Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods 1. Study protocol

Professor Eleni Th. Petridou from the Department of Hygiene, Epidemiology and Medical Statistics, Medical School, National and Kapodistrian University of Athens, Greece has invited two former graduates (both magna cum laudae) of the same School, notably Alkistis Skalkidou, Associate Clinical Professor of Obstetrics and Gynecology, Uppsala University, Sweden and Stella S. Daskalopoulou, Assistant Professor of Internal Medicine, McGill University, Canada to collaborate in order to advance a review project entitled "age and menopause and postmenopausal depression" she had assigned in the context of graduate training in Epidemiology to Marios K. Georgakis. Prof Petridou is expected to recruit a team of younger colleagues among students who excel in their medical studies and PhD candidates as well as to guarantee the harmonization of their training in order to participate in the proposed systematic review and meta- analysis.

Title

Age at menopause and duration of reproductive period in association with depression in postmenopausal women: a systematic review and meta-analysis.

Background

Estrogens are known for their neuroprotective and anti-depressive effects; yet, the association of indices of reduced endogenous estrogens, notably early age at menopause and shorter duration of the reproductive period (defined as age at natural menopause minus age at menarche) with the risk for postmenopausal depression has not been systematically explored. This is in contrast with the on-going debate regarding the overall health benefits of Hormone Therapy (HT).

Aim

To explore the possible association between age at natural menopause or duration of the reproductive period, as indices of lifetime exposure to endogenous estrogens with the risk of depression in postmenopausal women.

Research plan

List of variables of interest:

i. Exposure variables:

Age at menopause: defined preferably as one year following last menstruation or as age at the last menstruation

Reproductive period duration: defined as age at menopause minus age at menarche

ii. Outcome variable*:*

Depression: defined by clinically diagnosed criteria or validated questionnaires in the context of research projects.

Systematic review methodology

Search strategy and selection of studies

A systematic literature search of MEDLINE database using a pretested algorithm ((menopause OR menopausal OR climacteric OR perimenopause OR perimenopausal OR peri-menopause OR peri-menopausal OR postmenopause OR postmenopausal OR post-menopause OR post-menopausal OR ((reproductive) AND (period OR years OR lifetime OR life-time OR lifespan OR life-span OR span))) AND (dementia OR demented OR Alzheimer OR Alzheimer's OR MCI OR "mini mental" OR mmse OR cognitive OR cognition OR depressed OR depressive OR depression OR ((mood OR affective) AND (disorder OR disorders OR disturbance OR disturbances OR disease OR diseases))) NOT "animals"[MeSH Terms: noexp]) combining appropriate terms will be conducted. Search results (titles and abstracts) will be transferred to a processing electronic platform that will distribute them in pairs of reviewers who will work indepndently and blindly to each other. The platform is designed to secure blindness between reviewers.

The derived articles will be firstly blindly evaluated by the pairs of reviewers based on their title and abstract. For studies that cannot be evaluated by their title and abstract, the full-text will be searched. Articles will thereafter be characterized as follows:

1. "Eligible" will be case-control, cohort or cross-sectional studies providing an effect estimate (odds ratio, relative risk, hazard ratio, incidence rate ratio) for the association between age at menopause or duration of the reproductive period with depression in postmenopausal women with naturally occuring menopause. Eligible will be studies providing either continuous or categorical analysis. No language or publication year resrictions are set. Randomized clinical trials and intervention studies will be considered for eligiblity only if they provide depression measurements at the baseline before the intervention phase.

Exclusion criteria:

- Case series
- Case reports
- *In vitro* studies
- Animal studies
- Studies encompassing solely depressed or solely non-depressed women
- Studies assessing depression as a self-reported symptom
- Studies encompassing only women with artificial menopause. For studies including women with both naturally and artificially occurring menopause, the corresponding authors will be contacted aiming to receive effect estimates referring solely to the population with natural menopausal transition. If this will not be possible the study will be considered for eligibility with the published results.
- Studies encompassing only perimenopausal women
- Studies including only breast cancer survivors with medically induced menopause
- Studies with a population of subjects with severe preexisting psychiatric disorders or diseases that predispose or are closely associated with depression.

2. "Letters" will be characterized all studies not directly fulfilling the eligibility criteria and not excluded based on the exclusion criteria but with possibly available data for testing our hypothesis. In particular, "Letters" will be all studies providing assessment of depression via clinical dagnostic criteria or questionnaires with validated cut-off points, as well as clear evidence that exposure variables have been measured. Authors of these articles will be later contacted to provide us with results of a statistical analysis between the exposure and outcome variable.

3. "Reviews": already published systematic reviews, meta-analyses, letters to the editor,

comments and review articles referring to the above hypothesis. The reference lists of these article wll be hand searched for tentative identification of eligble articles following a ”snowball procedure”.

4. “Irrelevant” will be all articles that based on their title, abstract or full-text are not eligible for our meta-analysis and cannot be characterized as letters or reviews. Articles that will be excluded after their full-text has been evaluated will be characterized as ”Excluded with reasons”.

5. “Potentially relevant”: Articles characterized as “potentiall relevant” will be those that the reviewer cannot classify in any of the aforementioned categories. This category contains two major types of articles. Firstly, articles that the full-text is not available for evaluation (for management of these articles see below); secondly, articles with available full-text that the reviewer cannot classify (see below).

Full-text search: Articles, to the full-text of which, the reviewers have no access will be recorded in an Excel file by PMID and access will be sought by the collaborating institutes abroad or ordered.

Consensus between reviewers: After selection of studies has been completed, consensus will be reached between pairs of reviewers. The electronic platform provides the differences between reviewers only after the selection has been completed. During this process articles that have been characterized by either reviewer as “potentially relevant” will also be re-evaluated. In case of persisting different points of view, consensus will be sought in the whole team.

Snowball procedure: After completing selection of studies derived via MEDLINE, the reference lists of all studies characterized as “Eligible” and “Reviews” will be hand searched for potential eligible articles. In an Excel file, all articles searched during snowball will be characterized similarly to the articles found through the platform, as aforementioned.

Contact of authors

E-mails will be sent to all studies characterized as “letters”. The authors of these articles will be asked to provide results of statistical analysis for variables of interest or raw data. Electronic addresses will be searched via Google and PubMed, and in cases of non-respondance a reminder will be sent.

E-mails may also be sent to “eligible” studies for clarifications regarding their published data or additional results.

Data extraction

Two pairs of researchers will blindly extract data using a pre-designed Excel file working independently and blindly to each other. The following data will be extracted:

a) General information: year, author, title, journal, region of origin, and study period
b) Study characteristics: design, duration of follow-up, inclusion and exclusion criteria of the participants
c) Characteristics of the participants: 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
d) Statistical analysis: adjusting factors, reference category, type of the effect estimate and

results (effect size and confidence intervals).

Effect estimates derived from analyses with the highest level of adjustment will be preferred.

Consensus disagreements during the data extraction procedure will be resolved by consensus between abstractors. Insisting differences will be resolved in consensus of the whole team.

Overlapping populations: If multiple publications using the same cohort are identified, the most recent or complete publication will be used for data extraction but information from all relevant publications will be used if required. Studies excluded because of overlapping populations will be thereafter characterized as "excluded due to overlap"

Assessment of quality of studies

The quality of the included studies will be assessed using the Newcastle-Ottawa Scale (NOS) for Systematic Reviews by 2 pairs of reviewers independently and blindly to each other. For comparability questions, age is set *a priori* as the most important matching or adjustment factor, while the cut-off point for informative follow-up time is set at 1 year, with a completeness percentage of more than 80%. In case of cross-sectional studies, the NOS subscale for longitudinal cohort studies will be used after excluding questions 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"). Disagreements in assessment of quality procedure will be resolved by consensus.

