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

Marios K. Georgakis, MD; Thomas P. Thomopoulos, MD; Andreas-Antionios Diamantaras, MD; Eleni I. Kalogirou, MD; Alkistis Skalkidou, MD, PhD; Stella S. Daskalopoulou, MD, MSc, DIC, PhD; Eleni Th Petridou, MD, MPH, PhD

IMPORATANCE 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.

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 lifespan4 and have been consistently associated with adverse health outcomes, including cardiovascular disease5,6 and all-cause mortality.7

Sex discrepancies have been described in the epidemiologic studies5-13 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 perimenopausally13 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 production16 and a gradual attenuation of sex differences in the prevalence of depression in the elderly population.18 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 guidelines17 (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-analysis19-24 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. 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. For comparability questions, age was set as a priori as the most important matching or adjustment factor. Publication bias was assessed by the Egger test. 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.

### 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, 24-27 133 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, 20-24,31-40 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 non-overlapping eligible studies (67 714 unique women). Ten of the studies were cross-sectional19,21,22,24,33-38 and 4 were cohort20,23,39,40 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, 33,35,19,40 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,19,21,23,36,37,40,40,40 and only 1 study included only women not using HT.35 The main continuous analysis for age at menopause included 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.
study 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), body mass index and obesity (11 studies), educational level (10 studies), smoking status (10 studies), marital status (10 studies), and HT use (7 studies).

Quality of Studies
Quality assessment of the eligible studies using the Newcastle-Ottawa Scale is provided in eTable 3 in the Supplement. One study scored 6 of 6 possible points, 8 scored 5 of 6 possible points, and the remaining 5 scored 4 of 6 possible points. 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, 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, 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 (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

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample Size</th>
<th>Participants</th>
<th>Type of Menopause</th>
<th>Assessment of Menopause</th>
<th>Assessment of Depression</th>
<th>Exposure</th>
<th>Age, educational level, smoking, HT use, BMI, marital status, and parity</th>
<th>Adjustment Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bove et al, 2014</td>
<td>38</td>
<td>Postmenopausal women (age, ≥65 y) not residing in assisted-living centers with no history of cardiovascular disease or cancer</td>
<td>Type: age at menopause; definition: 1 y after last menstrual period</td>
<td>Interview by trained staff (retrospective)</td>
<td>Self-administered questionnaire (retrospective)</td>
<td>NR</td>
<td>Age, smoking, HT use, BMI, marital status, and parity</td>
<td>Same as above</td>
</tr>
<tr>
<td>Bączyk et al, 2013</td>
<td>2013</td>
<td>Postmenopausal women (age, 50-70 y)</td>
<td>Type: reproductive period; definition: age at menopause minus age at first menses</td>
<td>Interview by trained staff (retrospective)</td>
<td>Natural</td>
<td>Age, educational level, smoking, HT use, BMI, marital status, and parity</td>
<td>Same as above</td>
<td></td>
</tr>
<tr>
<td>Perquier et al, 2014</td>
<td>1528/76</td>
<td>Postmenopausal women (age, 53-100 y)</td>
<td>Type: reproductive period; definition: age at menopause minus age at first menses</td>
<td>Interview by trained staff (retrospective at baseline and update at each follow-up)</td>
<td>Self-administered questionnaire (retrospective)</td>
<td>NR</td>
<td>Age, smoking, HT use, BMI, marital status, and parity</td>
<td>Same as above</td>
</tr>
<tr>
<td>Erez et al, 2012</td>
<td>51088/5939</td>
<td>Postmenopausal women (age, 46-82 y) in an osteoporosis clinic and recruited by telephone</td>
<td>Type: age at menopause; definition: age at final menstrual period, age at surgery, or age at start of hormone therapy</td>
<td>Interview by trained staff (retrospective)</td>
<td>Natural</td>
<td>Age, educational level, smoking, HT use, BMI, marital status, and parity</td>
<td>Same as above</td>
<td></td>
</tr>
<tr>
<td>Toffol et al, 2013</td>
<td>51088/5939</td>
<td>Postmenopausal women (age, 50-70 y)</td>
<td>Type: reproductive period; definition: age at menopause minus age at first menses</td>
<td>Interview by trained staff (retrospective)</td>
<td>Natural</td>
<td>Age, educational level, smoking, HT use, BMI, marital status, and parity</td>
<td>Same as above</td>
<td></td>
</tr>
<tr>
<td>Biczók et al, 2013</td>
<td>118/56</td>
<td>Postmenopausal women (age, 46-82 y)</td>
<td>Type: age at menopause; definition: age at final menstrual period, age at surgery, or age at start of hormone therapy</td>
<td>Interview by trained staff (retrospective)</td>
<td>Natural</td>
<td>Age, educational level, smoking, HT use, BMI, marital status, and parity</td>
<td>Same as above</td>
<td></td>
</tr>
<tr>
<td>Erez et al, 2014</td>
<td>954/397</td>
<td>Postmenopausal women (age, 46-82 y)</td>
<td>Type: age at menopause; definition: age at final menstrual period, age at surgery, or age at start of hormone therapy</td>
<td>Interview by trained staff (retrospective)</td>
<td>Natural</td>
<td>Age, educational level, smoking, HT use, BMI, marital status, and parity</td>
<td>Same as above</td>
<td></td>
</tr>
</tbody>
</table>

