies) were the most frequently examined lifestyle and behavioral characteristics.

Description of eligible studies

The eligible studies were published between 2012 and 2017. The studies ranged in sample size from 70 to 630,361 women, due to different methodologies and study aims. Two studies – one randomized controlled trial (51) and one functional magnetic resonance study (57) – included 100 women or fewer. In nine studies, the number of participants ranged between 246 and 389 (39,41,43,45,46,48,50,58,59), while five studies included 745-1774 women (44,47,52,53,55), and six studies enrolled more than 2020 women (40,42,49,54,56,60). Of these, three studies had more than 20,000 participants. Nineteen of the included studies were cross-sectional (39,44,46-50,53,55-60), two studies were longitudinal (45,54), and one study used a randomized controlled trial design (51).

Almost all studies were single-country studies and were conducted in 14 countries worldwide:

TABLE 6. Characteristics of the eligible studies

Nr.*	Author, year, reference nr. country, title	Study design/Participants	Assessment of exposure/ Confounding	Outcomes/Measures	Main findings
I	AlQuaiz et al., 2014 (38) Saudi Arabia, Determinants of the severity of menopausal symptoms among Saudi women in Riyadh city	CS/n=490 W aged >40 y (mean age=51.4 y) attending an outpatient clinic in Riyadh city Exclusion: Bilateral oophorectomy under 50 y, history of depression or antidepressant drugs use, HT or synthetic estrogen use	Demographics: Age, education, occupation, marital status, residence Reproductive histories: Menopausal status, parity, age at menarche, age at menopause Lifestyle characteristics: Exercise, BMI, consumption of a) vegetables, b) fruit, c) red tea, d) Arabic coffee	The severity of menopausal symptoms (MRS) Three domains: Urogenital, somatic, psychological	-Higher risk for moderate or severe symptoms (logistic regressions): (a) Urogenital: age 50-54 y, lower residence status, irregular exercise, not working, Arabic coffee consumption; (b) somatic: Irregular exercise, nulliparous w, perimenopausal w; (c) psychological symptoms: Obese w -Significant predictors of higher MRS total scores (linear regression): Increased BMI, irregular or no exercise, intake of Arabic coffee
II	Cabral et al., 2013, (47) Brazil, Determinants of sexual dysfunction among middle-aged women	CS/n=370 W attending public health-care facilities in Natal (mean age=49.8 y) Inclusion: Healthy w aged 40-65 y, minute 11 y of education Exclusion: Cognitive and neurologic diseases, use of psychiatric drugs, HT use	Demographics: Age, race, education, marital status, family income Clinical and behavioral characteristics: Menopausal status, hysterectomy, BMI, smoking, physical activity level (IPAQ, short form), climacteric symptoms (BKMI), quality of life (WHOQOL-Bref)	Sexual function (FSFI) Sexual dysfunction: Total score ≤26.55 points	-Significant associations with sexual dysfunction: Age 56-65 y, lower education, divorce or separation, menopausal w, lower physical activity, hysterectomy, more severe climacteric symptoms, lower quality of life -Logistic regression: W aged 56-65 y, w with moderate and strong climacteric symptoms and w with low and average quality of life were most likely to develop sexual dysfunction
III	da Câmara et al., 2015, (58) Brazil, Menopausal status and physical performance in middle-aged women: A cross-sectional community-based study in Northeast Brazil	CS/n=389 W aged 40-65 y living in Parnamirim, recruited in primary care centers Exclusion: Neurological impairments and painful conditions, smoking, double oophorectomy, hysterectomy	Menopausal status Covariates: Age, family income, education, BMI, reproductive history (parity, age at menarche, age at first birth), walking time per week, sitting time per day, hypertension	Physical performance Handgrip strength test (Kgf): The mean of three trials Gait speed test (m/s): A 4-m walk The chair stands test (s): 5-times quick stand-ups and sit downs	-Premenopausal w performed significantly better in grip strength and chair stands than peri- and postmenopausal w. Gait speed did not vary significantly by menopausal status -Linear regressions: The effect of menopausal status remained significant only for grip strength (adjustment: Age, family income, education, BMI, parity, age at first birth)

(*Contd...*)

TABLE 6. *(Continued)*

Nr.*	Author, year, reference nr. country, title	Study design/Participants	Assessment of exposure/ Confounding	Outcomes/Measures	Main findings
IV	DiBonaventura et al., 2015, (55) US and Western Europe, The association between vulvovaginal atrophy symptoms and quality of life among postmenopausal women in the United States and Western Europe	CS/n=6527, all countries (n=3267 the US; n=3801 EU countries: France, Germany, Italy, Spain, and the UK) Postmenopausal w selected from the IWHS internet survey Inclusion: Postmenopausal w aged 40-75 y	VVA symptoms (vaginal dryness) item from the MRS) Vasomotor symptoms ('hot flushes' item from the MRS) Comorbidities: CCI; ten chronic conditions prevalent in menopausal w Work productivity (for employed w) and activity impairment (WPAI) Demographics and health history: Country, age, marital status, education, household income, BMI, exercise, smoking, alcohol use	Quality of life (EuroQol-5D-3) Five dimensions: Pain/ discomfort, anxiety/depression, mobility, self-care, usual activities (responses converted to a health utility score based on how the population in each country values that health state)	-General linear models: (1) Each incremental level of severity of VVA symptoms was associated with a significant decrement in the adjusted quality of life score for all countries and five EU countries (adjustment: Demographics and health history, CCI); (2) The perceived quality of life burden for moderate/severe VVA symptoms was comparable to the effects of moderate to severe vasomotor symptoms and the effects of dangerous medical conditions (e.g., arthritis, asthma, irritable bowel syndrome) on adjusted quality of life score for all countries and five EU countries
V	Field et al., 2013, (48) United Kingdom, Associations between health and sexual lifestyles in Britain: Findings from the third National Survey of Sexual Attitudes and Lifestyles (Natsal-3)	CS/n=5994 men and 8452 w aged 16-74 y This review: Outcomes for w aged 45-64 y (n=2031) Natsal-3: Multistage, clustered, and stratified probability sample design Inclusion: w who reported one or more sexual partner(s) over the lifetime	Clinical characteristics: Self-assessed general health, longstanding illness or disability, comorbidities (number of chronic conditions), menopausal status, difficulty walking up stairs due to health problems, depressive symptoms (PHQ-2), assessment whether health condition or disability affected sex life, seeking help or advice about sex life, Covariates: Age, relationship status	Sexual lifestyles Recent sexual activity (past 4 weeks), satisfaction with sex life (in the past year), sexual response problems for at least 6 months in the last year (erectile difficulties for men and vaginal dryness for w)	-Logistic regressions: W aged 45-64 y reporting bad or very bad health engaged less in sexual activity than w with good and very good health (adjustment for relationship status). Sexual activity was less frequent and vaginal dryness more common in post- than in premenopausal w (adjustment for covariates and comorbidities) -Only 20.6% of postmenopausal w reporting a health condition or disability affecting their sex life in the past year had sought clinical advice, mostly from general practitioners

(Contd...)

TABLE 6. (*Continued*)

Nr.*	Author, year, reference nr. country, title	Study design/Participants	Assessment of exposure/ Confounding	Outcomes/Measures	Main findings
VI	Gartoulla et al., 2015, (39) Australia, Moderate to severe vasomotor and sexual symptoms remain problematic for women aged 60 to 65 y	CS/n=2020 W aged 40-65 y (mean age = 52.6 y) recruited from a database based on Australian electoral roll; community-based, nationally representative sample Exclusion: Insufficient knowledge of English	Menopausal status Demographics: Age, residential location, education, relationship status Clinical and behavioral characteristics: Hysterectomy, bilateral oophorectomy, BMI, smoking, alcohol consumption	The prevalence of moderate to severe vasomotor symptoms (MENQOL), four domains: Vasomotor, sexual, physical, psychological The current use of prescription therapy for menopausal symptoms: Systemic hormonal contraception, HT, non-hormone therapy for menopausal symptoms, "bioidentical" estrogen, vaginal estrogen	-Vasomotor symptoms (logistic regressions): The greatest likelihood for any and moderate/severe symptoms was found in postmenopausal w aged <55 y and smokers. A BMI of 25 to 29.9 kg/m2 was associated with moderate/severe, and a BMI of ≥40 kg/m2 with any symptoms. Education was inversely associated with moderate to severe vasomotor symptoms (adjusted for all variables) -Moderate/severe vasomotor and sexual symptoms remain highly prevalent and untreated even in w aged 60-65 y. The use of vaginal estrogen and non-hormonal therapy is low
VII	Ghazanfarpour et al., 2015, (55) Iran, The relationship between women's attitude towards menopause and menopausal symptoms among postmenopausal women	CS/n=349 Postmenopausal w attending primary health care centers in Shiraz (mean age=54.87 y) Inclusion: Natural menopause status Exclusion: Hysterectomy, HT use	Menopausal symptoms (MENQOL), scores for individual symptoms Demographics: Age, educational level, marital status, number of children, income, husband's educational level Clinical and behavioral characteristics: Smoking, history of chronic diseases	The attitude toward menopause (ATM), 35 items	-Significant associations were found between the severity of menopausal symptoms and negative attitudes toward menopause for most of the items from the MENQOL. Stepwise regression: Among all symptoms as predictors, only night sweats, memory loss, and sleeplessness were significantly related to negative attitudes toward menopause (no adjustment for other variables)
VIII	Hunter et al., 2016, (51) United States, Predictors of the impact of vaginal symptoms in postmenopausal women	CS/n=745 Postmenopausal w aged 41-81 y (mean age=56.2 y) selected from the community-based sample of 2016 w who participated in RRISK3 study in Northern California Inclusion: W who reported at least one vaginal symptom in the past month	Demographics: Age, race/ ethnicity, educational level, marital status Clinical characteristics: BMI, general health status, comorbidities (diabetes, weakly urinary incontinence, hot flushes, depression symptoms– HADS, bilateral oophorectomy) Sexual activity: Frequency in the past 3 months Use of vaginal estrogen, systemic estrogen, and SSRIs	The impact of vaginal symptoms (DIVA) Four dimensions: Activities of daily living, emotional well-being, self-concept and body image, sexual functioning	-Multivariable regressions: W with comorbid depression reported greater impact of vaginal symptoms on all DIVA dimensions and w with weekly urinary incontinence on daily activities, emotional well-being, and self-concept. W who were sexually active less than weekly reported greater impact on self-concept/body image and sexual functioning (adjustment: All predictors) -Lower education, poor health, higher BMI, and moderate/severe hot flushes also predicted more significant impact in at least one domain

