Original Investigation | META-ANALYSIS

Association of Age at Menopause and Duration of Reproductive Period With Depression After Menopause
A Systematic Review and Meta-analysis

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IMPORTANCE Estrogens have neuroprotective and antidepressive effects; however, associations between indices of reduced endogenous estrogens and risk for postmenopausal depression have not been systematically explored.

OBJECTIVE To investigate the association of age at menopause and the duration of the reproductive period with the risk for depression among postmenopausal women with naturally occurring menopause.

DATA SOURCES A search strategy for use of MEDLINE was developed (through January 1, 2015) using the key terms *menopause*, *climacteric*, *reproductive period*, *depression*, and *mood disorders*. References of included studies and reviews were also screened; authors were contacted to maximize synthesized evidence.

STUDY SELECTION A total of 12 323 articles, without language restriction, were screened by pairs of reviewers to identify observational studies related to the study hypothesis; 14 studies were eligible for meta-analysis.

DATA EXTRACTION AND SYNTHESIS Pairs of reviewers independently extracted information on study design and type of analysis by participants' characteristics and methods of depression ascertainment. Study quality was assessed using the Newcastle-Ottawa Scale, and fixed- or random-effects models were implemented.

MAIN OUTCOMES AND MEASURES Pooled-effect estimates for depression, defined by psychiatric evaluation or validated instruments, by age at menopause and duration of the reproductive period.

RESULTS The 14 studies included in the meta-analysis represented 67 714 women. An inverse association (reported as odds ratio [OR]; 95% CI of 2-year increments) with depression in postmenopausal women was shown for increasing age at menopause (0.98; 0.96-0.99 [67 434 unique participants; 13 studies]) and duration of the reproductive period (0.98; 0.96-0.99 [54 715 unique participants; 5 studies]). Menopause at age 40 or more years compared with premature menopause was associated with a 50% decreased risk for depression (3033 unique participants; 4 studies). Pooling of studies examining severe depression showed a 5% decrease in risk of severe depression with increasing (2-year increment) age at menopause (52 736 unique participants; 3 studies); sensitivity analysis of studies controlling for past depression revealed similar results for age at menopause (0.98; 0.96-1.00 [48 894 unique participants; 3 studies). No heterogeneity or publication bias was evident in the main analyses.

CONCLUSIONS AND RELEVANCE Longer exposure to endogenous estrogens, expressed as older age at menopause and longer reproductive period, is associated with a lower risk of depression in later life. Identifying women at higher risk for depression due to early menopause who could benefit from psychiatric intervention or estrogen-based therapies could be useful in the clinical setting.

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Editorial

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Mental disorders are an important public health issue,[1] with the lifetime prevalence of major depression approximating 15% in high-income countries and 11% in low-income countries.[2] Late-life depression affects up to 10% of the elderly population.[3] Moreover, depressive disorders have been recognized as the second leading cause of disability across a person's lifespan[4] and have been consistently associated with adverse health outcomes, including cardiovascular disease[5,6] and all-cause mortality.[7]

Sex discrepancies have been described in the epidemiologic studies[2,8] of depression, with a doubled lifetime risk of major depression among women compared with men; this disparity is more profound during women's reproductive years.[9] Intense fluctuations of ovarian hormones observed premenstrually,[10,11] during pregnancy and postpartum,[12] and perimenopausally[13] have been associated with depression and have been proposed as the reason for this female preponderance during the specified time windows. Estrogens are thought to exert neuroprotective actions via receptors that have been recognized in the brain.[14] Furthermore, the higher vulnerability of women to stressful events and sex differences in stress response could partly explain the discrepancy.[15]

Transition in the postmenopausal period is linked to a relatively abrupt decrease in estrogen production[16] and a gradual attenuation of sex differences in the prevalence of depression in the elderly population.[14] Therefore, an advanced age at menopausal transition as a marker of longer exposure to endogenous estrogens could indicate a longer exposure to neuroprotective and antidepressive effects of estrogens. In this context, the aim of this systematic review and meta-analysis was to synthesize and quantify the results of published studies on the association between age at menopause or the duration of the reproductive period as markers of cumulative lifelong estrogen exposure and the risk of depression in postmenopausal women.

Methods

This systematic review was based on a predefined protocol (eMethods 1 in the Supplement). It was conducted in accordance with the Meta-analysis of Observational Studies in Epidemiology guidelines[17] (eTable 1 in the Supplement).

Search Strategy and Eligibility Criteria

Relevant published scientific articles were sought in MEDLINE through January 1, 2015, using combinations of the following Medical Subject Headings: *menopause*, *climacteric*, *reproductive period*, *depression*, and *mood disorders*. The detailed search strategy is available in eMethods 2 in the Supplement. No restrictions on language, publication year, or study design were applied. Reference lists of the included studies and relevant reviews were thereafter hand searched for additional potentially eligible studies (snowball procedure).