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Table. Characteristics of the 14 Eligible Studies (continued)

<table>
<thead>
<tr>
<th>Source</th>
<th>Country (Study Period)</th>
<th>Study Design/ Sample Size/ Incident Cases</th>
<th>Participants</th>
<th>HT Use</th>
<th>Type of Menopause</th>
<th>Assessment of Depression</th>
<th>Assessment of Exposure</th>
<th>Exposure</th>
<th>Adjustment Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ünsal et al,24 2011</td>
<td>Turkey (2009)</td>
<td>Cross-sectional/ 744/184</td>
<td>Postmenopausal women (age, 45-65 y) residing in Sivrihisar and recruited through the community health center</td>
<td>NR</td>
<td>Natural</td>
<td>BDI-21 ≥17 (depression)</td>
<td>Interview by members of the research team (retrospective)</td>
<td></td>
<td>None</td>
</tr>
<tr>
<td>Berecki-Gisolf et al,35 2009</td>
<td>Australia (1996-2007)</td>
<td>Cohort/ 864/977</td>
<td>Randomly selected citizens, permanent residents, refugees, and immigrants (age, 45-50 y) of Australia</td>
<td>Ever users, 33%</td>
<td>Natural</td>
<td>History of physician-diagnosed depression</td>
<td>Response to mailed questionnaire (prospective)</td>
<td></td>
<td>Age, educational level, smoking, BMI, life events, ability to manage on available income, area of residence, and marital status</td>
</tr>
<tr>
<td>Ryan et al,21 2008</td>
<td>France (1999-2001)</td>
<td>Cross-sectional/ 1013/171</td>
<td>Community noninstitutionalized, nondocumented French women (age, 65-94 y) recruited from electoral rolls</td>
<td>Natural, 81.4%;</td>
<td>Natural</td>
<td>CES-D ≥23 (severe depression)</td>
<td>Interview by trained staff (retrospective)</td>
<td></td>
<td>Age, educational level, marital status, insomnia, disability, cognitive impairment, number of drugs, past depression, antidepressive treatment, HT, and oral contraceptive use</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cohort/ 1013/171</td>
<td></td>
<td>surgical, 5%; and other, 8.8%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ünsal et al,24 2008</td>
<td>Turkey (2007)</td>
<td>Cross-sectional/ 475/94</td>
<td>Women (age, 40-95 y) residing in Sivrihisar and recruited through the local family health center</td>
<td>NR</td>
<td>Natural</td>
<td>BDI ≥17 (depression)</td>
<td>Interview by trained staff (retrospective)</td>
<td></td>
<td>Type: age at menopause; definition: age at menopause minus age at first menses</td>
</tr>
<tr>
<td>Jasienska et al,35 2005</td>
<td>Poland (NR)</td>
<td>Cross-sectional/ 601/232</td>
<td>Randomly selected female-registered residents of Krakow (age, 45-64 y) with no history of hysterectomy and no use of hormonal medications</td>
<td>0</td>
<td>Natural</td>
<td>CES-D ≥16 (depression)</td>
<td>Interview by trained staff (retrospective)</td>
<td></td>
<td>Age, educational level, smoking, marital status, and BMI</td>
</tr>
<tr>
<td>Whalley et al,39 2004</td>
<td>Scotland, United Kingdom (1947-2001)</td>
<td>Cohort/ 240/17</td>
<td>Women born in 1936 (age, 65 y) matched through local health registry and recruited by local family physicians</td>
<td>Natural, 22.9%</td>
<td></td>
<td>HADS-D ≥8 (depression)</td>
<td>Interview by trained staff (prospective, reassessment by telephone after 2 y)</td>
<td></td>
<td>Smoking, marital status, BMI, and HT use</td>
</tr>
<tr>
<td>Bezicioglu et al,39 2004</td>
<td>Turkey (NR)</td>
<td>Cross-sectional/ 280/NR</td>
<td>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</td>
<td>Current users, 23.2%</td>
<td>Natural</td>
<td>HADS-D ≥8 (depression)</td>
<td>Interview by trained staff (retrospective)</td>
<td></td>
<td>Same as above</td>
</tr>
</tbody>
</table>