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TABLE 6. (*Continued*)

Nr.*	Author, year, reference nr. country, title	Study design/Participants	Assessment of exposure/ Confounding	Outcomes/Measures	Main findings
IX	Jacobs et al., 2016, (59) United States, Impact of sex and menopausal status on episodic memory circuitry in early midlife	CS/n=186 94 men and 92 w aged 45-55 y Population-based fMRI study; a subsample of offspring of the NEFS representative sample of w receiving prenatal care in the Boston–Providence area Exclusion: Neurologic, heart, endocrine, and alcohol-related diseases, psychoses, other illnesses that may alter CNS function, CNS damage, head injury, MRI contraindications	Sex Menopausal status Demographics: Age, race, education, parental socioeconomic status Clinical characteristics: BMI, medical and reproductive history Endocrine assessments: Sex steroids and gonadotropins Neuropsychological assessment: A digit span, verbal fluency (COWAT-FAS), verbal IQ (ANART), two episodic memory tasks (FNAME & FAS), anxiety (STAI), mood profile (POMS)	Changes in memory circuitry during verbal encoding 1-hour MRI scanning session (fMRI, structural MRI, Diffusion Tensor Imaging) Verbal encoding task during fMRI scanning Memory retrieval task during fMRI scanning (response time and accuracy)	-Analyses of revealed significant effects of menopausal status on memory-encoding hippocampal activity and functional connectivity acrossrelated brain regions, independent of age. Pre- and perimenopausal w exhibited more significant activity in the left hippocampus than postmenopausal w, while postmenopausal w displayed enhanced bilateral hippocampal connectivity -The loss of ovarian estradiol during menopause plays a significant role in shaping memory circuitry. Lower 17β-estradiol was related to more pronounced alterations in hippocampal activity and connectivity, and poorer performance on a subsequent memory task
X	Jaspers et al., 2016, (52) The Netherlands, Sex steroids, sex hormone-binding globulin and cardiovascular health in men and postmenopausal women: The Rotterdam Study	CS/n=1647 men (mean age=68.6 y), and 1564 postmenopausal w (mean age=69.6 y) aged >50 y from the population-based cohort study (Rotterdam Study) Exclusion: Female steroid use, surgical menopause	Estradiol (E₂) Testosterone Sex hormone-binding globulin Free androgen index (only in w) Covariates: Age, y since menopause, cohort, ethnicity, marital status, education, chronic diseases, waist-to-hip ratio	Cardiovascular health Seven health factors and behaviors: Total cholesterol, glucose, blood pressure, physical activity, BMI, smoking, diet Total score=0-14 Optimal cardiovascular health=score of 11-14	-Optimal cardiovascular health was reached by 10.4% of postmenopausal w -Logistic regression: Optimal cardiovascular health was associated with lower levels of free androgen index and higher levels of sex hormone-binding globulin in postmenopausal w (model with all covariates and independent variables)

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TABLE 6. (*Continued*)

Nr.*	Author, year, reference nr. country, title	Study design/Participants	Assessment of exposure/ Confounding	Outcomes/Measures	Main findings
XI	Javadivala et al., 2013, (40) Iran, Modeling the relationship between physical activity and quality of life in menopausal-aged women: A cross-sectional study	CS/n= 273 W aged 40-60 y recruited from two health service centers in Tabriz, clustered random sampling Inclusion: w who reported irregularity in menstrual cycle or experienced no menstrual periods	Physical activity (IPAQ, short form) Total ((low, moderate or high) activity: MET- minute/walk; frequency of activities on weekdays and time spent in each-hours/week Demographics: 7Age, marital status, education, employment, miscarriage, age at menarche, self-reported menopausal status, self-reported menses irregularity status, BMI, HT XIII use, use of contraceptives, chronic diseases, smoking	Menopausal symptoms (MRS) Three domains: Urogenital, somatic, psychological (11 symptoms) Scores for intensity (not severe to very severe) and duration (per year) of each symptom Health-related quality of life (WHOQOL-Bref) Four domains: Physical, social, psychological, environmental Chronic diseases (diabetes, heart disease)	-Univariate general linear models: W with very severe physical and mental exhaustion symptom performed less physical activity than w without this symptom. Increased PA was related to higher severity of sexual problems, vaginal dryness, and joint-muscular discomfort and a shorter duration of joint-muscular discomfort symptom. PA was positively associated with all quality of life domains -Multivariate general linear model (including all outcomes): Increased PA was significantly associated with lower intensity and duration of the physical–mental exhaustion symptom and a higher quality of life in the psychological domain
XII	Jonusiene et al., 2013, (49) Lithuania Sexual function, mood and menopause symptoms in Lithuanian postmenopausal women	CS/n=246 Postmenopausal w (mean age=55.5 y) attending an outpatient clinic in Kaunas Inclusion: 45-65 y, >12 months of amenorrhea without HT or with HT for longer than 3 months, living with a partner, sexual activity in previous 4 weeks Exclusion: Chronic disease or an acute condition, mental illness and psychotropic medication use, addictions, sexual abuse, hysterectomy and ovariectomy	Use of HT (current) Emotional status (HADS): Anxiety and depression symptoms scales Menopausal symptoms (GCS): Somatic, vasomotor, psychological (anxiety and depression) symptoms scales; probe for sexual dysfunction Covariates: Age	Sexual function (FSFI) Total and domain scores: Desire, arousal, lubrication, orgasm, satisfaction, pain Sexual dysfunction=total score ≤26.55 points	-Univariate analyses: Sexual function (total and domain scores) significantly decreased with age and was better in HT users than non-users -Logistic regressions: HT use increased the likelihood of higher desire, lubrication, satisfaction and lower pain (FSFI, adjusted for age); HT use reduced the likelihood of psychological (GCS) and depression symptoms (GCS, HADS) and increased the likelihood of vasomotor (GCS) symptoms (adjusted for age) -A higher risk for the development of sexual dysfunction: Depressed and anxious w (HADS), w with more markedly expressed menopausal symptoms (GCS total score) and older w. Non-usage of HT was not a significant risk factor for sexual dysfunction

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TABLE 6. (*Continued*)

Nr.*	Author, year, reference nr. country, title	Study design/Participants	Assessment of exposure/ Confounding	Outcomes/Measures	Main findings
XIII	Kutob et al., 2017, (53) United States, The relationship between marital transitions, health behaviors, and health indicators of postmenopausal women: Results from the Women's Health Initiative	LS/n=79.094 A prospective cohort of w participating in WHI study, recruited from 40 clinical centers across the US, 3-year follow-up Inclusion: Postmenopausal w, age 50-79 y, plan to reside in the study area for at least three y Exclusion: Predicted survival of <3 y, participation in another trial, dementia, mental illness, alcoholism, drug dependency	Marital transition status: Marital status at baseline and y 3 Marital status: Unmarried (divorced/ separated, widowed or never married) and married (presently married or in a marriage-like relationship) Demographics (covariates): Age, race/ethnicity, education, income Psychosocial measures (covariates): Emotional well-being (SF-36), social functioning (SF-36), depression (CES-D), social support (MOSQ)	Health indicators Blood pressure, waist circumference, BMI Diet/health behaviors Overall dietary quality (WHI-FFQ), alcohol intake, smoking, physical activity (MET-hour/ week)	-Marriage or similar relationship were associated with less desirable behaviors and a more significant increase in BMI and alcohol intake. Divorce/separation was associated with a reduction in BMI and waist circumference and improvements in diet quality and physical activity relative to remaining married (linear and logistic regressions, adjustment for covariates).
XIV	Li et al., 2012, (41) China, Factors associated with the age of natural menopause and menopausal symptoms in Chinese women	CS/n=20.275 W aged 40-65 y (mean age=48.55 y) attending health screening in 13 cities of Jiangsu Province of China (systematic sampling) Exclusion: w with hysterectomy, pregnancy or lactate	Demographics: Age, marital status, employment, education, income Health-related variables: BMI, family history, chronic diseases, use of medicines, history of fracture Reproductive factors: Menopausal status, age at menarche, parity, breastfeeding, menopausal age Lifestyle factors: Physical activity, consumption of dairy products, smoking	Menopausal age The median age of natural menopause Menopausal symptoms (KMI) Symptomatic=total score >6 points; subscale scores: Somatic ≥3, psychological >0, urogenital >0	-The overall median age at natural menopause was 50 y. Lower educational level, poor economic status, lower BMI, age at menarche <14 y, nulliparity, and smoking were associated with earlier onset of natural menopause (Cox regressions) -Predictors of severity of menopausal symptoms (KMI total score): Poor educational background, low income, divorce, higher BMI, higher parity, smoking, and chronic diseases (logistic regressions, adjusted for salient variables).
XV	Lo, 2015, (54) China, Bone health status of postmenopausal Chinese women	CS/n=1507 Postmenopausal w (mean age=58.2 y) who attended health service in Hong Kong Inclusion: Chinese w, w who had never received HT or osteoporosis treatment	Bone density: Densitometry Health-related risk factors for osteoporosis (checklist) Demographics: Age, duration of menopause, BMI	The prevalence of osteoporosis T-score <-2.5 at the spine or hip Treatment adherence Consultation records of w with osteoporosis	-Osteoporosis was diagnosed in 25.7% of w. Among them, only 30.7% complied with the treatment protocol -Risk factors for osteoporosis: Older age, longer duration of menopause, BMI of <18.5 kg/m2, and positive parental history of osteoporosis or hip fracture (stepwise logistic regression)