Cohort, case-control, and cross-sectional studies exploring the association of depression with age at menopause and/or duration of the reproductive period in postmenopausal women with naturally occurring menopause were considered eligible. Age at menopause was preferably defined as 1 year following the last menstruation,[18] but studies examining age at final menstruation were also considered for eligibility. Duration of the reproductive period was determined as the age at menopause minus the age at menarche. The diagnosis of depression must have been based on clinical diagnostic criteria or validated cutoff-point questionnaires. Case series, case reports, in vitro studies, animal studies, and investigations using nonvalidated instruments, questionnaires with no defined cutoff point, or questionnaires assessing depression as a self-reported symptom by a single question were excluded. Studies that included only women with depression and those that examined a population with preexisting severe psychiatric disorders were not eligible. Studies were also excluded if the population was limited to perimenopausal participants, breast cancer survivors with medically induced menopause, or women with surgically induced menopausal transition. When the participants included women who underwent naturally occurring or surgically induced menopause, the quantitative synthesis was limited to the cohort with naturally occurring menopause if those data were available; otherwise, the original effect estimates were included. Randomized clinical trials or intervention studies were considered for eligibility if they provided depression measurements at the preintervention phase. The investigators in those studies were contacted to provide appropriate analyses, potential clarifications, or missing data.

Investigators in nondirectly eligible studies (ie, including both exposure and outcome variables) were contacted to provide the multivariate regression analysis effect estimates of age at menopause and/or the duration of the reproductive period on depression encompassing at least the following adjusting factors: age, educational level, hormone therapy (HT) use, premenopausal depression history, smoking, body mass index, marital status, and parity. These variables were principally selected by confounding factors used by the studies included in this meta-analysis[19-24] to achieve homogeneous effect estimates. Reminders were sent to investigators 1 month after the initial contact. In case of multiple publications referring to the same cohort, the most recent publication or the one with the largest sample was selected for inclusion in the meta-analysis, but information from all relevant studies was retained. The selection of eligible studies was performed by 6 investigators (including M.K.G., T.P.T., A.-A.D, and E.I.K.) in 3 pairs who independently screened the titles, abstracts, and full text of identified articles; consensus was provisioned to resolve any disagreement.

Data Extraction and Assessment of Quality

Abstracted descriptive data included general information (ie, year, author, title, journal, region of origin, and study period), study characteristics (ie, design, duration of follow-up, and inclusion and exclusion criteria of the participants), and characteristics of the participants (ie, cohort size and number of incident cases, number of cases and controls, matching factors in case-control studies, mean age, age range, ethnicity, definition and ascertainment of depression, ascertainment of age at menopause and duration of reproductive period, type of

menopause, and HT use). Statistical analysis of the abstracted data included adjusting factors, reference category, and type of the effect estimate and results (ie, odds ratios [ORs] and 95% CIs). Maximally adjusted effect estimates were preferred. If the aforementioned data were not presented in the article, crude effect estimates and 95% CIs were de novo calculated from 2 × 2 tables using data available in the article.

The quality of the included studies was evaluated using the 9-item Newcastle-Ottawa Scale for cohort and case-control studies.[25] However, because the effect estimates of all eligible studies were derived from cross-sectional analyses, the cohort subscale of the Newcastle-Ottawa Scale (6 items) after excluding items 4 ("demonstration that outcome of interest was not present at start of study"), 8 ("was follow-up long enough for outcomes to occur"), and 9 ("adequacy of follow-up of cohorts") was used.[26] For comparability questions, age was set a priori as the most important matching or adjustment factor. Publication bias was assessed by the Egger test in analyses including at least 10 study arms.[27] Statistical significance was set at $P < .10$. Four of us (M.K.G., T.P.T., A.-A.D., and E.I.K.) performed data abstraction and quality assessment independently in pairs of 2; consensus was reached for disagreements.

Statistical Analysis

The ORs and 95% CIs of the different studies were pooled using fixed-effects (Mantel-Haenszel)[28] or random-effects (DerSimonian-Laird)[29] models, and pooled-effect estimates were calculated. Between-study heterogeneity was measured by the I^2 and Cochran Q tests; significance was set at $P < .10$. In cases of significant between-study heterogeneity, a random-effects model was applied regardless of the I^2 estimation.[30] The significance level for the overall effect was set at $P < .05$.

Analysis was conducted separately for the effect of both independent variables of interest (ie, age at menopause and duration of the reproductive period) as continuous variables on the risk of depression. Based on the largest eligible study (51 088 women),[20] 2-year increments were chosen for the exposure variables. Different increment effect estimates of other included studies were thereafter converted to 2-year estimates to safeguard homogeneity. Studies reporting only category-specific ORs were included following ad hoc estimation of the log-linear trend using the generalized least-squares approach.[31] Because this method requires the number of cases and controls by category of exposure and the presence of at least 3 levels of exposure, including baseline, it could not be applied to all studies. Therefore, an alternative analysis was carried out that included studies presenting results for age at menopause as a dichotomous categorical variable (≥40 vs <40 years).

Two sensitivity analyses were performed retaining studies controlling for the presence of premenopausal depression, as well as studies controlling for HT use. In a subanalysis, we examined the effect of age at menopause on severe postmenopausal depression, as defined by instruments used by the individual studies. A sensitivity analysis was then conducted including only studies defining age at menopause by the internationally accepted definition of 1 year following the last menstruation. Raw data contributed by authors who we contacted were modeled in multivariate logistic regression analyses to derive individual effect estimates that were subsequently synthesized in the meta-analysis (eMethods 2 in the Supplement). All statistical analyses were performed using Stata, version 11.1 (StataCorp).[32] Data analysis was conducted from June 10 to August 13, 2015.