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.
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\(^{26,21,33,35-37,39,40}\) (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, \( I^2 = 0.0\% \); \( P = .75 \) [48 097 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, 0.49; 95% CI, 0.29-0.81; 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\(^{40}\) 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, \( I^2 = 0.0\% \); \( P = .41 \) [36 27 unique participants]). Because of the paucity of studies reporting on reproductive

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### Table 1. Association Between Duration of Reproductive Period and Postmenopausal Depression

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Events</th>
<th>Total No. of Participants</th>
<th>OR (95% CI)</th>
<th>Weight, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bove et al,(^{40}) 2014</td>
<td>76</td>
<td>1528</td>
<td>1.00 (0.92-1.08)</td>
<td>3.66</td>
</tr>
<tr>
<td>Perquier et al,(^{20}) 2013</td>
<td>5939</td>
<td>51 088</td>
<td>0.98 (0.96-1.00)</td>
<td>82.62</td>
</tr>
<tr>
<td>Toffoli et al,(^{37}) 2013</td>
<td>397</td>
<td>954</td>
<td>1.00 (0.95-1.06)</td>
<td>7.09</td>
</tr>
<tr>
<td>Ryan et al,(^{21}) 2008</td>
<td>171</td>
<td>1013</td>
<td>0.94 (0.88-1.00)</td>
<td>6.13</td>
</tr>
<tr>
<td>Whalley et al,(^{39}) 2004</td>
<td>8</td>
<td>132</td>
<td>0.91 (0.74-1.14)</td>
<td>0.50</td>
</tr>
<tr>
<td>Overall; ( I^2 = 0.0% ), ( P = .57 )</td>
<td>6591</td>
<td>54 715</td>
<td>0.98 (0.96-0.99)</td>
<td>100</td>
</tr>
</tbody>
</table>

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.