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TABLE 6. (*Continued*)

Nr.*	Author, year, reference nr. country, title	Study design/Participants	Assessment of exposure/ Confounding	Outcomes/Measures	Main findings
XVI	Ornat et al., 2013, (42) Spain, Sexual function, satisfaction with life and menopausal symptoms in middle-aged women	CS/n=260 W aged 40-59 y (median age=47 y) attending gynecological consultations at the outpatient clinics in Northeast Spain Exclusion: w with psychological or physical incapacity	Demographics: Age, parity, partner status (yes/no), nationality, ethnicity, residence, education, economic problems, employment Health: Age at menarche, menopausal status, BMI, waist circumference, HT use, contraception, use of medicines Behavior and lifestyle: Smoking, alcohol, regular exercise, healthiness, psychiatric treatment, stress urinary incontinence, intimate violence Self-perception of sexual satisfaction Partner's demographics, healthiness, behaviors, and sexual dysfunction	Sexual functioning (CSFQ-14) Total and subscale scores: Pleasure and satisfaction, desire, arousal, orgasm Sexual dysfunction=total score ≤41 Satisfaction with life (SWLS) Menopausal symptoms (MRS) total and subscale scores: Somatic, psychological, urogenital	-Sexual functioning was associated positively with satisfaction with life and inversely with the severity of menopausal symptoms -Significant predictors of better sexual functioning (total score): Higher satisfaction with life, younger age and less-severe menopausal symptoms (linear regression) -Significant predictors of higher satisfaction with life: Better sexual functioning, higher BMI, less economic problems, less tobacco use, less-severe menopausal symptoms, healthiness, having a partner, and partner's healthiness (linear regression)
XVII	Pallikadavath et al., 2016, (57) India, Natural menopause among women below 50 y in India: A population-based study	CS/n=630.361 Ever-married w aged 15-49 y (n=53.031 in natural menopause, n=577.330 not in menopause); data from the Indian DLHS-3, nationally representative sample Exclusion: w aged 50 y or more, hysterectomy, w who never menstruated	Demographics: Marital status, parity Socio-economic factors: Educational status, wealth index, religion, caste, tribes (indigenous population), type of locality (rural/urban), a region of residence Family planning variables: Use of contraceptive pills, adoption of female sterilization, abortion	The prevalence of natural menopause below 50 y of age Natural menopause: W who reported that they were in menopause and who had not menstruated in the past 12 months	-About 8.4% of w aged 15-49 y were in natural menopause; appx. 1.5% of w were in natural premature menopause (below 40 y) -A higher risk of natural menopause: Widowhood or divorce/separation, poverty, low parity, no schooling, Muslim religion, caste (lower strata of the caste system), rural residence, Western region, never using contraceptive pills, not sterilized or not having an abortion (Cox regression, adjusted for all variables)

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TABLE 6. (*Continued*)

Nr.*	Author, year, reference nr. country, title	Study design/Participants	Assessment of exposure/ Confounding	Outcomes/Measures	Main findings
XVIII	Prairie et al., 2015, (43) United States, Symptoms of depressed mood, disturbed sleep, and sexual problems in midlife women: Cross-sectional data from the Study of Women's Health Across the Nation	CS/n=1716 W (mean age=49.8 y) included in the US longitudinal study (SWAN); data from y 4 Inclusion: Age 42-52 y at baseline, intact uterus, at least one menstrual period, no HT use in the previous 3 months Exclusion: W without partnered sexual activity	Demographics: Age, ethnicity, educational status, marital status, annual income Menopausal status HT use: Current or previous Social support: 4 items from MOSQ Stressful life events: Self-ratings, 18 items Health status: 1 item from SF-36 (MOSQ)	Sleep disturbance Three items: Frequency of difficulties with sleep initiation and sleep maintenance, early morning awakening Depressed mood (CES-D) Total score ≥16=elevated levels of depressive symptoms Sexual problems (SWAN) Sexual function subset (5 items)	-16.5% of w had depressed mood, 36.6% had a sleep problem, and 42.2% had any sexual problem. 5% of w experienced all three symptoms - W with the symptom triad, compared with those without, had lower household income, less education, were surgically late perimenopausal or postmenopausal, rated their general health as fair or poor, had more stressful life events and lowered social support (logistic regressions)
XIX	Sis Çelik & Pasinlioğlu, 2017, (44) Turkey, Effects of imparting planned health education on hot flush beliefs and quality of life of climacteric women	L/n=247 Pre-test and post-test semi-experimental design (121 w in EG, mean age=50.6 y; 126 w in CG, mean age=50.9 y) Randomly selected w from a family health center in Erzurum Inclusion: Age <65 y, hot flushes within the past month, no HT use	Planned health education EG: Three 1-hour educational sessions at 2-week intervals, CG: No training. Post-test data after 6 months Demographics: Age, education, spouse's education, occupation, income, marital status, family type Menopause (m) characteristics: Age at m, mode of m, menopausal status, the perception of m, knowledge about m -Smoking, exercise >3 times/ week	Hot flushes beliefs (HFBS) Total and domain scores: Social, coping, psychological perception Menopause-specific quality of life (MENQOL) Total and domain scores: Vasomotor, psychosocial, physical, sexual	-Differences between EG and CG in mean pre-test scores on all variables were not significant -Pre-test and post-test differences (t-tests): The negative beliefs concerning hot flushes of w who received planned health education (EG) decreased, and their menopause-related quality of life improved (significant differences in total score and all subscale scores for both instruments). W who did not receive any education (CG) did not change their hot flush beliefs and quality of life

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TABLE 6. (*Continued*)

Nr.*	Author, year, reference nr. country, title	Study design/Participants	Assessment of exposure/ Confounding	Outcomes/Measures	Main findings
XX	Som et al., 2014, (45) India, Menopause-specific quality of life of a group of urban women, West Bengal, India	CS/n=250 Bengali-speaking w of Hindu ethnic group aged 40-65 y from urban areas of the district of North Paraganas, West Bengal; a multistage random sampling Inclusion: Married w, at least one child and at least 10 y of English language education	Menopausal status Demographics (covariates): Age, education, working status, husband's education and occupation, monthly household expenditure, ages at menarche, marriage and menopause, parity, foetal loss, use of oral contraceptives, duration of breastfeeding the last child	Menopause-specific quality of life (MENQOL) Total and domain scores: Vasomotor, psychosocial, physical, sexual	-Total menopause-specific quality of life and domain mean scores for menopausal symptoms (except vasomotor), were significantly higher among the postmenopausal w compared to the perimenopausal w -After adjustment for covariates (analysis of covariance), postmenopausal status was significantly associated only with more severe physical domain symptoms
XXI	Tungmunsakulchai et al., 2015, (50) Thailand, Effectiveness of a low dose testosterone undecanoate to improve sexual function in postmenopausal women	RCT/n=70 Randomized, double-blinded, placebo-controlled trial. Mean age=53.8 y in treatment, and 52.7 y in the placebo group Inclusion: Postmenopausal w, age 40-60 y, sexually active w, diagnosed sexual dysfunction Exclusion: Severe vasomotor symptoms, history of relevant diseases and psychiatric disorders, abnormal liver function or lipid profiles, HT or psychiatric drugs used in the past 3 months, partner with sexual dysfunction	Testosterone undecanoate -8-week treatment -Treatment group: Addition of oral testosterone undecanoate 40 mg twice a week to daily oral estrogen Placebo group: Addition of oral placebo 40 mg twice a week to daily oral estrogen Demographics and baseline data: Age, BMI, age at menopause, type of menopause, marital status, vasomotor symptoms, sexual history, blood count, liver enzymes, lipid profile, testosterone level, FSFI scores Records of adverse effects of drugs (post-treatment)	Sexual function (FSFI) Total and domain scores: Desire, arousal, lubrication, orgasm, satisfaction, pain Sexual dysfunction=total score ≤26.5 points	- Compared to baseline, sexual function (total score) significantly improved in both groups of postmenopausal w after 8 weeks of treatment -The post-treatment FSFI score and arousal score from the testosterone group were significantly higher than in the placebo group (analysis of covariance). Addition of 40 mg of testosterone undecanoate to daily oral estrogen twice a week significantly improved w's overall sexual function, especially the arousal domain -There was no difference in adverse effects between the two groups