Results

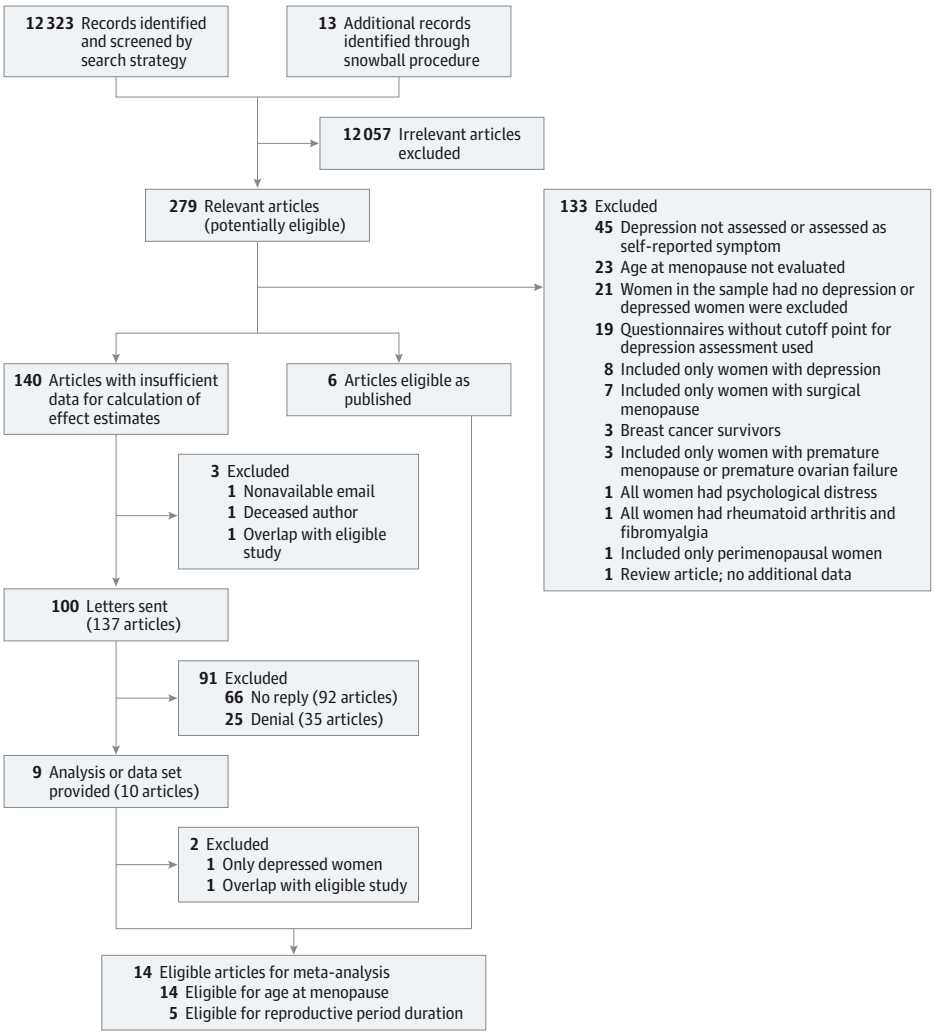
Search Strategy and Contact of Authors

Figure 1 depicts the flowchart of the study selection process. The database search yielded 12 323 records; 12 057 of these were deemed irrelevant by title or abstract. The full text of the remaining 266 articles was assessed along with 13 potentially eligible articles derived from the snowball process. Of these 279 articles, 6 were eligible,[19-24] 133 were excluded (eTable 2 in the Supplement), and the authors of the remaining 140 articles were contacted for clarification. Of these 140 articles, 8 studies provided the requested analysis or raw data for analysis by the leading research team.[33-40] Details regarding selection of the studies and contacting of the authors, as well as the full reference list, are available in eMethods 2 and the eReferences in the Supplement.

Thirteen of the 14 eligible studies contained data that could be included in the analysis on treating age at menopause as a continuous variable,[20-24,33-40] and 4 studies were included in the analysis on treating age at menopause as a categorical variable.[19,22,24,40] Five studies contributed data for analysis of the duration of the reproductive period, which was considered a continuous variable.[20,21,37,39,40]

The **Table** summarizes the abstracted data of the 14 nonoverlapping eligible studies (67 714 unique women). Ten of the studies were cross-sectional[19,21,22,24,33-38] and 4 were cohort[20,23,39,40] studies. Depression was diagnosed by validated self-report instruments in 12 studies.[19-22,24,33-39] The *DSM-III-R* criteria were used for diagnosis of major depression in one study,[40] and a history of physician-diagnosed depression was used in another study.[23] Women not meeting the criteria determined in studies for the diagnosis of depression composed the control group. Among 12 studies reporting the type of menopause, only 4 provided separate analyses for naturally occurring menopause,[33,35,39,40] whereas 8 studies included women who had undergone surgical menopause as well.[19-24,36,37] Eight of 9 studies providing information for HT use included current or past users,[19-21,23,36,37,39,40] and only 1 study included only women not using HT.[35] The main continuous analysis for age at menopause included 67 434 postmenopausal women, among whom 8565 were considered to have postmenopausal depression, whereas the alternative main analysis including the duration of the reproductive period as the exposure of interest comprised 6591 women with depression symptoms among the 54 715 participants. All but 2 studies[22,24] concerning age at menopause and all but 1