Publication bias

Publication bias will be assessed by Egger's test in analyses including at least 10 study arms and statistical significance level is set at $P < .10$.

Statistical analysis

Using the STATA Software a meta-analysis will be carried out preferring the effect estimates of the highest level of adjustment provided by eligible studies or after contact with authors in order to calculate the effect of age at menopause and reproductive period duration on risk of depression in postmenopausal women.

In case of raw data provided after contact with authors, multivariate logistic regression models will be designed and the retrieved effect estimates will be synthesized in the meta-analysis.

Ideally, if provided by the published studies, both continuous and categorical analyses will be conducted for the exposure variables of the respective data are available. The increments and the respective categories will be determined by the statistical analysis performed by the eligible studies.

The effect estimates along with the 95% confidence intervals of the different studies will be combined using fixed-effect (Mantel-Haenszel) or random-effect (DerSimonian–Laird) models. Between-study heterogeneity will be measured using Cochran Q statistic and by estimating I^2. Significance level is set at $P < .10$ and in case of significant heterogeneity between studies, a random-effect model will be applied, irrespective of the I^2 estimation. For the overall effect statistical significance level is set at $P < .05$. Forest plots will be designed for graphical representation.

The role of potential confounders, including history of premenopausal depression, HT use, cognitive impairment, age range and race will be subsequently explored via sensitivity, subgroup and meta-regression analyses. However, whether these analyses will be possible to be carried out will be determined based on the amount of available data. Additional subgroup analyses will be conducted by age group and race if this will be possible using available data.

Data management

All relevant to the study data (full-texts of relevant articles, algorithm, protocol, manuscript, figures, tables, analyses) will be archived in shared folders. Access will be granted only to participants of the study.

Team meetings

Progress and potential methodological issues will be discussed in team meetings scheduled for specific dates. In each meeting all members will present their progress regarding the tasks distributed during the previous meeting. New tasks and deadlines will be determined and the date of the next meeting will be scheduled. Minutes of all meetings will be recorded and stored.

Date: April 5th, 2014.

On behalf of the 3 collaborating Institutions

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eMethods 2. Supplementary Material on Methodology and Results

Search strategy

Algorithm used for search of PubMed database:
(menopause OR menopausal OR climacteric OR perimenopause OR perimenopausal OR peri-menopause OR peri-menopausal OR postmenopause OR postmenopausal OR post-menopause OR post-menopausal OR ((reproductive) AND (period OR years OR lifetime OR life-time OR lifespan OR life-span OR span)))
AND
(dementia OR demented OR Alzheimer OR Alzheimer's OR MCI OR "mini mental" OR mmse OR cognitive OR cognition OR depressed OR depressive OR depression OR ((mood OR affective) AND (disorder OR disorders OR disturbance OR disturbances OR disease OR diseases)))
NOT "animals"[MeSH Terms: noexp]
End of search: 1/1/2015
12,323 results

Results of search strategy

Figure 1 depicts the flow chart of the study selection process. The database search yielded 12,323 records. The full-texts of 266 articles were evaluated for eligibility, as well as 13 articles identified through the "snowball procedure"[1-13]. Out of the total of 279 articles, 133 were excluded with reasons[12,14-145] (eTable 2). Six studies were considered eligible[13,146-150], while 140 articles required further clarifications, and their authors were contacted[1-11,151-279].

Contact of authors

The left panel of the flow chart (Figure 1) presents the successive steps followed regarding author's contact. No e-mail or other contact details could be retrieved for 2 studies[151,187], while the study by Perquier *et al*[274] was excluded due to overlap with an already eligible study[148]. Letters were sent to the remaining 137 studies which provided indication of assessment of age at menopause and/or reproductive period, as well as depression. As some studies had the same corresponding author, 100 letters in total were sent.

Out of those, we received 34 replies (corresponding to 45 published studies[2,8,153,160,162,164,173,174,177,184,188,190,191,194,200,208,212,215-217,222,224-228,231,232,236,237,239,247,251-254,256,258-261,271,275,277,279]), while 66 letters (corresponding to 92 published studies[1,3-7,9-11,152,154-159,161,163,165-172,175,176,178-183,185,186,189,192,193,195-199,201-207,209-211,213,214,218-221,223,229,230,233-235,238,240-246,248-250,255,257,262-270,272,273,276,278]) were not answered.

Of the 34 authors who replied, 25 (corresponding to 35 studies[2,153,160,162,164,173,174,177,188,190,191,194,208,212,215-217,222,225-228,232,236,239,247,253,254,256,258-261,275,277]) could not provide the requested analyses for several reasons. These included retirement of the principal investigator, lack of access to the data, no further available data, as well as inappropriate data for our analyses. Requested data were provided by 9 authors (corresponding to 10 studies[8,184,200,224,231,237,251,252,271,279]). Specifically, 5 authors (corresponding to 6 studies[8,224,231,251,252,271]) provided the results of the requested analyses, while 4 provided raw data of the requested variables[184,200,237,279]. The study by van Die *et al*[200], was eventually excluded after the raw data were received as no postmenopausal women had a normal Hamilton Depression Rating Scale scoring (lower than 7). In addition, in case of 2 studies the authors clarified that they referred to the same population[224,231]. Given that the sample size was the same, the more recent study by Lambrinoudaki *et al*[224] was deemed eligible, whereas the previous study by Zervas *et al*[231] was excluded.

Eligible articles

Six studies were eligible based solely on the information provided in the original article[13,146-150]. Out of those, 3 presented the association between age at menopause or reproductive period and risk of depression as continuous variable[148-150] and the remaining 3 studies provided a respective categorical analysis for age at menopause[13,146,147]. We contacted the authors of the latter studies requesting an analysis of age at menopause as a continuous variable, but we received either no or a negative reply. Therefore, we converted categorical analyses to continuous using the generalized least squares methods[280] in studies providing the number of cases and controls for at least 3 age at menopause categories[13,146], while an alternative analysis was also performed treating age at menopause as a categorical variable[13,146,147,279].

After the additional data/analyses were sent by the contacted authors, 14 studies in total were deemed eligible for inclusion in the meta-analysis of age at menopause[8,13,146-150,184,224,237,251,252,271,279]: 13 of them were included in the analysis for age at menopause as a continuous variable[8,13,146,148-150,184,224,237,251,252,271,279], wherea 4 of them in the respective categorical analysis[13,146,147,279].

Sensitivity analyses were performed, retaining studies (i) controlling for the presence of premenopausal depression, (ii) controlling for HT use, (iii) examining the association with severe depression, as defined by self-reported instruments and (iv) defining age at menopause as 1 year following the last menstruation. In the first sensitivity analysis 3 studies were included that controlled for the presence of past depression. The study by Perquier et al[148] provided separate sub-analysis among women with no history of past psychological disorders and Ryan et al[150] adjusted for presence of past depression. In addition, Lambrinoudaki et al[224] following personal communication confirmed that no women in the study had history of premenopausal depression. In the sub-analysis for HT use, 7 studies that provided adjusted effect estimates for HT use[148,150,184,224,251,252,279] were included along with the study by Jasienska et al.[8] that included only non-HT users. The third sensitivity analysis was restricted to studies examining severe depression, as defined by the respective cut-off points in depression questionnaires, namely Center for Epidemiological Studies- Depression scale score $\geq$23[148,150] and 15-item Geriatric Depression Scale score $\geq$11[271]. Lastly, the 7 studies defining age at menopause as 1 year after the final menstrual period[13,146,150,224,251,252,271] and not as age at the last menstruation were included in a sensitivity analysis. Regarding duration of reproductive period, only 1 study mentioned in the published manuscript the effect estimate for the association with depression[150], while 2 studies provided the results for this analysis after our request[148,251]. Lastly, Whalley *et al*[184] and Bove *et al*[279] provided raw data including both age at menopause and age at menarche to be included in the respective analyses for the impact of reproductive period. Reproductive period was only treated as a continuous variable.