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TABLE 6. (*Continued*)

Nr.*	Author, year, reference nr. country, title	Study design/Participants	Assessment of exposure/ Confounding	Outcomes/Measures	Main findings
XXII	Yim et al., 2015, (46) Korea, Prevalence and severity of menopause symptoms and associated factors across menopause status in Korean women	CS/n=1774 W aged 44-56 y (mean age=48.6 y) the sample of 2204 w recruited at two healthcare centers in Seoul and Suwon (the KSHS) Exclusion: Pregnancy, breastfeeding, artificially induced menopause, gynaecological cancers, HT use	Menopausal status Demographics: Age, education, income, marital status, employment, parity Clinical and lifestyle characteristics: BMI, blood pressure, physical activity (IPAQ, short form), smoking, alcohol consumption	Prevalence and severity of menopausal symptoms (MENQOL), scores for each item and domain scores: Vasomotor, psychosocial, physical, sexual	- Menopausal status was a significant predictor of the severity of symptoms across all domains, with postmenopausal w experiencing the most severe symptoms. Age was associated with increased severity of vasomotor and sexual symptoms. Obesity was associated with increased severity of vasomotor and physical symptoms. Physically active w had less-severe physical symptoms (linear regression, adjustment for all variables)

*Number in roman numerals I-XXII. Study design: CS: Cross-sectional; L: longitudinal; RCT: Randomized controlled trial. AHEI: ANART: American National Adult Reading Test; ATM: Attitude Toward Menopause Scale; BKMI: Blatt-Kupperman Menopausal Index; BMI: Body mass index; CCI: Charlson Comorbidity Index; CES-D: Center for Epidemiological Studies Depression scale; CG: Control group; COWAT (FAS): Controlled Oral Word Association Test for verbal fluency (to the letters F, A, and S); CSFQ: Changes in Sexual Functioning Questionnaire; DIVA: Day-to-day Impact of Vaginal Aging questionnaire; DLHS-3: District Level Household Survey-third round; EG: Experimental group; EuroQol-5D-3: Euro Quality of Life (5 dimensions, 3 levels); FFQ: Food Frequency Questionnaire; fMRI: Functional magnetic resonance; FNAME: Face Name Associative Memory Exam; FSFI: Female Sexual Function Index; GCS: Green Climacteric Scale; HADS: Hospital Anxiety and Depression Scale; HFBS: Hot Flush Beliefs Scale; HT: Hormone therapy; IPAQ: International Physical Activity Questionnaire; IWHS: International Women's Health Study; KMI: Kupperman Menopause Index; KSHS: Kangbuk Samsung Health Study; MET: Metabolic equivalents; MENQOL: Menopause-Specific Quality of Life Questionnaire; MOSQ: Medical Outcomes Study Questionnaire; MRS: Menopause Rating Scale; Natsal-3: The third National Survey of Sexual Attitudes and Lifestyles; NEFS: New England Family Study; PHQ-2: two-question Patient Health Questionnaire; POMS: Profile of Moods Questionnaire; RRISK3: The third wave of the Reproductive Risks of Incontinence Study at Kaiser; SF-36: Short Form–36; SRT: Selective Reminding Test; SSRI: Selective serotonin reuptake inhibitor; STAI: State-Trait Anxiety Inventory; SWAN: Study of Women's Health Across the Nation; SWLS: Satisfaction with Life Scale; VVA: Vulvovaginal atrophy; WHI-OS: Women's Health Initiative Observational Study; WHOQOL-Bref: WHO Quality of Life 26 questionnaire; WPAI: Work Productivity and Activity Impairment questionnaire; w: Women; y: Year(s)

TABLE 7. Independent variables and/or covariates in 22 eligible studies

Independent variables/covariates	Study number in roman numerals I-XXII
Sociodemographic variables	
Age (years or age groups)	I-XXII
Age at marriage	XX
Cohort	X
Country/region	XVII
Education	I-IV, VI-XI, XIII-XIV, VI-XX, XXII
Family type	XIX
Income	II-IV, VII, XIII-XIV, XVI-XX, XXII
Marital/relationship status	I-II, IV-VIII, X, XI, XIII-XIV, XVII-XIX, XXII
Nationality/country origin	XVI
Occupation/employment	I, XI, XIV, XVI, XIX, XX, XXII
Parental socioeconomic status	IX
Partner's age	XVI
Partner's/husband's education	VII, XVI, XIX, XX
Partner's/husband's occupation	XVI, XX
Partner's nationality and ethnicity	XVI
Place of residency	I, VI, XVI-XVII
Race/ethnicity	II, VIII-X, XIII, XVI, XVIII
Religious affiliation	XVII
Caste (low strata of the caste system)	XVII
Sex	IX (results for women abstracted)
Reproductive histories	
Age at first birth	III
Age at menarche	I, III, XIV, XVI, XX
Age at menopause	I, XIV, XV, XIX-XXI
Duration of menopause	X
Bilateral oophorectomy	VI, VIII
Breastfeeding/duration of breastfeeding	XIV, XX
Ever been sterilized	XVII
Hysterectomy	II, VI
Induced abortions	XVII
Menopausal status	I-VI, IX, XIV, XVI, XVIII-XX, XXII
Miscarriage/foetal loss	XI, XX
Parity	I, III, VII, XIV, XVI-XVII, XX, XXII
Type of menopause	XVIII, XIX, XXI
Use of contraceptives	XI, XVII, XX
Hormonal therapy	
Addition of testosterone to daily oral estrogen	XXI
Duration of hormonal therapy	XII
Use of estrogen (vaginal and systemic) and SSSRIs	VIII
Use of hormonal therapy (past or current)	XI-XII, XV-XVI, XVIII
Sex hormones	
Sex steroids, sex hormone-binding globulin, free androgen index	X

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TABLE 7. (*Continued*)

Independent variables/covariates	Study number in roman numerals I-XXII
Sexual function	
The assessment of whether health condition or disability affected sex life	V
Partner's sexual dysfunction	XVI
Seeking help or advice about a sex life	V
Sexual activity	VIII
Sexual history	XXI
Sexual satisfaction	XVI
Clinical characteristics	
Abdominal circumference	XVI
Body mass index	I-VI, VIII, IX, XI, XIV-XVI, XXI-XXII
Bone density	XV
Family history	XIV-XV
Functional impairment, work and activity impairment (WPAI)	IV-V
General health status	V, VIII, XVI, XVIII
Health-related risk factors for osteoporosis	XV
History of fracture	XIV-XV
Hypertension status	III-XX
Intimate violence	XVI
Longstanding illness or disability	V
Number or presence of various diseases	IV-V, VII-VIII, X, XIV
Partner's healthiness	XVI
Psychiatric treatment	XVI
Stress urinary incontinence	XVI
Use of medicines	XIV, XVI
Waist-to-hip ratio	X
Menopausal symptoms	
Climacteric symptoms (BKMI)	II
Somatic, vasomotor, psychological (anxiety and depression) symptoms (GCS)	XII
Vulvovaginal atrophy and vasomotor symptoms 'vaginal dryness'and 'hot flushes' items on the MRS)	IV
Knowledge and education about menopause	
Perception of menopause	XIX
Knowledge about menopause	XIX
Planned health education	XIX
Behavioral/lifestyle characteristics	
Alcohol consumption	IV, VI, XVI, XXII
Consumption of: Vegetables, fruits, red tea, Arabic coffee	I
Consumption of dairy products	XIV
Partner's behavioral and lifestyle characteristics	XVI
Physical activity (IPAQ, short form)	II, XI, XXII
Physical activity/exercise	I, III, IV, XIV-XVI, XIX
Sitting and walking time	III
Smoking	II, IV, VI, XI, XIV-XVI, XIX, XXII
Neuropsychological assessments	
Memory, verbal fluency, verbal IQ	IX

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TABLE 7. (*Continued*)

Independent variables/covariates	Study number in roman numerals I-XXII
Psychosocial characteristics	
Anxiety (STAI, HADS)	IX, XII
Depression symptoms (PHQ-2, HADS, CES-D)	V, XII-XIII
Emotional well-being and social functioning (SF-36)	XIII
Mood profile (POMS)	XIX
Quality of life (WHOQOL-Bref)	II
Social support (MOSQ)	XII-XIII
Stressful life events	XVIII

BKMI: Blatt–Kupperman Menopausal Index; CCI: Charlson Comorbidity Index; CES-D: Center for Epidemiological Studies Depression; GCS: Greene Climacteric Scale; HADS: Hospital Anxiety and Depression Scale; IPAQ: International Physical Activity Questionnaires; IQ: intelligence quotient; MOSQ: Medical Outcomes Study Questionnaire; MRS: Menopause Rating Scale; PHQ-2: two-question Patient Health Questionnaire; POMS: Profile of Moods States Questionnaire; SF-36: Short Form-36; SSRI: selective serotonin reuptake inhibitor; STAI: State-Trait Anxiety Inventory; WHOQOL-Bref: Word Health Organisation Quality of Life-26 questionnaire; WPAIQ: Work Productivity and Activity Impairment questionnaire

Australia (40); Brazil (26,58); China (42,55); India (46,60); Iran (41,59); Korea (47); Lithuania (50); the Netherlands (53); Saudi Arabia (39); Spain (43); Thailand (51); Turkey (45); the United Kingdom (49); and the United States (44,52,54,57). One study (56) included women from the United States and five Western European countries (France, Germany, Italy, Spain, and the United Kingdom).