Figure 1. Flowchart on the Selection of Eligible Studies



study[21] containing data on the duration of the reproductive period provided multivariate analysis-derived effects. The most common adjusting factors (eTable 3 in the Supplement) included age (12 studies[19-21,23,33-40]), body mass index and obesity (11 studies[19,20,23,33-40]), educational level (10 studies[19-21,23,33-38]), smoking status (10 studies[19,20,23,33-36,38-40]), marital status (10 studies[19-21,23,33,35-37,39,40]), and HT use (7 studies[20,21,33,36,37,39,40]).

Quality of Studies

Quality assessment of the eligible studies using the Newcastle-Ottawa Scale is provided in eTable 4 in the Supplement. One study scored 6 of 6 possible points,[40] 8 scored 5 of 6 possible points,[19,21,22,24,35,37-39] and the remaining 5 scored 4 of 6 possible points.[20,23,33,34,36] The quality of the studies was most often compromised by the assessment of outcome; as expected in research projects, most studies used validated instruments to assess depression without subsequent clinical evaluation. An additional shortcoming in the 5 lower-quality studies pertained to the self-administered questionnaires used for the ascertainment of the 2 exposure variables instead of direct interviews.

Data Synthesis

Age at Menopause

After pooling effect estimates of the 15 study arms, which corresponded to 13 studies with age at menopause treated as a continuous variable,[20-24,33-40] increasing age at menopause (2-year increments) was associated with a 2% decrease in the risk of depression in postmenopausal women (OR, 0.98; 95% CI, 0.96-0.99; heterogeneity I^2 = 7.6%; P = .37 [67 434 unique participants]) (**Figure 2**). Excluding the study by Perquier et al,[20] corresponding to a weight of 62% did not materially change the results (OR, 0.97; 95% CI, 0.95-0.99; heterogeneity, I^2 = 11.2%; P = .33 [16 346 unique participants]).

The sensitivity analysis performed on 3 studies[20,21,36](4 study arms) controlling for premenopausal depression did not alter the inverse association of age at menopause with postmenopausal depression (OR, 0.98; 95% CI, 0.96-1.00;

Table. Characteristics of the 14 Eligible Studies

Source	Country (Study Period)	Study Design/ Sample Size/ Incident Cases	Participants	HT Use	Type of Menopause	Assessment of Depression	Assessment of Exposure	Exposure	Adjustment Factors
Lambrinoudaki et al,[36] 2015	Greece (NR)	Cross-sectional/ 143/19	Postmenopausal women (age, 40-73 y) registered in a menopause clinic database without premature menopause or premature ovarian failure, no use of phytoestrogens or antidepressants, and not recent quitters (<6 mo) of HT	Current users, 23.2%	Natural, 86.7%; surgical, 13.7%	ZSDS ≥50 (depression)	Self-administered questionnaire (retrospective)	Type: age at menopause; definition: 1 y after last menstrual period	Age, educational level, smoking, HT use, BMI, marital status, and parity
Tsiligianni et al,[38] 2014	Greece, Cyprus, and Malta (NR)	Cross-sectional/ 635/133	Randomly selected, population-based women (age, ≥65 y) not residing in assisted-living centers with no history of cardiovascular disease or cancer	NR	NR	GDS-15 ≥ 11 (severe depression)	Interview by health scientists (retrospective)	Type: age at menopause; definition: age at final menstrual period	Age, educational level, smoking, obesity, living alone, physical activity, income, MedDiet score, hypertension, T2DM, and hypercholesterolemia
Bove et al,[40] 2014	United States (1993-2014)	Cohort/ 1534/78	MAP: older women (age, 53-100 y) from Chicago free of known dementia at baseline; ROS: older Catholic nuns free of known dementia at baseline MARS: African American women (age, ≥65 y) free of dementia at baseline	Ever users, 30.6%	Natural	*DSM-III-R* criteria (major depression)	Interview by trained staff (retrospective)	Type: age at menopause; definition: age at final menstrual period	Age, smoking, HT use, BMI, marital status, dementia, and race
		Cohort/ 1528/76						Type: reproductive period; definition: age at menopause minus age at first menses	Same as above
Perquier et al,[20] 2013	France (1990-2005)	Cohort/ 51 088/5939	French women born between 1925-1950 (mean [SD] age, 63.8 [6.1] y), insured by a national health insurance plan primarily covering teachers	Past users, 48.7%; current users, 23.3%	Natural, artificial	CES-D ≥23 (severe depression)	Self-administered questionnaire (retrospective at baseline and update at each follow-up)	Type: age at menopause; definition: age at final menstrual period, age at surgery, or age at HT start	Age, educational level, smoking, HT use, oral contraceptive use, BMI, marital status, psychological difficulties at work, physical activity, alcohol intake, sleep duration, history of cancer, T2DM, and cardiovascular disease
		Cohort/ 51 088/5939						Type: reproductive period; definition: age at menopause minus age at first menses	Same as above
Toffol et al,[37] 2013	Finland (1997-2007)	Cross-sectional/ 2009/829	Representative, randomly selected nationwide sample of the general population of Finland (age, 40-74 y) recruited for 2 studies (Health 2000 and FINRISK)	Ever users, 28.32%	Natural, surgical	BDI-21 ≥10 or BDI-13 ≥5 (depression)	Interview by trained staff (retrospective)	Type: age at menopause; definition: 1 y after last menstrual period	Age, educational level, HT use, BMI, marital status, and parity
		Cross-sectional/ 954/397						Type: reproductive period; definition: age at menopause minus age at first menses	Same as above
Bączyk et al,[33] 2013	Poland (2007-2008)	Cross-sectional/ 185/36	Postmenopausal women (age, 50-70 y) in a menopause and osteoporosis outpatient clinic (osteoporosis cases and controls) with maintained internal reproductive organs and no secondary osteoporosis	NR	Natural	HADS-D ≥8 (depression)	NR	Type: age at menopause; definition: 1 y after last menstrual period	Age, educational level, smoking, HT use, BMI, and marital status
Erez et al,[34] 2012	Israel (2006-2009)	Cross-sectional/ 118/56	Postmenopausal women (age, 46-82 y) independently visiting a bone mineral density clinic and recruited by telephone	NR	NR	ZSDS ≥50 (depression)	Self-administered questionnaire (retrospective)	Type: age at menopause; definition: age at final menstrual period	Age, educational level, smoking, BMI, and employment