Overlap between studies

Besides the aforementioned overlap of the studies of Zervas *et al*[231] and Lambrinoudaki *et al*[224], no other overlapping population was found among the included studies. Of note, both the studies by Unsal *et al* (2008 and 2011)[13,146] were conducted in the same region (Sivrihisar and Eskisehir, Turkey) but it is explicitly stated that the participants were recruited during different time periods (2007 and 2009, respectively).

Statistical analysis of primary data

The study by Whalley *et al*[184] is a birth cohort including women born in 1936. The authors provided an Excel file including: date of birth, age at menopause (years), use of hormone therapy (HT), age at menarche (years), weight (kg) and height (cm) allowing calculation of the body mass index (BMI), scoring of the depression subscale of Hospital Anxiety and Depression Scale (HADS-D), smoking status (never, past smoker, current smoker) and marital status (single/never married, married/co-habit, widowed, divorced/separated). Thereafter, multivariate logistic regression models were developed with depression (HADS-D ≥8 vs. HADS-D<8) as the dependent variable and use of HT (yes vs. no), BMI (categorical; <25, 25-29.9, 30-34.9, ≥35 kg/m^2), smoking status (ever vs. never) and marital status (married vs. non-married) as independent variables. Age at menopause (continuous; 1-year increment) and duration of reproductive period (calculated as age at menopause minus age at menarche; continuous; 1-year increment) were subsequently included separately in the models and adjusted odds ratios (OR) along with their 95% confidence intervals (95% CI) were derived. The 1-year effects of age at menopause and reproductive period were converted to 2-year effects and were included in the meta-analyses.

The authors of the study by Erez *et al*[237] provided raw data, including age at menopause (years), Zung Self-reported Depression Scale (ZSDS) scoring, age (years), educational level (≥12 years vs. <12 years), smoking (yes, no), BMI (kg/m^2) and employment status (employed, non-employed); multivariate logistic regression analysis was, thereafter, conducted including depression (ZSDS ≥50 vs. ZSDS<50) as dependent variable and age (continuous; 1-year increment), education ((≥12 years vs. <12 years), BMI (ordered; <25, 25-29.9, 30-34.9, ≥35 kg/m^2), smoking (yes vs. no), employment status (employed vs. non-employed) and age at menopause (continuous; 1-year increment). The adjusted OR calculated for increasing age at menopause by 1-year was converted to a 2-year effect and was also included in the meta-analysis. Due to the low number of participants in both of these studies it was not possible to calculate ORs for age at menopause as a dichotomous variable (≥40 years vs. <40 years) and depression for inclusion in the categorical analyses.

The study by Bove *et al*[279] refers to 2 distinct populations of 2 cohort studies, namely the Memory and Aging Project (MAP)[281]and the Religious Orders Study (ROS)[282]. Following communication, the authors provided raw data pertaining to these 2 studies, as well as those for a third cohort which is conducted under the responsibility of the same centre, namely the Minority Aging Research Study (MARS)[283] all including: marital status (ever married, non-married), current marital status (married, separated, divorced, widowed), ever use of HT (yes, suspect, no), type of HT (oral, injection, vaginal cream or suppository, skin patch), age at first use of HT (years), age at last use of HT (years), current use of HT (yes, no), age at menarche (years), age at menopause (years), type of menopause (natural, surgical), participating study (MAP, ROS, MARS), clinical diagnosis of major depression at baseline and at last visit (highly probable, probable, possible, no depression), clinical diagnosis of dementia at baseline and last visit (no cognitive impairment, mild cognitive impairment, mild cognitive impairment and other diagnosis, Alzheimer's disease, Alzheimer's disease and other dementia diagnosis, other dementia diagnosis), age at baseline, 10-item Center for Epidemiological Studies Depression scale scoring at last visit (0-10), global cognitive score at baseline and last visit, race (White, Afroamerican, Native American/Indian, Asian/Pacific Island), smoking status (never, former smoker, current smoker) and BMI at baseline and last visit (kg/m^2). We performed a cross-sectional analysis using only baseline data minding homogeneity with the remaining included studies. Therefore, multivariate logistic regression models were run including only women with natural menopause and depression (bivariate; highly probable or probable or possible vs. no depression) as dependent variable. Independent variables were: age at baseline (continuous; 1-year increment), ever use of HT (yes or suspect vs. never), marital status (ever married vs. never married), cognitive status

(ordered; no cognitive impairment, mild cognitive impairment, dementia), BMI [categorical; <18.5, 18.5-24.9 (reference), 25-29.9, 30-34.9, ≥35 kg/m^2], smoking (ever vs. never) and race (white vs. others). Age at menopause as continuous (1-year increment) or categorical variable (≥40 years vs. <40 years) and reproductive period duration (continuous; 1-year increment) were subsequently alternatively introduced in the aforementioned model. The calculated OR and 95%CI for age at menopause as categorical variable was included in the respective meta-analysis, while ORs and 95%CI calculated for increasing age at menopause and increasing reproductive period by 1-year were converted to 2-year effects in order to be included in the respective continuous analyses. Statistical analysis of primary data was carried out using SAS statistical software (SAS V9.2, SAS Institute Inc., Cary, NC, USA).

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eTable 1. Meta-analysis of Observational Studies in Epidemiology (MOOSE) Guidelines Checklist for Authors

Criteria		Brief description of how the criteria were handled in the meta-analysis
Reporting of background should include		
√	Problem definition	Estrogens are known to exert neuroprotective and anti-depressive effects, but associations between indexes of exposure to endogenous estrogens and risk for subsequent depression have not been consistently explored.
√	Hypothesis statement	Age at menopause and duration of reproductive period may be associated with postmenopausal depression
√	Description of study outcomes	Depression
√	Type of exposure or intervention used	Age at menopause/ Reproductive period
√	Type of study designs used	Case-control/cohort/cross-sectional
√	Study population	Postmenopausal women
Reporting of search strategy should include		
√	Qualifications of searchers (eg, librarians and investigators)	The credentials and affiliations of the investigators are provided in the author list.
√	Search strategy, including time period included in the synthesis and keywords	PubMed, up to January 1st, 2015
√	Effort to include all available studies, including contact with authors	If the required data for the meta-analysis were not readily available in the published article, crude effect estimates and 95% CIs were calculated by means of 2x2 tables presented in the articles. Authors were also contacted in cases the studies did not meet the inclusion criteria, but provided measures for age at menopause and/or reproductive period or indications that they were evaluated or measures that would allow their quantification, as well as a depression assessment through diagnostic criteria or validated instruments.
√	Databases and registries searched	PubMed
√	Search software used, name and version, including special features used (eg, explosion)	We did not employ special search software.