Description of study participants

The age of the study participants varied depending on the different aims and inclusion criteria of the included studies, ranging between 15 and 81 years of age. Most studies included women aged 40-65 years or similar (40-43,46,48,50,51,58). Two studies included participants from their mid-40s to their mid-50s (47,57), while three studies included middle-aged women and older whose differences in age ranged from 30 to 40 years (52,54,56). One study that examined the age of natural menopause (60) included women aged 15-49 years, while three studies (44,55,59) did not state the age range of the participants, and three studies reported only lower or upper age limit (39,45,53). Participants in one study were men and women aged 16-74 years, and we abstracted data available for women aged 45-64 years who reported on their menopausal status (49). Only nine studies reported the mean age of all the participants (39,40,42,44,47,50,53,55,59) and three studies (45,46,51) reported the mean age

of women in specific subgroups, but not in the total sample.

Eight studies included only postmenopausal women (50-56,59), three studies enrolled premenopausal and menopausal women (48,49,60), and two studies included peri- and postmenopausal women (41,46). Nine studies enrolled pre-, peri-, and postmenopausal women (39,40,42-45,47,57,58). In all studies, amenorrhea for longer than 12 months was the criterion for menopause, while irregular menstruation within the previous 12 months was the criterion for perimenopause. Menopausal status was diagnosed based on women's reproductive histories in all studies, and one study also included hormonal evaluations (57). Study participants included women who had either natural or surgically-induced menopause. Based on the inclusion/exclusion criteria related to the type of menopause, four studies included women in natural menopause (47,53,59,60) and two studies excluded women who had undergone bilateral oophorectomy (39,58). Three studies examined the effects of type of menopause and enrolled naturally and surgically menopausal women (44,45,51). The effects of bilateral oophorectomy were controlled in the data analyses of two studies (40,52). Five studies did not specify the type of ovariectomy as an exclusion criterion (50), exclude women based on hysterectomy (42,44,50), or control for the effects of hysterectomy (40,48). Eight studies did not include variables related to the mode

of menopause (41,43,46,49,54-57). Seven studies stated that women using hormonal therapy (HT) had been excluded (39,45,47,48,51,55,59), one study included women who had not been on HT in the previous 3 months (44), and one study included women who were not on HT and those who had been on HT for longer than 3 months (50).

Assessment of menopausal symptoms

Nine studies assessed menopausal symptoms as either one of the outcomes or the main outcome (39-47), and five studies assessed menopausal symptoms as predictors of other outcomes (48,50,52,56,59). Eleven studies used a validated tool for assessing the frequency and/or severity of menopause-related symptoms: Specifically, the Menopause Rating Scale (MRS) (39,41,43); the Menopause-Specific Quality of Life Questionnaire (MENQOL) (40,45-47,59); the Blatt-Kupperman Menopausal Index (KMI) (42,56); or the Greene Climacteric Scale (GCS) (50). Of these, three studies provided results for total and/or each symptom score(s) (41,48,59), while menopausal symptoms presented in other studies were classified based on the validated scales as somatic, urogenital, and psychological (MRS and KMI); somatic, vasomotor, and psychological (GCS); or vasomotor, physical, sexual, and psychological (MENQOL). One study (44) examined the symptom triad during the menopausal transition; this included the assessment of sleep disturbance and sexual function using subsets of questions from the questionnaire applied in the study of Women's Health Across the Nation, as well as the assessment of depressed mood with a validated instrument (the Center for Epidemiological Studies Depression [CES-D]). Two studies assessed vulvovaginal atrophy symptoms (56) and hot flushes (52,56), with one item only.

RESULTS

Socio-demographic predictors of menopausal symptoms

The eligible studies included a wide range of potential determinants of menopausal symptoms. The most frequent independent variables in studies with menopausal symptoms as outcomes were educational status (39-60) and women's age (39-60).

Other frequently assessed variables were those related to economic status: Women's occupation or employment (39,41-43,45-47); family income (42,44,45,47) or expenditure (46); economic problems (43); and residence status (39). The effects of marital or relationship status were examined in six studies (39-42,44,45). Some studies also controlled for partner's demographic, lifestyle, and clinical characteristics (43) or husband's educational level (45,46), and occupation (46). Significant effects of age, independent of menopausal status and other relevant variables, were found in two studies. Women from Saudi Arabia aged 50-54 years had a higher risk of experiencing moderate/severe urogenital symptoms (measured with the MRS) (39), while a study of Korean women found a significant positive association between women's age and severity of vasomotor and sexual symptoms, measured with the MENQOL (47). Three studies demonstrated that women's educational level was inversely related to the severity of menopausal symptoms, independent of other variables. Studies conducted in the United States (40,44) showed that lower educational status was associated with a higher risk of experiencing moderate to severe symptoms in the vasomotor domain of the MENQOL (40) and the symptom triad consisting of sleep disturbances, depressed mood, and sexual problems (44). One study in China found that poor educational background was associated with higher total symptom scores, as well as with the physical and urogenital domain scores of the KMI. This study also showed that total scores and each subscale score of the KMI significantly increased for separation or divorce (42). Some studies also found significant independent effects of different indicators of economic status on menopausal symptoms. Women who generally experienced more severe menopausal symptoms as well as urogenital symptoms (42), and women with the symptom triad (44), lived in households with lower income. A higher incidence of moderate to severe urogenital symptoms was also found for homemakers and women living in apartments or small houses compared to working women and women living in large houses (39). Menopausal symptoms were assessed with the MENQOL as predictors of women's attitudes toward menopause in one study with postmenopausal women in Iran (59). This study

also focused on the relationships between the severity of menopausal symptoms in different domains (the MENQOL) and various demographic and health characteristics. Univariate analyses showed that the educational level of the husband, but not the woman herself, was related to menopausal symptoms. Women who had an illiterate husband reported significantly more vasomotor and physical symptoms than women whose husband had at least some primary education.

Reproductive factors as determinants of menopausal symptoms

Seven studies examined the effects of menopausal status on the severity of menopausal symptoms and compared subgroups of pre-, peri-, and postmenopausal women (39,40,42-44,46,47), while in two studies menopausal status was included either as an inclusion variable (41) or for comparison of baseline characteristics between the experimental and control groups (45). Three studies additionally classified postmenopausal women into subgroups according to the duration of this reproductive stage (45), women's age (40) or the type of menopause (44), two studies differentiated between subgroups of early and late perimenopausal women (44,47), and two studies included only peri- and postmenopausal women (41,46). Six studies found significant independent effects of menopausal status on the severity of menopausal symptoms (39,40,43,44,46,47), but their results differed for specific symptom domains. Postmenopausal status was associated with a higher risk of experiencing more severe menopausal symptoms in all studies except one (39). Gartoulla et al. (40) examined predictors of the vasomotor domain symptoms assessed with the MENQOL; the highest likelihood for any and moderate to severe vasomotor symptoms was found in postmenopausal women under 55 years of age. Another study in India (46), using the same instrument, found that vasomotor domain scores were not related to menopausal status, while the total menopause-specific quality of life mean scores – and those in the physical, sexual, and psychological domains – were significantly higher among the postmenopausal women than the perimenopausal women. However, after adjustment for covariates, postmenopausal status was significantly associated only with more severe physical domain

symptoms. Among women in Korea, menopause status showed significant independent effects on the severity of symptoms across all domains of the MENQOL, with postmenopausal women experiencing the most severe symptoms. The most significant increase of severity of menopausal symptoms and the most significant differences between menopausal status groups were observed in vasomotor and sexual domain scores (47). Postmenopausal status was associated with more severe total, somatic and urogenital symptoms assessed by the MRS among women in Spain (43). Praire et al. (44) found a significant independent effect of menopause status on the occurrence of the symptom triad among women in the United States. Late perimenopausal and surgically postmenopausal women experienced symptom triad sleep disturbance, depressed mood and sexual problems more often than premenopausal, early perimenopausal and naturally menopausal women. The results of a study of women living in Saudi Arabia showed that perimenopausal women had a higher risk of experiencing moderate to severe somatic symptoms compared to pre- and postmenopausal women (39), while the effects of menopausal status on total symptoms experienced as well as on urogenital and psychological symptoms were not significant. A study of Chinese women found that menopausal status was not significantly associated with menopausal symptoms assessed by the KMI (42). One intervention study in Turkey showed that women who received planned health education related to the climacteric period improved their menopause-related quality of life (significant differences in their MENQOL total score and all subscale scores). These effects were independent of women's perception of menopause, the previous knowledge about menopause and other relevant factors (45). Apart from menopausal status, parity was the most frequently examined independent variable (39,42,43,46,47). Two studies demonstrated that higher parity was associated with more severe menopausal symptoms, but the effects varied according to the symptom domains and instruments used. Among women from Saudi Arabia, nulliparous women had nearly 3 times more risk of experiencing severe/moderate somatic symptoms measured with the MRS compared to women who became pregnant 5 times or more (39). Another study in China showed that women

obtained significantly higher total scores on the KMI, as well as scores on somatic and urogenital subscales when the parity was 2 times higher or more (42). Four studies examined the effects of age at menarche (39,42,43,46) and age at menopause (39,42,45,46) and found no significant relationships between these variables and the severity of menopausal symptoms. Studies that examined various menopausal symptoms as outcomes rarely controlled for HT use and type of menopause. Women on HT were excluded in three studies (39,45,47). Some studies also excluded women with a bilateral oophorectomy under 50 years of age (39), women with a hysterectomy (42), and women with artificial menopause due to hysterectomy or radiation (47). One study included a hysterectomy and bilateral oophorectomy as independent variables. Hysterectomy was associated with a higher likelihood of moderate to severe vasomotor symptoms, but this effect was not significant when the relationships with other relevant variables were controlled for in a logistic regression analysis (40). Pregnancy or breastfeeding was an exclusion variable in one study (47), and two studies that examined the effects of breastfeeding (42,46) found no significant relation between this variable and menopausal symptoms.