(continued)

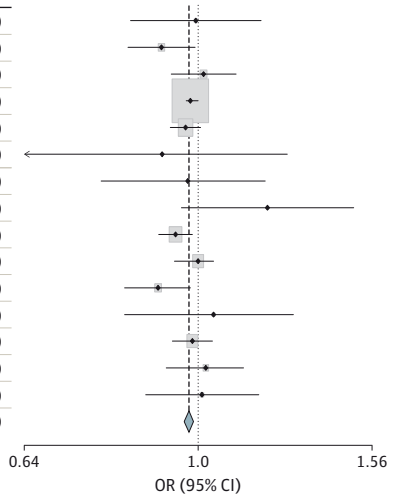
Table. Characteristics of the 14 Eligible Studies (continued)

Source	Country (Study Period)	Study Design/ Sample Size/ Incident Cases	Participants	HT Use	Type of Menopause	Assessment of Depression	Assessment of Exposure	Exposure	Adjustment Factors
Ünsal et al,[22] 2011	Turkey (2009)	Cross-sectional/ 744/184	Postmenopausal women (age, 45-65 y) residing in Sivrihisar and recruited through the community health center	NR	Natural, 84.7%; surgical, 15.3%	BDI-21 ≥17 (depression)	Interview by members of the research team (retrospective)	Type: age at menopause; definition: 1 y after last menstrual period/ age at surgery	None
Berecki-Gisolf et al,[23] 2009	Australia (1996-2007)	Cohort/ 8649/777	Randomly selected citizens, permanent residents, refugees, and immigrants (age, 45-50 y) of Australia	Ever users, 33%	Natural, 88%; surgical, 9%	History of physician-diagnosed depression	Response to mailed questionnaire (prospective)	Type: age at menopause; definition: age at final menstrual period	Age, educational level, smoking, BMI, life events, ability to manage on available income, area of residence, and marital status
Ryan et al,[21] 2008	France (1999-2001)	Cross-sectional/ 1013/171	Community noninstitutionalized, nondemented French women (age, 65-94 y) recruited from electoral rolls	Past users, 19.8%; current users, 14.8%	Natural, 81.4%; surgical, 9.8%; and other, 8.8%	CES-D ≥23 (severe depression)	Interview by trained staff (retrospective)	Type: age at menopause; definition: 1 y after last menstrual period	Age, educational level, marital status, insomnia, disability, cognitive impairment, number of drugs, past depression, antidepressive treatment, HT, and oral contraceptive use
		Cohort/ 1013/171						Type: reproductive period; definition: age at menopause minus age at first menses	None
Ünsal et al,[24] 2008	Turkey (2007)	Cross-sectional/ 475/94	Women (age, 40-95 y) residing in Sivrihisar and recruited through the local family health center	NR	Natural, surgical	BDI ≥17 (depression)	Interview by trained staff (retrospective)	Type: age at menopause; definition: 1 y after last menstrual period	None
Jasienska et al,[35] 2005	Poland (NR)	Cross-sectional/ 601/232	Randomly selected female-registered residents of Krakow (age, 45-64 y) with no history of hysterectomy and no use of hormonal medications	0	Natural	CES-D ≥16 (depression)	Interview by trained staff (retrospective)	Type: age at menopause; definition: age at final menstrual period	Age, educational level, smoking, marital status, and BMI
Whalley et al,[39] 2004	Scotland, United Kingdom (1947-2001)	Cohort/ 240/17	Women born in 1936 (age, 65 y) matched through local health registry and recruited by local family physicians	Ever users, 22.09%	Natural	HADS-D ≥8 (depression)	Interview by trained staff (prospective, reassessment by telephone after 2 y)	Type: age at menopause; definition: 1 y after last menstrual period	Smoking, marital status, BMI, and HT use
		Cohort/ 132/8						Type: reproductive years; definition: age at menopause minus age at first menses	Same as above
Bezircioglu et al,[19] 2004	Turkey (NR)	Cross-sectional/ 280/NR	Women (age, 45-55 y) born in area of study or immigrants recruited through the local family health center with no surgical menopause due to cancer, mental illness, physical deficiency, lactation, or pregnancy	Current users, 23.2%	Natural, 86.4%; surgical, 13.6%	HADS-D ≥8 (depression)	Interview by trained staff (retrospective)	Type: age at menopause; definition: 1 y after last menstrual period	Age, educational level, employment, marital status, number of pregnancies, abortion, smoking, BMI, diabetes mellitus, cardiovascular disease, psychiatric disease, family history of psychiatric disease, drug use for chronic illness, seeking menopause-related advice, mammography, bone densitometry, and disability