√	Use of hand searching (eg, reference lists of obtained articles)	Reference lists of relevant reviews and eligible articles were systematically searched for relevant articles in a “snowball” procedure.
√	List of citations located and those excluded, including justification	Details of the literature search process and excluded studies are outlined in the flow chart (Figure 1) and in Supplementary Table 1. Full reference list of all eligible, potentially eligible and excluded articles is also provided as online supplementary material.
√	Method of addressing articles published in languages other than English	We placed no restrictions on language.
√	Method of handling abstracts and unpublished studies	The search of potentially relevant items in the reference lists was not restricted upon full-text articles, but also conference abstracts and unpublished studies were evaluated during the “snowball” procedure.
√	Description of any contact with authors	Authors were also contacted in cases the studies did not meet the inclusion criteria, but provided measures for age at menopause and/or reproductive period or indications that they were evaluated or measures that would allow their quantification, as well as a depression assessment through diagnostic criteria or validated instruments. The e-mail address of the corresponding author or co-authors was used, and reminders were sent 1 month after the initial contact in case of non-respondance.
Reporting of methods should include		
√	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	The inclusion criteria are presented in the “Search strategy and eligibility criteria” section.
√	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	The list of extracted data from each study pertained to the population characteristics, study design, exposure, outcome, and possible effect modifiers of the association; the detailed list is provided in the “Data extraction and assessment of quality of included studies” section.
√	Documentation of how data were classified and coded (eg, multiple raters, blinding, and inrerrater reliability)	Data were independently extracted and analyzed by independent reviewers working in pairs and blindly to each other and final decision was reached by consensus.
√	Assessment of confounding (eg comparability of cases and controls in studies where appropriate)	Table 1 present the adjustment factors as well as matching factors for each study.
√	Assessment of study quality, including blinding of quality assessors; stratification or	Study quality was assessed through the Newcastle-Ottawa scale.

	regression on possible predictors of study results	
√	Assessment of heterogeneity	Heterogeneity of the studies was assessed using Cochrane Q of heterogeneity and I^2 statistic.
√	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	Description of methods of meta-analyses, sensitivity analyses and assessment of publication bias are detailed in the "Statistical analysis" section.
√	Provision of appropriate tables and graphics	One main table and two supplementary tables are provided. Two forest plots appear in the main text and five supplementary graphics are provided in the Supplementary Figures.
Reporting of results should include		
√	Graph summarizing individual study estimates and overall estimate	Figures 2-3; eFigures 1-5
√	Table giving descriptive information for each study included	Table 1
√	Results of sensitivity testing (eg, subgroup analysis)	eFigures 1-4
√	Indication of statistical uncertainty of findings	95% confidence intervals were presented with all summary effect estimates.
Reporting of discussion should include		
√	Quantitative assessment of bias (eg, publication bias)	Results, "Publication bias" section.
√	Justification for exclusion (eg, exclusion of non-English-language citations)	No exclusion regarding language was performed.
√	Assessment of quality of included studies	The shortcomings of the individual studies reflected upon their quality ratings are discussed in a detailed paragraph.
Reporting of conclusions should include		
√	Consideration of alternative explanations for observed results	The role of premenopausal depression, as well as cognitive and cardiovascular disorders were alternatively considered in

		the Discussion.
√	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	In the Discussion the need for accumulation of further data from non-western communities in order to guarantee generalizability of the findings has been stated.
√	Guidelines for future research	The need for large prospective studies, controlling for potential confounders and assessing depression via psychiatric evaluation was highlighted in the conclusion.
√	Disclosure of funding source	Disclosed in the relevant section.

eTable 2. Excluded Studies and Reasons for Exclusion

Ref.	First Author, Year	Journal	Reason(s) for exclusion
[14]	Thomson J et al., 1977	British Medical Journal	Age at menopause was not evaluated
[15]	Wiklund et al. 1992	Maturitas	A questionnaire with no cut-off point for depression was used
[16]	Holte, 1992	Maturitas	A questionnaire with no cut-off point for depression was used
[17]	Ballinger et al., 1987	Maturitas	A questionnaire with no cut-off point for depression was used
[18]	McKinley et al., 1987	America Journal of Epidemiology	Depressive symptoms were not assessed
[19]	Hallstrom et al., 1985	Acta Obstetricia Gynecologica Scandinavica	Age at menopause was not evaluated
[20]	Abe et al., 1985	Tohoku Journal of Experimental Medicine	A questionnaire with no cut-off point for depression was used
[21]	McKinley et al., 1974	Brit. J. prev. soc. Med.	Depression was assessed only as a self-reported symptom
[22]	Burger et al., 1984	Maturitas	Depression was assessed only as a self-reported symptom
[23]	Hamara et al., 1984	Maturitas	Depression was assessed only as a self-reported symptom
[24]	Greene, 1983	Maturitas	Depression was assessed only as a self-reported symptom
[25]	Ramoso-Jalbuena, 1994	Maturitas	Depression was assessed only as a self-reported symptom
[26]	Canney et al., 1999	Clinical Oncology	All participants were breast cancer survivors
[27]	Pansini et al., 1994	European Journal of Obstetrics and Gynecology	Depression was assessed only as a self-reported

		and Reproductive Biology	symptom
[28]	Arden et al, 1994	Lupus	Depression was assessed only as a self-reported symptom
[29]	Von Muhlen et al., 1995	Maturitas	Depression was assessed only as a self-reported symptom
[30]	Cramer et al., 1996	Maturitas	No evaluation of postmenopausal depression
[31]	Huerta et al., 1995	Psychoneuroendocrinology	Age at menopause was not assessed
[32]	Egarter et al., 1996	Maturitas	Age at menopause was not assessed
[33]	Saletu et al., 1996	Maturitas	Age at menopause was not assessed
[34]	Szklo et al., 1996	American Journal of Epidemiology	A questionnaire with no cut-off point for depression was used
[35]	Irvin et al., 1996	Journal of Psychosomatic Obstetrics and Gynecology	A questionnaire with no cut-off point for depression was used
[36]	Greendale et al., 1998	Obstetrics and Gynecology	Depression was assessed only as a self-reported symptom
[37]	Wolf et al., 1999	Psychoneuroendocrinology	A questionnaire with no cut-off point for depression was used
[38]	Reginster et al., 1999	Maturitas	A questionnaire with no cut-off point for depression was used
[39]	Girdler et al., 1999	Journal of women's health and gender-based medicine	Women with depression were excluded
[40]	Fitzpatrick et al., 2000	Journal of women's health and gender-based medicine	A questionnaire with no cut-off point for depression was used
[41]	Strickler et al, 2000	Obstetrics & Gynecology	Depression was assessed only as a self-reported symptom
[42]	Verghese et al., 2000	Neurology	Only women with surgical

			menopause participated
[43]	Albertazzi et al., 2000	Maturitas	Women with depression were excluded
[44]	Liao et al., 2000	J Psychosom Obstet Cyneco	Only women with premature menopause participated
[45]	Koike et al., 2004	Clin Neuropharmacol	Only women with depression participated
[46]	Conde et al., 2006	Gynecological Endocrinology	A questionnaire with no cut-off point for depression was used
[47]	Wegesin et al., 2007	Aging, Neuropsychology, and Cognition	Only women without depression participated
[48]	Yao et al., 2008	Maturitas	Only women with depressive symptoms participated
[49]	Rohl et al., 2008	American Journal of Obstetrics and Gynecology	Only women with surgical menopause participated
[50]	Sadreddini et al., 2008	European Journal of Internal Medicine	Age at menopause was not evaluated
[51]	Pien et al., 2008	Sleep	Only perimenopausal women participated
[52]	Marinho et al., 2008	Maturitas	Only women without depression participated at baseline
[53]	Spetz et al., 2009	Menopause	Depression was assessed only as a self-reported symptom
[54]	Hachul et al., 2008	International Journal of Gynecology and Obstetrics	Depression was assessed only as a self-reported symptom
[55]	Martinez-Perez et al., 2009	Maturitas	Depression was assessed only as a self-reported symptom
[56]	Bayer et al., 2009	Hormones and Behavior	A questionnaire with no cut-off point for depression was used
[57]	Kapur et al., 2009	Menopause: The Journal of The North American Menopause Society	Depression was assessed only as a self-reported symptom
[58]	Lucas et al., 2009	American Journal of	All women had