Clinical characteristics of the participants associated with menopausal symptoms

Five studies included BMI as an independent variable (39,40,42,43,47) and found significant effects on menopausal symptoms, while one study provided only descriptive data on BMI (11). AlQuaiz et al. (39) found that obese women were at higher risk of experiencing more severe psychological symptoms compared to normal and overweight women. Increased BMI, measured as a continuous variable, was a significant predictor of the total MRS score. Another study also found significant positive correlations between BMI and MRS total, somatic, and urogenital scores. However, this study did not examine predictors of menopausal symptoms in a multivariate model, controlling for other significant relationships (43). Higher BMI was associated with higher total and all three subscale scorings of the KMI (after adjustment for confounding factors) (42). Two studies showed that BMI is also a significant predictor of menopausal symptoms measured

with the MENQOL. A BMI that is usually classified as "overweight" (25-29.9 kg/m^2) was associated with a higher risk of experiencing moderate to severe vasomotor symptoms, while obese women (a BMI of ≥40 kg/m^2) were at higher risk of experiencing any vasomotor symptoms (40). Another study of women in Korea showed that obesity was positively associated with severity of vasomotor and physical symptoms. This study classified BMI according to Asian-specific criteria, with a BMI of 25 kg/m^2 or higher considered "obese" (47). Two studies found significant effects of other clinical characteristics on menopausal symptoms. History of chronic diseases was a significant predictor of higher total and all three subscales scores of the KMI (42). The symptom triad of sleep disturbance, depressed mood, and sexual problems occurred most often among women who had experienced more stressful life events, had lower social support and rated their general health as fragile (44). One study that assessed menopausal symptoms as predictors of sexual dysfunction found significant associations of current hormone therapy (HT) use and menopausal symptoms (of the GCS), adjusted for age. HT use reduced the likelihood of total psychological domain symptoms and depression subdomain symptoms but increased the likelihood of vasomotor symptoms (50).

Behavioral and lifestyle characteristics as predictors of menopausal symptoms

Six studies measured women's physical activity either with a standard validated instrument, i.e., the International Physical Activity Questionnaire-Short Form (41,47) or with a scale that included the assessment of weekly physical activity or exercise (39,42,43,45). Among them, four studies examined independent effects of this variable on menopausal symptoms, while two studies used physical exercise data only for comparison of sample subgroups (45) or for a description of respondents' characteristics (43). Three studies found significant independent effects of physical activity on different symptoms or domains, with women who regularly exercised experiencing less-severe menopausal symptoms. Among women in Saudi Arabia, those regularly performing physical activity had significantly less-severe somatic, urogenital and total MRS symptoms compared to women who did not

exercise or exercised irregularly (39). Another study, in Iran, examined the effects of physical activity on each symptom of the MRS. Multivariate analysis showed that women who had more physical activity had less-severe physical and mental exhaustion symptom (41). Moderate or high physical activity was also associated with less-severe physical symptoms on the MENQOL among Korean women (47). Other behavioral and lifestyle characteristics examined were smoking (40-43,45,47), alcohol consumption (40,43,47), and dietary habits (39,42). One study that included measures of various characteristics of women and their partners provided only descriptive data for tobacco and alcohol use (43), and one study compared baseline differences in smoking habits among women in the experimental and control group (45). Studies did not find significant effects of alcohol consumption on menopausal symptoms (40,47). Smoking was associated with greater likelihood of experiencing any vasomotor symptoms and moderate to severe vasomotor symptoms of the MENQOL (40), as well as with more severe total, and domain-specific, symptoms measured with the KMI (42). A study with Saudi Arabian women found that intake of Arabic coffee significantly predicted the severity of overall menopausal symptoms measured with the MRS and symptoms in the urogenital domain (39).

The prevalence of menopausal symptoms

Five studies provided data on the prevalence of menopause-related symptoms in different countries, and all studies except one (43) included large samples of women. These studies showed that the incidence of menopausal symptoms, assessed with different scales, is highest among postmenopausal women – especially the incidence of sexual problems. The most frequent symptoms (>50%) assessed with the KMI in postmenopausal women in China were sexual problems, muscle/joint pain, and insomnia. Sexual problems were reported significantly more frequently in postmenopausal than in pre- and perimenopausal women (42). A study with Australian women showed that the prevalence of any vasomotor symptoms assessed with the MENQOL ranged from 32.7% in premenopausal women to 74.2% in postmenopausal women younger than 55 years. The prevalence of

sexual symptoms ranged from 43.5% in premenopausal women to 68% in postmenopausal women. Vasomotor symptoms persisted in 42.1% and sexual symptoms persisted in 62.5% of women aged between 60 and 65 years. This study also showed that nearly 10% of women aged 60-65 years were current HT users, while the use of non-hormonal prescription therapies with proven efficacy was low (40). Among women in Korea, the highest prevalence of most of the menopause symptoms in the MENQOL (18 of 29 items) was found among postmenopausal women. The mean domain scores showed that the most bothersome symptoms for perimenopausal women were in the physical domain, while postmenopausal women were most bothered by sexual symptoms (47). The study that identified a symptom triad related to the menopausal transition among women in the United States also provided data on the prevalence of these symptoms: About 16.5% of women had CES-D scores indicating a high depressive symptom burden, 36.6% had a sleep problem, and 42.2% had a sexual problem; only 5% of women experienced all three symptoms (44). Finally, a study in Spain with a smaller sample of 260 women aged 40-59 years found that 14.6% of women in the total sample had severe menopausal symptoms assessed with the MRS. The incidence of severe menopausal symptoms was the highest (39.5%) in postmenopausal women who did not use hormonal contraception (44).

Sexual functioning

Some of the abovementioned studies examined the determinants of menopausal symptoms in women. The urogenital scales of the MRS and the KMI include sexual problem items and vaginal dryness items that are classified as sexual symptoms in some studies. The results of four studies that assessed sexual symptoms with a sexual subscale of the MENQOL are described in the previous section (40,45-47). Seven independent studies examined various determinants of sexual functioning and sexual lifestyles (43,44,48-52). Four studies assessed sexual functioning and diagnosed sexual dysfunction using standard questionnaires, such as the Female Sexual Function Index (FSFI) (48,50,51) and the 14-item Changes in Sexual Functioning Questionnaire

(CSFQ) (43). Three studies analyzed subsets of data from questionnaires applied in national studies. One of these included postmenopausal women with at least one vaginal symptom (e.g., dryness, itching, irritation, soreness, or pain during sexual activity). Respondents reported the impact of vaginal symptoms (in the past 4 weeks) using the sexual functioning subscale of the Day-to-Day Impact of Vaginal Aging (DIVA) questionnaire. The questionnaire had slightly different versions for sexually active and inactive women (52). Another study examined sexual function problems as part of the menopause-related symptom triad, using the sexual function subset of the questionnaire applied in the Study of Women's Health Across the Nation. This subset included five questions on desire, arousal, satisfaction, orgasm, and vaginal dryness (44). Significant predictors of the symptom triad are described in the previous section. Finally, Field et al. (49) analyzed data on sexual lifestyles from the third National Survey of Sexual Attitudes and Lifestyles in Britain. These included questions on sexual activity in the past 4 weeks, sexual satisfaction in the past year, and sexual problems due to vaginal dryness.

Socio-demographic predictors of sexual functioning

Two of the studies that applied the FSFI examined the effects of various socio-demographic characteristics of the respondents on their sexual function and sexual dysfunction (48,50), while the third study (with a randomized controlled trial design) included relevant demographic variables for the comparison of treatment and placebo groups (51). A study in Brazil that included healthy women aged 40-65 found significant associations with sexual dysfunction for women aged 56-65, women with lower education, and divorced or separated women. However, in a logistic regression with other relevant predictors, significant independent effects were found only for age, with women aged 56-65 at higher risk of sexual dysfunction (48). This study diagnosed sexual dysfunction with the FSFI (total score of ≤26.55 points). Another study in Lithuania also found a significant independent effect of age, with older women being at higher risk for the development of sexual dysfunction, diagnosed with the same instrument (50).