Abbreviations: BDI-13, 13-item Beck Depression Inventory; BDI-21, 21-item BDI; BMI, body mass index; CES-D, Center for Epidemiological Studies–Depression scale; GDS-15, 15-item Geriatric Depression Scale; HADS-D, Hospital Anxiety and Depression Scale–Depression subscale; HT, hormone therapy; MAP, Memory and Aging Project; MARS, Rush Minority Aging and Research Study; NR, not reported; ROS, Religious Orders Study; T2DM, type 2 diabetes mellitus; ZSDS, Zung Self-rating Depression Scale.

Figure 2. Association Between Age at Menopause and Postmenopausal Depression

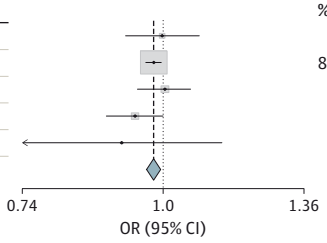
Source	Depression: No. of Events	Depression: Total No. of Participants	OR (95% CI)	Weight, %
Lambrinoudaki et al,[36] 2015	19	143	0.99 (0.84-1.18)	0.51
Tsiligianni et al,[38] 2014	133	635	0.91 (0.84-0.99)	1.94
Bove et al,[40] 2014	78	1534	1.01 (0.93-1.10)	2.07
Perquier et al,[20] 2013	5939	51088	0.98 (0.97-1.00)	61.90
Toffol et al,[37] 2013	829	2009	0.97 (0.93-1.01)	9.62
Bączyk et al,[33] 2013 (osteoporosis cases)	19	85	0.91 (0.64-1.26)	0.13
Bączyk et al,[33] 2013 (controls)	17	100	0.97 (0.78-1.19)	0.32
Erez et al,[34] 2012	56	118	1.19 (0.96-1.49)	0.29
Ünsal et al,[22] 2011	184	744	0.94 (0.90-0.99)	7.64
Berecki-Gisolf et al,[23] 2009	777	8649	1.00 (0.94-1.04)	5.68
Ryan et al,[21] 2008 (<12 y of education)	110	580	0.90 (0.83-0.98)	2.02
Ryan et al,[21] 2008 (≥12 y of education)	61	433	1.04 (0.83-1.28)	0.31
Ünsal et al,[24] 2008	94	475	0.99 (0.94-1.04)	5.42
Jasienska et al,[35] 2005	232	601	1.02 (0.92-1.12)	1.46
Whalley et al,[39] 2004	17	240	1.01 (0.87-1.17)	0.68
Overall: I^2 = 7.6%, P = .37	**8565**	**67434**	0.98 (0.96-0.99)	100



Thirteen studies (15 arms) reported the association of age at menopause as a continuous variable (2-year increments) with depression in postmenopausal women (P < .001). Odds ratios (ORs) in the individual studies are indicated by the data markers (shaded boxes around the data markers reflect the statistical weight of the study); 95% CIs are indicated by the error bars. The pooled-effect estimate with its 95% CI is depicted as a diamond.

Figure 3. Association Between Duration of Reproductive Period and Postmenopausal Depression

Source	Depression: No. of Events	Depression: Total No. of Participants	OR (95% CI)	Weight, %
Bove et al,[40] 2014	76	1528	1.00 (0.92-1.08)	3.66
Perquier et al,[20] 2013	5939	51088	0.98 (0.96-1.00)	82.62
Toffol et al,[37] 2013	397	954	1.00 (0.95-1.06)	7.09
Ryan et al,[21] 2008	171	1013	0.94 (0.88-1.00)	6.13
Whalley et al,[39] 2004	8	132	0.91 (0.74-1.14)	0.50
Overall: I^2 = 0.0%, P = .57	**6591**	**54715**	0.98 (0.96-0.99)	100



Five studies explored the effect of the duration of the reproductive period (continuous by 2-year increments) on depression in postmenopausal women (P = .007). Odds ratios (ORs) in the individual studies are indicated as data markers (shaded boxes around the data markers reflect the statistical weight of the study); 95% CIs are indicated by the error bars. The pooled-effect estimate with its 95% CI is depicted as a diamond.