		Clinical Nutrition	psychological distress and those with severe depression were excluded
[59]	Ishiwata et al., 2009	Menopause	A questionnaire with no cut-off point for depression was used
[60]	Pamuk et al., 2009	Clin Rheumatol	Only women with rheumatoid arthritis and fibromyalgia participated
[61]	Nicklas et al., 2009	American Journal of Clinical Nutrition	Women with depression were excluded
[62]	Carson et al., 2009	Support Care Cancer	All participants were breast cancer survivors
[63]	Woods et al., 2009	Menopause	Age at menopause was not evaluated
[64]	Hachul et al., 2009	European Journal of Obstetrics and Gynecology and Reproductive Biology	Depression was assessed only as a self-reported symptom
[65]	Iglesias et al., 2009	Actas Espanolas de Psiquiatria	Only women with depression participated
[66]	Dorigochoo et al., 2010	Breast Cancer Res Treat.	All participants were breast cancer survivors
[67]	Pae et la., 2009	Psychiatry and Clinical Neurosciences	Only women with depression participated
[68]	Maki et al., 2009	Menopause	Women with depression were excluded
[69]	Verit et al., 2009	Maturitas	No woman had depression
[70]	Utian et al., 2009	Maturitas	A questionnaire with no cut-off point for depression was used
[71]	Yao et al., 2009	Journal of Cerebral Blood Flow and Metabolism	Only women with depression participated
[72]	Schaafsma et al., 2010	Climacteric	A questionnaire with no cut-off point for depression was used
[73]	Resnick et al., 2009	The Journal of Clinical Endocrinology and Metabolism	No woman had depression
[74]	Bachmann et al., 2010	Climacteric	Depression was assessed only as a self-reported

			symptom
[75]	Cubeddu et al., 2010	Menopause	A questionnaire with no cut-off point for depression was used
[76]	Woods et al., 2010	Journal of Women's Health	Depression was assessed only as a self-reported symptom
[77]	Abdul Rahman et al., 2010	Asia Pacific Family Medicine	Depression was assessed only as a self-reported symptom
[78]	Ojeda et al., 2011	Climacteric	Depression was assessed only as a self-reported symptom
[79]	Cabness, 2010	Social Work in Health Care	Only women with surgical menopause participated
[80]	Berent-Spillson et al., 2010	Menopause	Women with depression were excluded
[81]	Nisar et al., 2009	The Journal of the Pakistan Medical Association	Depression was assessed only as a self-reported symptom
[82]	Piauilino et al., 2010	Memory	Women with depression were excluded
[83]	Mitchell et al., 2010	Climacteric	Depression was assessed only as a self-reported symptom
[84]	Tom et al., 2010	Menopause	Depression was assessed only as a self-reported symptom
[85]	Alhola et al., 2010	The Journal of Obstetrics and Gynaecology Research	No woman had depression
[86]	Silverman et al., 2011	Psychoneuroendocrinology	Women with depression were excluded
[87]	Soares et al., 2010	Journal of Clinical Psychopharmacology	Only women with depression participated
[88]	Santos-Galdur et al., 2010	Brazilian Journal of Medical and Biological Research	Women with depression were excluded
[89]	Karsidag et al., 2010	Journal of Psychosomatic	No woman had depression

		Obstetrics and Gynecology	
[90]	Cambacciani et al., 2011	Climacteric	Depression was assessed only as a self-reported symptom
[91]	Schmidt et al., 2011	The Journal of Clinical Endocrinology and Metabolism	Only women with primary ovarian insufficiency participated
[92]	Garcia et al., 2010	Actas Espanolas de Psiquiatria	Only women with depression participated
[93]	Zhou et al., 2011	International Journal of Neuroscience	Age at menopause was not evaluated among women with natural menopause
[94]	Ogurlu et al., 2011	International Journal of Gynecology and Obstetrics	Depression was assessed only as a self-reported symptom
[95]	Epperson et al., 2011	Menopause	Women with depression were excluded
[96]	Woods et al., 2011	Menopause	Depression was assessed only as a self-reported symptom
[97]	Joffe et al.,	The Journal of Clinical Endocrinology and Metabolism	Only women with depression participated
[98]	Rahman et al., 2011	BMC Research Notes	Depression was assessed only as a self-reported symptom
[99]	Gorenstein et al, 2011	Archives of Women's Mental Health	Only women with surgical menopause participated
[100]	Delavar et al., 2011	Menopause	Depression was assessed only as a self-reported symptom
[101]	Deeks et al., 2011	Climacteric	Only women with premature menopause participated
[102]	Smith et al., 2011	The Journal of Clinical Endocrinology and Metabolism	No woman had depression
[103]	Cohen et al., 2011	Familial Cancer	Only women with surgical menopause participated

[104]	Hunter et al., 2011	An International Journal of Obstetrics and Gynaecology	Depression was assessed only as a self-reported symptom
[105]	Prakash et al., 1981	Indian Journal of Psychiatry	Depression was assessed only as a self-reported symptom
[106]	Tuomisto et al., 2012	Maturitas	Women with depression were excluded
[107]	Hammam et al., 2012	Maturitas	Depression was assessed only as a self-reported symptom
[108]	Sorpreso et al., 2012	Climacteric	Depression was assessed only as a self-reported symptom
[109]	Machado et al, 2012	Menopause	Depression was assessed only as a self-reported symptom
[110]	Stoeckl et al., 2012	Plos One	Depression was assessed only as a self-reported symptom
[111]	Veereus et al., 2012	BMC Research Notes	Depressive symptoms were not evaluated at baseline
[112]	Torres et al., 2012	Nutrition	A questionnaire with no cut-off point for depression was used
[113]	Canario et al., 2012	International Journal of Gynecology and Obstetrics	A questionnaire with no cut-off point for depression was used
[114]	Cheng et al., 2013	Climacteric	Women with depression were excluded
[115]	Taber et al., 2013	Climacteric	Depression was assessed only as a self-reported symptom
[116]	Legorreta et al., 2013	Climacteric	Depression was assessed only as a self-reported symptom
[117]	Moller et al., 2013	Gynecological Endocrinology	A questionnaire with no cut-off point for depression was used