Similarly, among women in Spain (43), older age was a significant independent predictor of worse sexual functioning (lower total CSFQ-14 score). A study in the United States (52) examined the effects of selected demographic characteristics on each of the DIVA domain scales (adjusted for HT use, other demographic variables, and clinical variables). Results for sexually active women (partnered or unpartnered sexual activity) showed that vaginal symptoms had lower sexual function impact scores among Latina/Hispanic women compared to Non-Latina women. Women who had been sexually inactive in the past 3 months, older women and women with a spouse or sexual partner reported higher scores on the sexual function impact scale.

Reproductive variables associated with sexual functioning

Three studies included only postmenopausal women (50-52), and three studies examined the effects of reproductive stages on sexual functioning (43,48) and sexual lifestyles (49). The significant independent effect of menopausal status was found in a study on sexual lifestyles in Britain, which showed that sexual activity was less frequent and vaginal dryness (a sexual response problem) was more common in postmenopausal women aged 54-65 than in premenopausal women (after adjustment for age, relationship status, and comorbidities). A study in Brazil found that menopausal status and hysterectomy were significantly associated with sexual dysfunction among healthy women, but these associations were not significant after adjustment for confounding factors in a logistic regression analysis (48). Similarly, a study with women in Spain showed that postmenopausal status was associated with worse sexual functioning and more severe menopausal symptoms. However, menopausal status was not a significant predictor of sexual functioning when relationships with other relevant variables were controlled for in a linear regression analysis (43).

Clinical variables associated with sexual functioning

Three studies demonstrated significant independent effects of menopausal symptoms on women's sexual functioning, assessed with different instruments.

These studies included healthy women and/or excluded women with comorbidities. Moderate to severe climacteric symptoms measured with the Blatt–Kupperman Menopausal Index showed significant independent effects on sexual dysfunction (diagnosed with the FSFI) among women in Brazil (48). A study with postmenopausal women in Lithuania that used the same instrument for the assessment of sexual dysfunction (50) also found a higher risk for the development of sexual dysfunction among women with more markedly expressed menopausal symptoms (total GCS score). A study with 260 women in Spain who attended gynecological consultations at outpatient clinics demonstrated that less-severe menopausal symptoms measured with the MRS had a significant independent effect on better sexual functioning; this study found that the prevalence of sexual dysfunction diagnosed with the CSFQ-14 was 46.5% in this sample (43). One study in the United States (52) showed that, among women who were sexually active (engaging in either partnered or unpartnered sexual activity), the impact of vaginal symptoms (measured by the sexual function domain of the DIVA) was higher for women who reported at least moderately bothersome hot flushes in the previous months (after adjustment for HT use, demographic, and clinical variables).

Two studies found that depression measured with the HUDS subscale was a significant independent predictor of worse sexual functioning. Women with comorbid depression were at higher risk of developing sexual dysfunction (diagnosed with the FSFI) (50) and reported a more significant impact of vaginal symptoms (measured with the DIVA sexual function subscale) compared to women without comorbid depression (52). Higher risk for the development of sexual dysfunction was also associated with more markedly expressed anxiety (measured with the HUDS subscale) among postmenopausal women (50). One study found a significant effect (adjusted for age) of the current use of HT on the sexual functioning of postmenopausal women. HT use increased the likelihood of higher desire, lubrication, satisfaction, and lower pain measured with the FSFI. Non-use of HT was not a significant risk factor for sexual dysfunction (50). A study in Thailand (51) with a randomized controlled trial design demonstrated the effectiveness of testosterone therapy for improving sexual functioning in postmenopausal women with sexual dysfunction. Treatment for 8 weeks with 40 mg of testosterone undecanoate and daily oral estrogen twice a week was associated with a significant improvement in women's overall sexual functioning and arousal domain (on the FSFI) than the use of estrogen alone; there were no differences in adverse effects between the treatment and placebo groups. General health status has significant effects on sexual activity and satisfaction. A study with a representative sample of men and women aged 16-74 years in Britain (49) showed that poor health was generally associated with decreased sexual activity and satisfaction among men and women at all ages. Women aged 45-64 years who reported bad or terrible health engaged significantly less often in sexual activity than women with excellent and perfect health (after adjustment for relationship status). Only 20.6% of postmenopausal women reporting a health condition or disability affecting their sex life in the past year had sought clinical advice. A study in the United States (52) showed that sexual activity was a significant independent predictor of the impact of vaginal symptoms (assessed with the DIVA's sexual function domain), with lower impact reported among women who were sexually active on at least a weekly basis compared to non-sexually active women and those who were sexually active less than weekly.

Behavioral and lifestyle characteristics associated with sexual functioning

Studies also found that physical activity, a better quality of life and satisfaction with life are positively associated with sexual functioning. Sedentary women and women with a low and average quality of life (measured with the WHO Quality of Life 26 questionnaire [WHOQOL-Bref]) were more likely to develop sexual dysfunction (diagnosed with the FSFI) compared to moderately and very active women and women with high quality of life, respectively (48). Similarly, higher satisfaction with life (measured with the SWLS) was a significant independent predictor of better sexual functioning, i.e. higher total CSFQ-14 scores (43).

Health indicators and health behaviors

Two studies examined health indicators as outcomes (i.e., cardiovascular health (53) and osteoporosis (55) in postmenopausal women), one study (54) examined the effects of marital transitions after menopause on various health indicators and health behaviors; and one study examined physical activity in women with diabetes and heart disease (41). Jaspers et al. assessed the association between oestradiol, testosterone, sex hormone-binding globulin (SHBG), and free androgen index (FAI) with optimal cardiovascular health (OCH) in men and naturally postmenopausal women who were on average 69.6 years of age (53). The findings related to naturally postmenopausal women indicate that sex steroids and SHBG might have a significant role in determining their cardiovascular health. Multivariate analysis showed that OCH in women was associated with lower levels of testosterone and FAI and higher levels of SHBG, irrespective of potential confounders (demographic and reproductive variables, chronic diseases, and other sex steroids). The definition of OCH was based on three health factors (total cholesterol, fasting glucose, and blood pressure) as well as on four health behaviors (physical activity, smoking, BMI, and diet). OCH was reported for 10.4% of women in this study. A study with peri- and postmenopausal women in Iran (41) found that women who had a history of cardiovascular disease and diabetes mellitus had significantly more physical activity compared to women without these chronic diseases, which may indicate that they were motivated to engage in physical activity to prevent the consequences of their diseases. The effect of physical activity was adjusted for women's quality of life and menopausal symptoms. This study also assessed relevant demographic and reproductive factors, BMI, HT use, and smoking, but provided only descriptive data for these variables. A study in Hong Kong with postmenopausal Chinese women (55) found that significant risk factors for osteoporosis were older age, longer duration of menopause, low BMI, and parental history of osteoporosis or hip fracture. Osteoporosis was diagnosed in 25.7% of women. Among these, less than one-third complied with treatment, while the other women discontinued or refused treatment. One longitudinal study in the United States examined the effects of marital transitions on health indicators

(blood pressure, waist circumference, and BMI) and health behaviors (dietary quality, alcohol intake, smoking, and physical activity) among postmenopausal women (54).

Interestingly, the results showed that marital transitions after menopause are accompanied by modifiable health outcomes that were more favorable for women experiencing divorce or separation compared to women entering a new marriage. Divorce or separation after menopause was associated with a reduction in BMI and waist circumference and improvements in diet quality and physical activity, while transition into marriage or marriage-like relationships was associated with an increase in BMI and alcohol intake. In this study, the effects of marital status were adjusted for relevant covariates (other demographic variables, emotional well-being and social functioning, depression, and social support).

Health-related quality of life

Two studies examined the determinants of health-related quality of life assessed with standard questionnaires (e.g., the Euro Quality of Life [5 dimensions, 3 levels] (EuroQol-5D-3) (56) and WHOQOL-Bref (41)), one study examined the determinants of general satisfaction with a life measured with Diener's Satisfaction With Life Scale (43), and one study examined the impact of vaginal symptoms of menopause-related quality of life with the DIVA questionnaire (52). Factors associated with the DIVA sexual functioning domain were described earlier. In this section, findings related to other dimensions of the DIVA questionnaire are presented. The results of the study that assessed the impact of vaginal symptoms on health-related quality of life measured with the DIVA questionnaire showed significant effects of some clinical and demographic characteristics of the participants on the different quality of life dimensions (52). Multivariate analysis showed that women who had higher HADS depression subscale scores, or who were experiencing urinary incontinence on at least a weekly basis, reported higher impact of vaginal symptoms on all three domains (activities of daily living, emotional well-being, and self-concept/body image). Furthermore, the impact on activities included in the daily living domain was higher among women

who reported only fair or poor overall health and among women who had higher BMI. Scores on the DIVA emotional well-being impact scale were lower among women with a spouse or sexual partner and higher among women who did not have a college degree. Scores reflecting the impact of vaginal symptoms on self-concept and body image domain items were lower among Latina/Hispanic women (compared with Non-Latina White women), older women, and women with diabetes. Another study analyzed data from the International Women's Health Study (56) and examined the association between vulvovaginal atrophy symptom severity and quality of life, after adjusting for demographics, health history, and health behaviors. The primary independent variable was assessed with only one item from the urogenital scale of the MRS (the vaginal dryness item). Quality of life was measured using the EuroQol-5D-3 instrument, which assesses the health state of the respondent at the time of completion based on five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). The results showed that, after pooling data from all countries together, each incremental level of severity of vulvovaginal atrophy symptoms (none through severe) was associated with a significant decrement in the quality of life scores. One study showed that physical activity was positively associated with the environmental, social, and psychological health-related quality of life domains of the WHOQOL-Bref (41). Multivariate analysis showed that increased physical activity had independent effects only on the psychological quality of life domain when the relationships with other quality of life domains, menopausal symptoms, and chronic diseases were statistically controlled for; however, this study did not test the effects of potential socio-demographic confounders. A study in Spain with women aged 40-59 years showed that menopausal status was not associated with women's global satisfaction with life, while various demographic, lifestyle, and clinical characteristics were significantly associated with life satisfaction. A linear regression analysis showed that significant predictors of higher satisfaction with life were better sexual functioning; higher BMI; fewer economic problems; less tobacco use; less-severe menopausal symptoms; healthiness; having a partner; and partner's healthiness (43).