heterogeneity, I^2 = 22.1%; P = .28 [48 894 unique participants]) (eFigure 1 in the Supplement). The same results were also found in the sensitivity analysis retaining the 8 studies[20,21,33,35-37,39,40] (10 study arms) controlling for HT use (OR, 0.98; 95% CI, 0.96-1.00; heterogeneity, I^2 = 0.0%; P = .75 [56 813 unique participants]) (eFigure 2 in the Supplement). Moreover, in a subanalysis restricted to studies examining severe depression defined by appropriate cutoff points,[20,21,38] (3 studies; 4 study arms) a 5% decrease was documented by a 2-year increase in age at menopause (OR, 0.95; 95% CI, 0.90-1.00; heterogeneity, I^2 = 53.6%, P = .09 [52 736 unique participants]) (eFigure 3 in the Supplement). Lastly, in the sensitivity analysis of 7 studies[21,22,24,33,36-38] (9 study arms) defining age at menopause as 1 year following the last menstruation, the results did not materially change (OR, 0.96; 95% CI, 0.94-0.98; heterogeneity, I^2 = 0.0%; P = .75 [4809 unique participants]) (eFigure 4 in the Supplement).

In 4 studies (3033 women) providing data on women with premature menopause (<40 years),[27-29,40] a sizeable doubling of risk of depression was found in this cohort compared with women who reported menopause at 40 years or older (OR, 0.49; 95% CI, 0.29-0.81; heterogeneity, I^2 = 54.2%, P = .09) (eFigure 5 in the Supplement).

Reproductive Period

Results from the 5 studies (6 study arms) providing effect estimates for the association of reproductive period duration with postmenopausal depression risk[20,21,37,39,40] yielded a same-size, statistically significant inverse association (2% for an increase of reproductive period duration by 2 years) as that found for age at menopause (OR, 0.98; 95% CI, 0.96-0.99; heterogeneity, I^2 = 0.0%; P = .57 [54 715 unique participants; 5 studies]) (**Figure 3**). A sensitivity analysis, excluding the study by Perquier et al[20] because of its substantial weight, showed an inverse but nonsignificant association between reproductive period and risk of depression (OR, 0.98; 95% CI, 0.94-1.01; heterogeneity, I^2 = 0.0%; P = .41 [3627 unique participants]). Because of the paucity of studies reporting on reproductive

period duration, it was not possible to conduct other sensitivity analyses as were performed for age at menopause.

Publication Bias

In the meta-analysis for age at menopause as a continuous variable, no publication bias was found (P = .83, Egger test). In the subsequent analyses and sensitivity analyses, publication bias was not assessed because fewer than 10 studies were included, which could potentially hamper the power of this test.

Discussion

An inverse association between the age at menopause, treated either as a continuous or categorical variable, and the risk of subsequent depression in postmenopausal women was shown in this meta-analysis. This effect was retained after controlling for premenopausal depression and HT use and was enhanced among studies examining the association of age at menopause with severe depression or among women with premature menopause. The same size effect estimate was found in alternative analyses using the duration of the reproductive period as an index of exposure to endogenous estrogens.

These findings indicate that a shorter exposure to endogenous estrogens that is linked to a longer duration of estrogen deficiency, assessed through proxy variables, increases the risk for subsequent late-life depression and emphasizes the importance of the neuroprotective and antidepressive properties of endogenous estrogens. Even though we excluded studies of women with surgically induced menopause to reduce confounding by indication, our findings are in accordance with previous studies reporting that early menopause due to oophorectomy increases the risk of depression later in life.[41,42] Older age at menopause has also been proposed to be an index of general health associated with lower risk for all-cause and cardiovascular-specific mortality.[43,44] Age at menarche does not seem to influence the risk of depression in postmenopausal women,[20,21] possibly because it is characterized by lower variance among women compared with age at menopause.[45] Thus, discrepancies in age at menarche may not reflect major differences in total exposure to endogenous estrogens.

The abundance and wide distribution of estrogen receptors across the brain and the association of their genetic polymorphisms with late-life depression[46] argue for the role of estrogens in the modulation of behavioral effects; however, the exact pathways for their action remain unclear.[47] Direct regulation of monoamine neurotransmitter systems that are involved in the pathogenesis of late-life depression, in addition to modulating actions on neuroplasticity and the hypothalamus-pituitary-adrenal axis, could partially mediate the antidepressive properties of estrogens.[48,49]

When considering the underlying pathologic mechanisms, the different disease properties between early-onset and late-life depression should be taken into account. Contrary to depression that occurs at younger ages, increasing evidence suggests that geriatric depression is more commonly associated with generalized cerebral abnormalities attributed to vascular dysregulation and neurodegeneration of frontal-subcortical neural circuits.[50-53] Epidemiologic evidence has shown that an early age at menopause is an independent risk factor for cardiovascular disease[54]; in addition, it has been suggested that early menopause or oophorectomy before menopause increases the risk for subsequent cognitive decline and dementia.[55-57] Therefore, the antidepressive effects of longer exposure to endogenous estrogens could be mediated through their action against cerebral atherosclerosis and neurodegeneration. Experimental studies have demonstrated a neuroprotective role of circulating estradiol, which acts in neurons and glial cells via the intracellular estrogen receptors α and β,[14,49] as well as antiatherogenic actions including enhancement of endothelial function, blockage of smooth muscle cell proliferation, and inhibition of inflammation.[58]