[118]	Oge et al., 2013	Climacteric	A questionnaire with no cut-off point for depression was used
[119]	Davison et al., 2013	Menopause	No woman had depression at baseline
[120]	Taavoni et al., 2013	Complementary Therapies in Medicine	Depression was assessed only as a self-reported symptom
[121]	Marahatta,, 2012	Nepal Medical College Journal	Depression was assessed only as a self-reported symptom
[122]	Stockl et al., 2014	BMC Women's Health	Depression was assessed only as a self-reported symptom
[123]	Terauchi et al., 2014	Menopause	Age at menopause was not evaluated
[124]	Borker et al., 2013	Journal of Mid-life Health	Depression was assessed only as a self-reported symptom
[125]	Nitkowska et al, 2014	Neurologia i neurochirurgia polska	Depressive symptoms were not assessed in the control group of women
[126]	Sengul et al., 2014	Turkish Journal of Medical Science	Age at menopause was not evaluated
[127]	Mantani et al., 2010	Psychiatry and Clinical Neurosciences	Only women with surgical menopause participated
[128]	Weber et al., 2012	Zeitschrift für Psychosomatische Medizin und Psychotherapie	Age at menopause was not evaluated
[129]	Tanaka et al., 2011	Shinrigaku Kenkyu: The Japanese Journal of Psychology	Age at menopause was not evaluated
[130]	Andrade- Junior et al., 2010	Revista brasileira de ginecologia e obstetrícia	Age at menopause was not evaluated
[131]	Martins et al., 2009	Revista brasileira de ginecologia e obstetrícia	Depression was assessed only as a self-reported symptom
[132]	Polisseni et al., 2009	Revista brasileira de ginecologia e obstetrícia	Age at menopause was not evaluated
[133]	Lai et al., 2007	Zhonghua Fu Cha Ken	Only women with

		Zha Zi	depression participated
[134]	Benediktsdóttir et al., 2000	Laeknabladid	Age at menopause was not evaluated
[135]	Horna Lopez et al., 2006	Ginecología y obstetricia de México	Depression was assessed only as a self-reported symptom
[136]	Chang et al., 2003	Taehan Kanho Hakhoe chi	Age at menopause was not evaluated
[137]	Wenderlein, 1982	Geburtshilfe und Frauenheilkunde	Age at menopause was not evaluated
[138]	Pisani et al., 1998	Minerva Ginecologica	Age at menopause was not evaluated
[139]	Knol et al., 1986	Psychiatrische Praxis	Review
[140]	Trombelli et al.,1992	Minerva Stomatologica	Depression was assessed only as a self-reported symptom
[141]	Baum, 1990	Psychotherapie, Psychosomatik, medizinische Psychologie	Depression was assessed only as a self-reported symptom
[142]	McKinlay and McKinlay, 1989	Progress in Clinical and Biological Research	Age at menopause was not evaluated
[12]	Amaducci et al., 1986	Neurology	Women with depression were excluded
[143]	Gramegna et al., 1996	Revista Medica de Chile	Age at menopause was not evaluated
[144]	Blumel et al., 1992	Revista Medica de Chile	Age at menopause was not evaluated
[145]	Diez et al., 1995	Actas luso-espanolas de neurologia, psiquiatria y ciencias afines	Age at menopause was not evaluated

eTable 3. Major Adjusting Factors in the Individual Studies

Study	Age	Education	HT use	Oral contraceptives	Past depression	Smoking	Marital status	Parity/ Number of pregnancies	BMI/ Obesity	Physical activity	Financial income	CVD risk factors*	Diabetes mellitus	Employment	Cognition/ dementia	Race	CVD	Alcohol intake	Sleep duration/ Insomnia
Lambrinoudaki et al., 2015 [224]	X	X	X			X	X	X	X										
Tsiligiannii et al., 2014 [271]	X	X				X			X	X	X	X	X						
Bove et al, 2014 [279]	X		X			X	X		X						X	X			
Perquier et al, 2013 [148]	X	X	X	X		X	X		X	X			X				X	X	X
Toffol et al., 2013 [251]	X	X	X				X	X	X										
Baczyk et al., 2013 [252]	X	X	X			X	X		X										
Erez et al., 2012 [237]	X	X				X			X					X					
Unsal et al., 2011 [146]																			

Berecki-Gisolf et al., 2009 [149]	X	X				X	X		X		X								
*Ryan et al., 2008 [150]***	X	X	X	X	X		X								X			X	X
Unsal et al., 2008 [13]																			
Jasienka et al., 2005 [8]	X	X				X	X		X										
Whalley et al., 2004 [184]	X***		X			X	X		X										
Bezircioglu et al., 2004 [147]	X	X				X	X	X	X				X	X			X		

HT: Hormone Therapy, BMI: Body Mass Index, CVD: Cardiovascular disease

* CVD risk factors include hypertension, diabetes mellitus type 2 and hypercholesterolemia

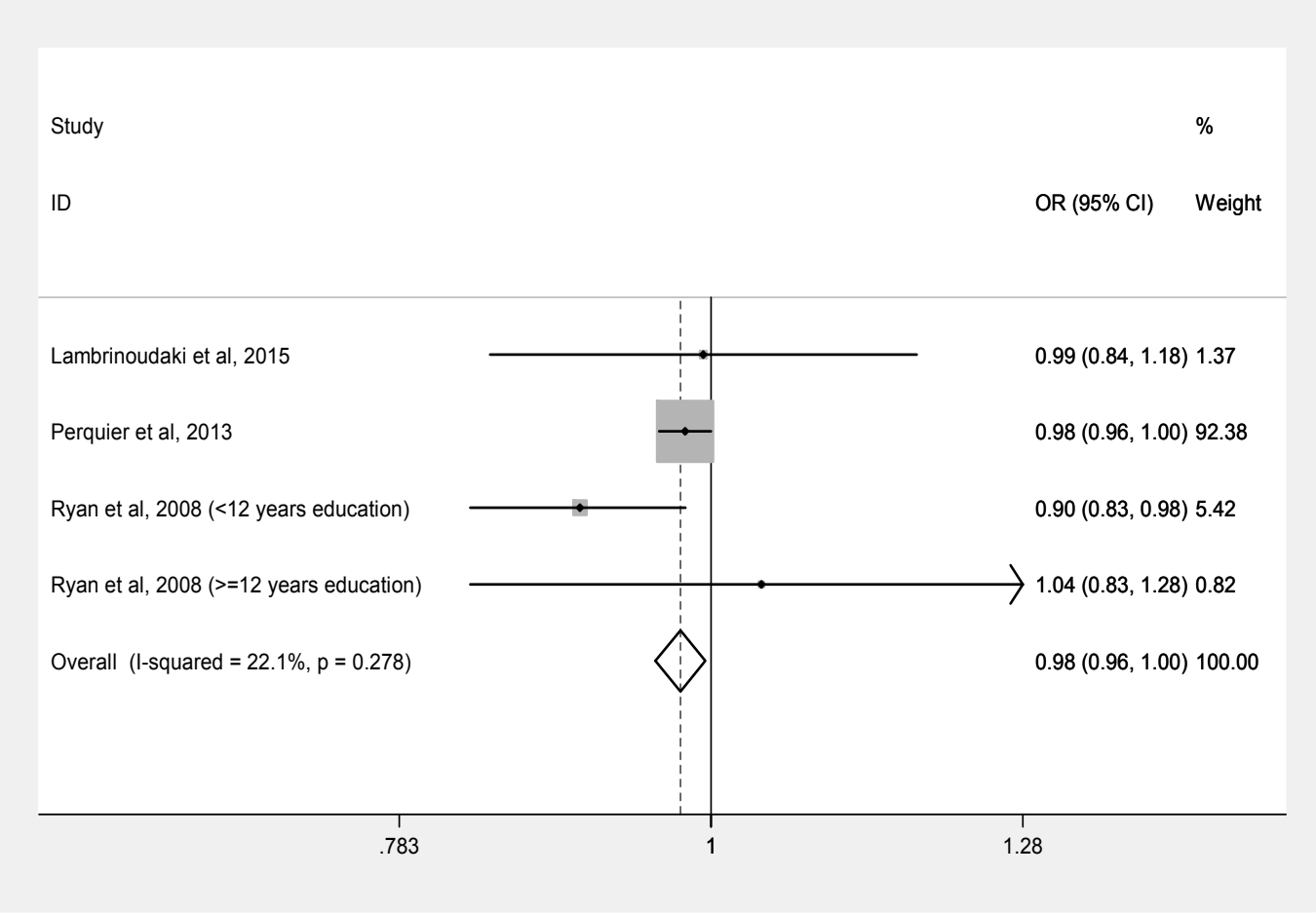
** The study by Ryan *et al.* [150] provided adjusted effect estimates only for the age at menopause analysis. The reproductive period duration analysis is unadjusted.