Physical performance and cognitive changes

Two studies found that menopausal transition affects women's physical performance and cognitive functioning (57,58). Premenopausal women performed significantly better in grip strength and chair stands than peri- and postmenopausal women. However, the effect of menopausal status remained significant only for grip strength, when the effects of other relevant demographic and reproductive variables were controlled for in a linear regression analysis (58). Jacobs et al. (57) examined the effects of menopausal status on changes in memory circuitry during verbal encoding and memory retrieval tasks among women aged 45-55 years. The results showed that menopausal status had a significant effect on cognitive functioning, independent of age. Postmenopausal women showed alterations that are more pronounced in hippocampal activity and connectivity, and poorer performance on a subsequent memory task compared to pre- and perimenopausal women. Endocrine assessments showed that the changes in memory circuitry were related to the loss of ovarian estradiol during menopause.

Attitudes

Studies also found significant associations between the severity of menopausal symptoms – specifically night sweats, memory loss, and sleeplessness – and negative attitudes toward menopause among postmenopausal women (59). Planned health education related to the climacteric period may be useful in changing women's negative attitudes and beliefs related to menopause. One study showed that the negative beliefs about hot flushes of women who received planned health education decreased, while women who received no education did not change their hot flush beliefs (45).

The prevalence and age of natural menopause

Two studies assessed the age of natural menopause and factors that are related to earlier onset of natural menopause in highly populated countries such as China (42) and India (60), where premature menopause may affect many women and, consequently, their health. Both studies indicate that socioeconomic and reproductive factors are risk factors for the onset of earlier menopause. Li et al. (42) found

that the overall median age at natural menopause was 50 years among Chinese women. Lower educational level, poor economic status, lower BMI, age at menarche (≤14 years), nulliparity, and smoking were associated with earlier onset of natural menopause. Pallikadavath et al (2016) found that about 8.4% of women aged 15-49 years were in natural menopause. A higher risk for natural menopause below 50 years of age was significantly associated with several socioeconomic and reproductive variables: Widowhood or divorce/separation breakdown; poverty; low parity; no schooling; Muslim religion; caste (i.e., lower strata of the caste system); rural residence; Western countries; never using contraceptive pills; not being sterilized; and not having an abortion.

DISCUSSION

Findings from this study show that socio-demographic predictors were the most common variables related to menopausal symptoms: Specifically education; age; socioeconomic status; family; income; expenditure; economic problems; residence status; marital status; and partner's socio-demographic status (39-45,48-50,52-60). Duration of the reproductive period, higher parity, late perimenopause, and surgical or pharmacological menopause were associated with severe menopausal symptoms (39,40,48,49,52,56-59). A BMI of ≥25 had a significant effect on the severity of menopausal symptoms (psychological, somatic urogenital, and vasomotor) (39,42,43,47). Impairment in physical strength measured by handgrip and memory test showed a significant relation to menopause (57,58). Aerobic exercise for 12-24 weeks had a positive effect on women's muscle strength and was associated with a reduction of menopausal problems (61).

Findings also indicate that lifestyle-related factors, such as smoking and coffee intake, were shown to be associated with several menopause-related symptoms, while regular physical activity was inversely associated with menopause-related symptoms (38-42,44,46). Coffee intake (as well as tea and soda) was positively related to a vasomotor symptoms-related problem in postmenopausal women (62). A Spanish study showed that high physical activity could have a positive effect on bone mass (63); moreover, aerobic exercise for 6 months among newly postmenopausal sedentary symptomatic women reduced typical menopausal symptoms – especially night sweats, mood swings, and irritability (62). These results are supported by the WHO's conclusions that menopause is part of life's various phases and is largely influenced by previous health status, reproductive and sexual health, lifestyle, and the environment.

Prescribing hormone substitute therapy requires careful consideration of benefit and risk and period for hormone intake (1). HT had a beneficial effect on menopause-related symptoms (36,62). To achieve good effects, the exact dosage of hormonal treatment is required, but this area is still being research (16). Hormone replacement therapy (estrogen-progesterone) is associated with increased cancer risk (64) and increased incidence of ischemic and hemorrhagic stroke in the first 6 months after beginning HT (65). The physical activity has a preventive effect against breast cancer but is eliminated by HT therapy (66). Testosterone treatment in postmenopausal women is favorable for sexual health (65) and may improve libido and arousal (66). Estrogen therapy may reduce the risk for depression in later life in menopausal women that are at higher risk for depression (67). Eriksen et al. (2018) conclude that women who start menopausal HT in their 50s have predominantly positive health effects. HT reduced the incidence of diseases such as osteoporosis, colon cancer, and diabetes and had a positive impact on the quality of life (e.g., fewer hot flushes and improved sleep and sexual function) (67). Other studies highlight that non-medical treatment, such as exercise, may offer mental and physical benefits (68,69). In a comparison of 10-year differences in menopausal status, it was shown that education, smoking, and physical activity play an important role in determining menopausal age. The physical activity was significantly related to a delay in menopause, while smoking was related to an earlier menopausal age (70). In the present study, with regard to reproductive variables related to poorer sexual function, vaginal dryness was the most commonly reported problem (44,49-51,53,55,59). The American Psychological Association has specified that sexual disorders related to menopause are a complex combination of physical and psychological

disorders impacted by external factors such as an individual's socioeconomic situation, culture, and environment (71). The World Health Organization describes sexual health as a combination of physical, emotional, and social experiences (72). Anxiety and panic disorders (73), as well as poor general health in postmenopausal women, influence sexual health negatively. Vulvovaginal symptoms after menopause impact women's sexual health negatively and are underdiagnosed and undertreated (74).

Study findings also indicate that socio-demographic, socioeconomic, and reproductive factors are risk factors for early menopause for women aged ≤50 years (42,60). Further, poor knowledge of menopause and its related symptoms is linked to negative attitudes, but these were possible to reverse through education (45); moreover, it was shown that postmenopause was significantly associated with higher severity of self-estimated menopause-related symptoms (40,42-44,47). The average duration of menopause-related symptoms, such as anxiety, perceived stress, and depressive symptoms, is approximately 4.5 years following last menstruation (3). Gracez' (2003) study showed that women in generally perceived menopause as part of life but that the majority were aware of the possibility to seek help from medical practitioners for menopausal symptoms (75).

Potential biases

This study may contain biases. Potential biases of the study may be the analysis of the factors associated with menopausal symptoms, not just the prevalence of symptoms, and the use of standardized instruments for the assessment of menopausal symptoms.

Included studies controlled for the effects of age, health history, family history, use of medication, and other relevant factors that might be associated with menopause-related symptoms, apart from the main exposure variables. However, one of the two biases in the studies reviewed is their lack of explanation regarding the inclusion of primary independent variables of interest and possible confounders, and their lack of focus on primary outcomes of interest in a study plan (some studies analyzed a broad range of variables based on data from more extensive studies, without specifying aims that were more focused on the outcomes measured). Furthermore, conclusions

related to bone health, cardiovascular health, physical strength and memory changes are limited, due to the dearth of studies that included these outcomes. The use of different types of scales or questionnaires to measure outcomes and the different definitions of the examined constructs may have contributed to inconsistencies in the results. An additional bias may be due to the target population, as there is more data needed on perimenopausal women and the factors associated specifically with the menopausal transition. Only one study included the duration of symptoms, but this study examined individual symptoms and did not provide data on validated scale scores that assess different symptom domains. Most studies measured the severity of symptoms or the impact of menopausal symptoms in the 2 weeks before the investigation, and more studies are needed on the long-term effects of menopause-related changes. Finally, a bias may be that most studies provided cross-sectional data, and thus the direction of the causality between exposure and outcome variables cannot be explored.

CONCLUSIONS

The research focusing on determinants of menopause-related symptoms in women during the transition to menopause and the postmenopausal period seems to be extensive, with a wide range of variables and instruments having been used. A significant and representative finding was the range of outcomes and independent variables associated with various outcomes from ethnically and geographically diverse populations. In summary, menopause is a consistent physiological condition that can affect the mental, physical, and social dimensions of a woman's life. Some factors linked to her body and the environment in which she lives influences each woman's experience of menopausal symptoms.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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