Regarding the potentially protective effect of estrogen supplementation for the treatment or prevention of postmenopausal depression, estrogens and HT—either as monotherapy or as adjunct therapy—have been reported to improve the outcome of perimenopausal depression[59-61] as opposed to the findings for depression in postmenopausal women,[62] indicating a possible window of opportunity during perimenopause for the effective use of estrogen therapy in depression.[63] Given the results of our study, it remains to be investigated whether women with menopause at younger ages could benefit by preventive use of HT against late-life depression, provided that adverse effects associated with long-term use are considered.[64] In this context, the development of estrogen receptor subtype-specific ligands could decrease the proportion of estrogen therapy adverse effects.[65,66]

A major strength of this meta-analysis lies in its sound methodologic approach according to current guidelines. Following an independent dual screening of more than 12 000 articles, rigorous communication with authors of potentially eligible articles was conducted, offering them the opportunity to deliver raw data for estimation of the individual study effect estimates (3 studies) so as to maximize the synthesized evidence. Eventually, the study participants contributing information in main analyses were more than 67 000 women, with no significant heterogeneity noticed among included studies. Most of these studies used important confounding factors: age, obesity, HT use, smoking, and marital status. Sensitivity analyses were further performed, when possible, to assess the effect of remaining potential confounding factors, whereas no publication bias was evident in the age at menopause analysis.

The meta-analysis bears certain inherent limitations that are mainly attributed to the design and effect estimates reporting in the included studies. Despite the absence of significant heterogeneity among the included studies, variable methods for defining depression were used, including self-reporting. Depression was determined by different cutoff points; notably, 3 studies used a cutoff point indicating severe depression, but the rest defined depression by lower cutoff points. However, the subsequent sensitivity analysis led to a higher effect among studies examining exclusively severe depression. Because the severity of depressive disorders seems to be associated with the severity of underlying cerebral abnormalities,[67,68] the differential risk may indicate

a dose-dependent association of duration of exposure to endogenous estrogens with underlying lesions and depression.

Given the cross-sectionally derived effect estimates, the direction of the causality between depression and exposure variables cannot be explored. History of preexisting (premenopausal) depression should be considered since it is a strong predictor of late-life depression[69,70] and has been associated with earlier menopause and ovarian aging.[71,72] To limit this drawback, a subanalysis of studies controlling for past depression was conducted, indicating that the observed inverse association of a later menopausal transition with postmenopausal depression remained significant.

Moreover, given the potential effect of exogenous estrogen on depression risk, the inclusion of current or past HT users in most of the studies may have influenced our findings. Although most of the included studies adjusted for HT use and a sensitivity analysis restricted to studies controlling for this factor did not materially change the results, there is a possibility for residual confounding; only studies excluding HT users could sufficiently control for this factor.

An additional limitation involves the self-reporting of age at menopause contrasted to determination by direct interview. This difference may have nominally lowered the quality of several eligible studies, whereas the retrospectively elicited information in different time periods after menopause has potentially led to differential recall bias.[73] Self-recalled age at menopause has been reported in one study to be in satisfactory agreement with gynecologic medical records,[74] but this assertion cannot preclude recall bias. This finding is of particular importance when considering that women recruited by eligible studies potentially started HT use before their last menstruation, making it cumbersome to determine the time of menopause. We attempted to assess heterogeneity regarding age at menopause definition through a sensitivity analysis confined to the 7 studies using the internationally accepted definition of 1 year after the last menstruation; the results remained essentially unchanged.

Because not all studies controlled for factors affecting lifetime estrogen exposure, including oral contraceptive use, breastfeeding, and number of pregnancies, residual confounding may remain an issue; the paucity of data in the published studies did not allow for meta-regression analyses. Similarly, none of the studies controlled for autoimmune diseases, and no meta-regression analyses could be conducted for cognition, cardiovascular disease, and psychological parameters, such as stressful experiences. Another limitation is that statistical power of the conducted subanalyses may have been hampered by the low number of included studies. Finally, participants in most of the studies were from Western communities, pointing to the need for more ethnically diverse populations and more generalizable findings given the geographic discrepancies in the timing of menopause.[75]

Conclusions

This meta-analysis suggests a potentially protective effect of increasing duration of exposure to endogenous estrogens as assessed by age at menopause as well as by the duration of the reproductive period. The findings provide epidemiologic support for the involvement of estrogen deficiency in the pathophysiology of late-life depression. If confirmed in prospective and culturally diverse studies controlling for potential confounders and assessing depression via psychiatric evaluation, these findings could have a significant clinical effect by allowing for the identification of a group of women at higher risk for depression who may benefit from psychiatric monitoring or estrogen-based therapies. Based on those data, health care professionals and health policy planners may recognize the extent of depression in the menopausal group and plan accordingly for treatment.

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