*** The study by Whalley *et al.* [184] is not directly adjusting for age, but it is a birth cohort, therefore all participants are of the same age.

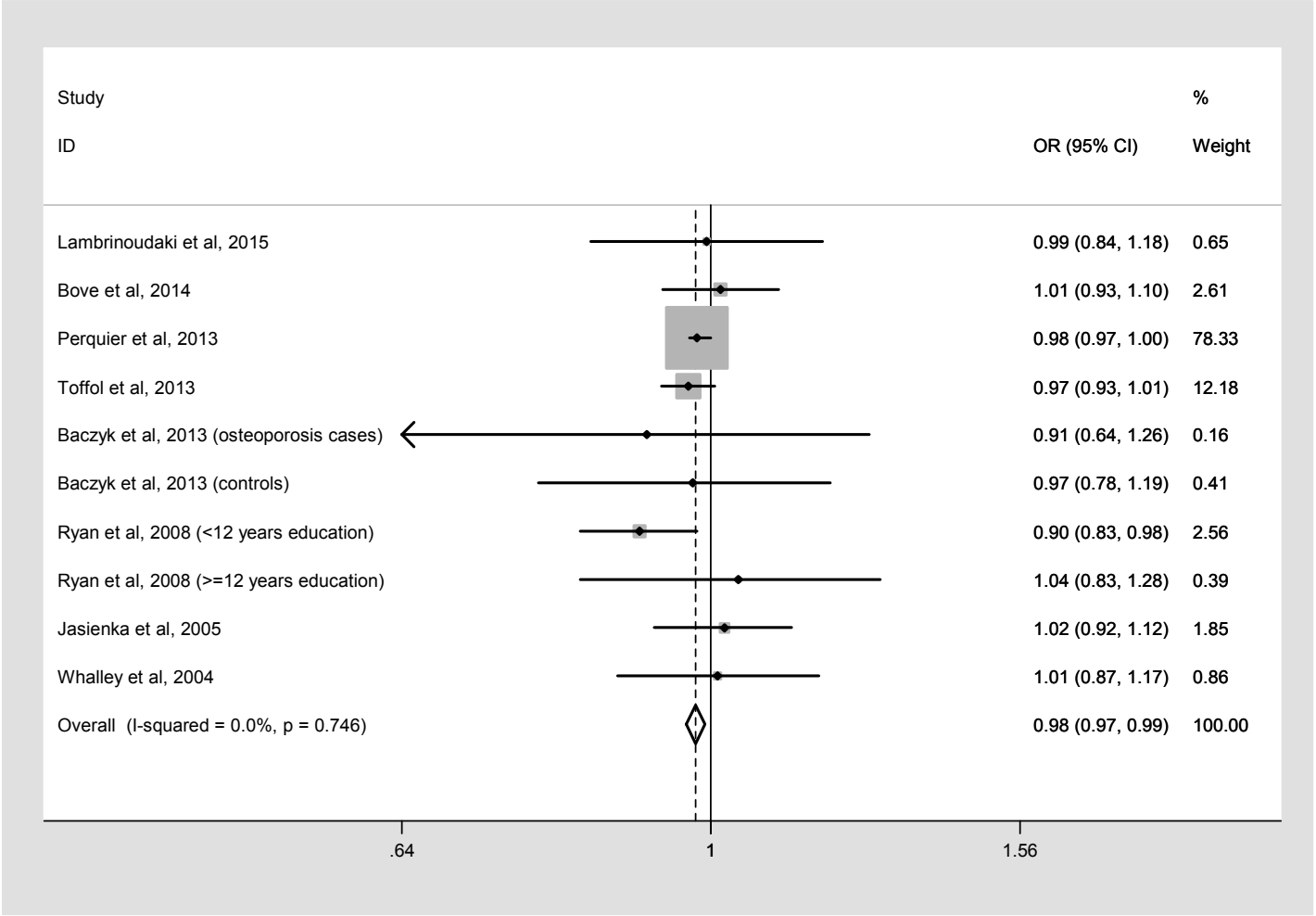
eTable 4. Evaluation of the Quality of the 14 Eligible Studies Based on the Newcastle-Ottawa Scale

	Selection			**Comparability**		**Outcome**	**Total**
Study	Representativeness of the Exposed Cohort	Selection of the Non-Exposed Cohort	Ascertainment of Exposure	On age	On other risk factors	Assessment of Outcome	
Lambrinoudaki et al, 2015 [224]	1	1	0	1	1	0	**4/6**
Tsiligianni et al, 2014 [271]	1	1	1	1	1	0	**5/6**
Bove et al, 2014 [279]	1	1	1	1	1	1	**6/6**
Perquier et al, 2013 [148]	1	1	0	1	1	0	**4/6**
Toffol et al, 2013 [251]	1	1	1	1	1	0	**5/6**
Baczyk et al, 2013 [252]	1	1	0	1	1	0	**4/6**
Erez et al, 2012 [237]	1	1	0	1	1	0	**4/6**
Unsal et al., 2011[146]	1	1	1	1	1	0	**5/6**
Berecki-Gisolf et al, 2009 [149]	1	1	0	1	1	0	**4/6**
Ryan et al, 2008 [150]	1	1	1	1	1	0	**5/6**
Unsal et al., 2008 [13]	1	1	1	1	1	0	**5/6**
Jasienska et al, 2005 [8]	1	1	1	1	1	0	**5/6**
Whalley et al, 2004 [184]	1	1	1	1	1	0	**5/6**
Bezircioglu et al, 2004 [147]	1	1	1	1	1	0	**5/6**