### Table 2. Association Between Age at Menopause and Postmenopausal Depression

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Events</th>
<th>Total No. of Participants</th>
<th>OR (95% CI)</th>
<th>Weight, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lambrinoudaki et al,(^{36}) 2015</td>
<td>19</td>
<td>143</td>
<td>0.99 (0.84-1.18)</td>
<td>0.51</td>
</tr>
<tr>
<td>Tsiligiani et al,(^{38}) 2014</td>
<td>133</td>
<td>635</td>
<td>0.91 (0.84-0.99)</td>
<td>1.94</td>
</tr>
<tr>
<td>Bove et al,(^{40}) 2014</td>
<td>78</td>
<td>1534</td>
<td>1.01 (0.93-1.10)</td>
<td>2.07</td>
</tr>
<tr>
<td>Perquier et al,(^{20}) 2013</td>
<td>5939</td>
<td>51 088</td>
<td>0.98 (0.97-1.00)</td>
<td>61.90</td>
</tr>
<tr>
<td>Toffoli et al,(^{37}) 2013</td>
<td>829</td>
<td>2009</td>
<td>0.97 (0.93-1.01)</td>
<td>9.62</td>
</tr>
<tr>
<td>Bączyk et al,(^{33}) 2013 (osteoporosis cases)</td>
<td>19</td>
<td>85</td>
<td>0.91 (0.64-1.26)</td>
<td>0.13</td>
</tr>
<tr>
<td>Bączyk et al,(^{33}) 2013 (controls)</td>
<td>17</td>
<td>100</td>
<td>0.97 (0.78-1.19)</td>
<td>0.32</td>
</tr>
<tr>
<td>Erez et al,(^{35}) 2012</td>
<td>56</td>
<td>118</td>
<td>1.19 (0.96-1.49)</td>
<td>0.29</td>
</tr>
<tr>
<td>Únsal et al,(^{24}) 2011</td>
<td>184</td>
<td>744</td>
<td>0.94 (0.90-0.99)</td>
<td>7.64</td>
</tr>
<tr>
<td>Berecki-Gisolf et al,(^{23}) 2009</td>
<td>777</td>
<td>8649</td>
<td>1.00 (0.94-1.04)</td>
<td>5.68</td>
</tr>
<tr>
<td>Ryan et al,(^{21}) 2008 (&lt;12 y of education)</td>
<td>110</td>
<td>580</td>
<td>0.90 (0.83-0.98)</td>
<td>2.02</td>
</tr>
<tr>
<td>Ryan et al,(^{21}) 2008 (≥12 y of education)</td>
<td>61</td>
<td>433</td>
<td>1.04 (0.83-1.28)</td>
<td>0.31</td>
</tr>
<tr>
<td>Únsal et al,(^{24}) 2008</td>
<td>94</td>
<td>475</td>
<td>0.99 (0.94-1.04)</td>
<td>5.42</td>
</tr>
<tr>
<td>Jasienska et al,(^{35}) 2005</td>
<td>232</td>
<td>601</td>
<td>1.02 (0.92-1.12)</td>
<td>1.46</td>
</tr>
<tr>
<td>Whalley et al,(^{39}) 2004</td>
<td>17</td>
<td>240</td>
<td>1.01 (0.87-1.17)</td>
<td>0.68</td>
</tr>
<tr>
<td>Overall; ( I^2 = 7.6% ), ( P = .37 )</td>
<td>8565</td>
<td>67 434</td>
<td>0.98 (0.96-0.99)</td>
<td>100</td>
</tr>
</tbody>
</table>

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.
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 depression46 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 fronto-subcortical neural circuits.50-53 Epidemiologic evidence has shown that an early age at menopause is an independent risk factor for cardiovascular disease44; 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 $\alpha$ and $\beta$,44,49 as well as antiatherogenic actions including enhancement of endothelial function, blockage of smooth muscle cell proliferation, and inhibition of inflammation.56

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 depression59-61 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.
32. Statacorp. *Stata Quick Reference and Index*. College Station, TX: Statacorp LP; 2009.


73. den Tonkelaar I. Validity and reproducibility of self-reported age at menopause in women participating in the DOM-project. *Maturitas*. 1997;27(2):117-123.