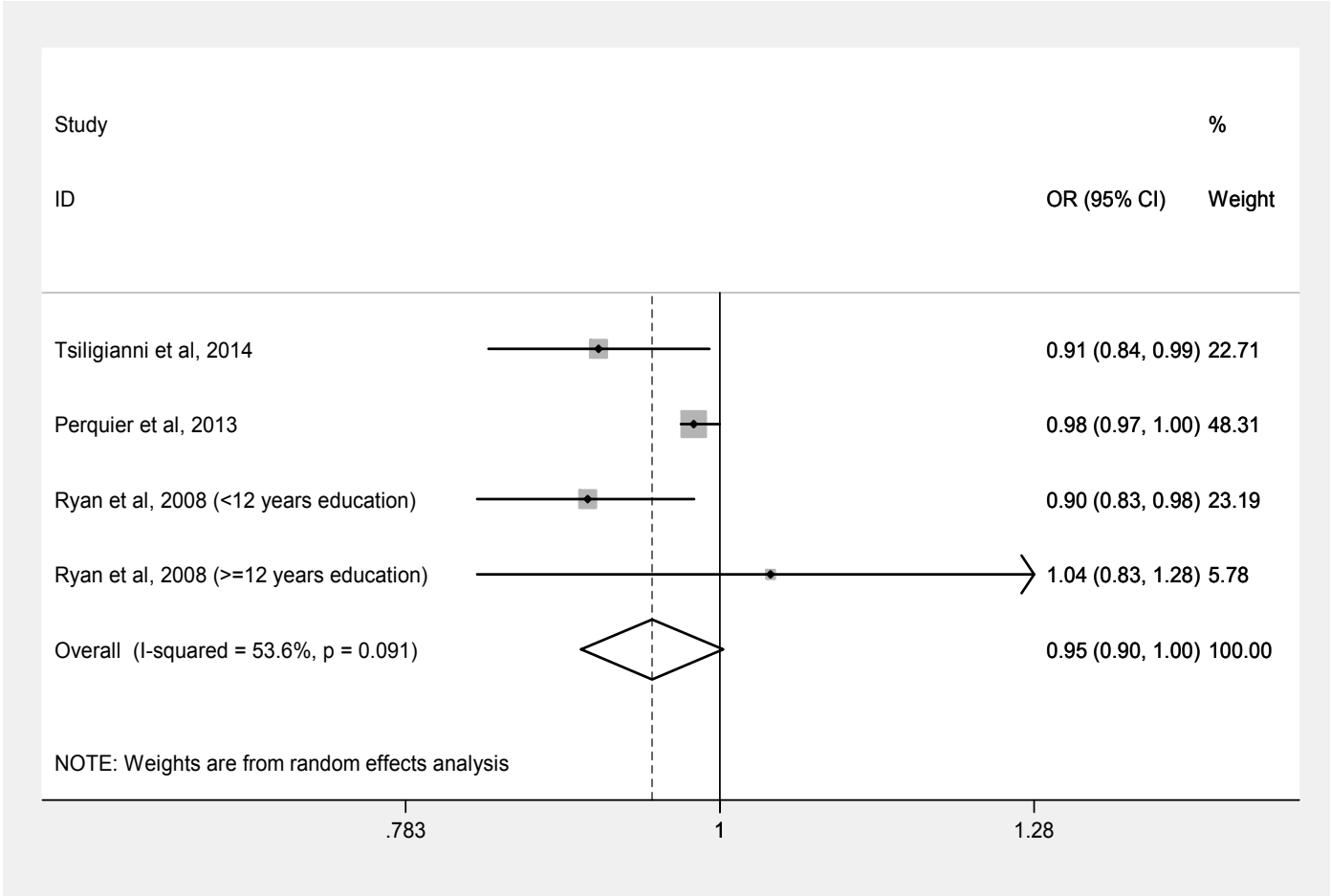
eFigure 1. Forest Plot Presenting the Association of Age at Menopause (2-Year Increment) With Depression in Postmenopausal Women
Sensitivity Analysis of Studies Controlling for the Presence of Past Depression (*P* = .02).



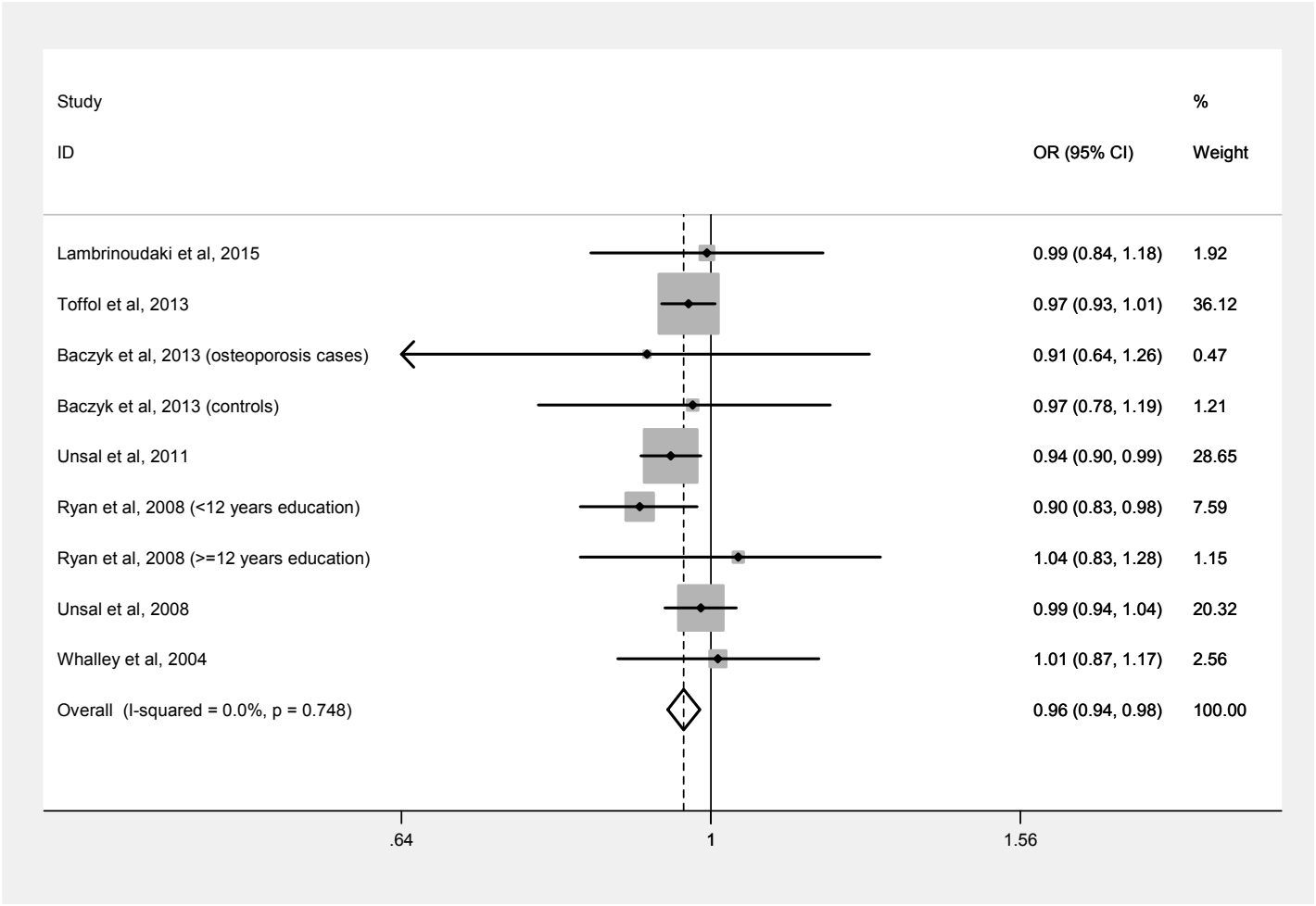
eFigure 2. Forest Plot Presenting the Sensitivity Analysis for the Association of Age at Menopause (2-Year Increment) With Depression in Postmenopausal Women
Sensitivity Analysis of Studies Controlling for the Hormone Therapy Use (*P* = .002)



eFigure 3. Forest Plot Presenting the Sensitivity Analysis for the Association of Age at Menopause (2-Year Increment) With Severe Depression in Postmenopausal Women (*P* = .06)



eFigure 4. Forest Plot Presenting the Sensitivity Analysis for the Association of Age at Menopause (2-Year Increment) With Depression in Postmenopausal Women
Sensitivity Analysis of Studies defining Age at Menopause as 1 year following last menstruation.(*P* = .001)



eFigure 5. Forest Plot Presenting Analysis for the Association of Age at Menopause as a Categorical Variable (≥40 vs <40 years) With Depression in Postmenopausal Women
(*P* = .005).