Journal of Affective Disorders 206 (2016) 174–180

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Review article

# Depression during the perimenopause: A meta-analysis

M. de Kruif [a,*], A.T. Spijker [b], M.L. Molendijk [c,d]

[a] PsyQ Depression Department, Women's Mental Health, Lijnbaan 4, 2512 VA The Hague, The Netherlands
[b] PsyQ Depression Department, Rotterdam, The Netherlands
[c] Institute of Psychology, Clinical Psychology Unit, Leiden University, Leiden, The Netherlands
[d] Institute for Brain and Cognition, Leiden University Medical Center, Leiden, The Netherlands

ARTICLE INFO

*Article history:*
Received 26 May 2016
Received in revised form
7 July 2016
Accepted 16 July 2016
Available online 22 July 2016

*Key words:*
Depression
Woman
Menopause

ABSTRACT

*Background:* Women are believed to be more vulnerable to develop a depression or depressive symptoms during the perimenopause. Estimates from individual studies are heterogeneous and hence true risk estimate is unknown.
*Objective:* This study investigated the risk on clinical depression and depressive symptoms during the perimenopause when compared to other female hormonal stages.
*Methods:* We performed a meta-analysis of 11 studies identified in Pubmed, Web of Science and the Cochrane library (up to July 2015). Studies were included when the perimenopause was defined according the criteria of Stages of Reproductive Aging Workshop (STRAW). The outcome measures were Odds Ratio's (OR) on depression diagnosis and depressive symptoms and standardized mean difference (Hedges's *g*) in depression scores during each menopausal stage.
*Results:* The odds to develop a *depression* were not significantly higher during the perimenopause than in the premenopause (OR=1.78 95% CI=0.99–3.2; p=0.054). A higher risk was found *on depressive symptoms* during the perimenopause as compared to the premenopause (OR=2.0, 95% CI=1.48–2.71; $p<0.001$) but not compared to the postmenopause (OR=1.07, 95% CI=0.737–1.571; $p=0.70$). There was a higher *symptom severity* of depression in the perimenopause when compared to the premenopause (Hedges's $g=0.44$, 95% CI=0.11–0.73, p=0.007). The odds on vasomotor symptoms and depression were 2.25 (95% CI=1.14–3.35; $p<0.001$) during the perimenopause.
*Limitations:* Time interval in measuring the depressive symptoms was different in studies. Menopausal symptoms possibly may have confounded our results by increasing the scores on depression questionnaires. Publication bias needs to be considered.
*Conclusion:* The perimenopause is a phase in which women are particular vulnerable to develop depressive symptoms and have higher symptom severity compared to the premenopause. There are indications that vasomotor symptoms are positively related to depressive symptoms during menopausal transition.



**Contents**



* Corresponding author.
*E-mail address:* m.dekruif@psyq.nl (M. de Kruif).

http://dx.doi.org/10.1016/j.jad.2016.07.040
0165-0327/

## 1. Introduction

The perimenopause is the transitional phase to non reproductive life. During the perimenopause ovarian follicular function declines, leading to fluctuating and in the end decreased levels of estrogen and progesterone and high levels of Follicle Stimulating Hormone (FSH). The presence of the hormonal fluctuations during perimenopause results in menstrual cycle irregularity (Burger et al., 2008; Gibbs et al., 2013), vasomotor instability (WHO, 1996) and cognitive (Weber et al., 2013), metabolic (Liczano and Guzmán., 2014), and somatic changes (Ripa et al., 2015).

Definitions for the different menopausal stages have been changed over the years. Before 2001, the perimenopause was described as a phase with changed lengths of the menstrual cycle length compared to the established premenopausal pattern (McKinlay et al., 1992; WHO, 1996). In 2001 consensus was reached with the Stages of Reproductive Aging Workshop (STRAW) criteria for defining menopausal stages (Soules et al., 2001). The STRAW criteria provide a uniform definition to determine the menopausal stages. The premenopausal phase is based on a bleeding pattern with regular menstrual cycles in the 22–35 d range. The perimenopause is characterized by changes in cycle length of 7 days or longer in either direction from the participant's own baseline for at least 2 cycles to 11 months of amenorrhea. Women in the postmenopausal phase have amenorrhea for at least 12 months. These strict definitions for menopausal stages pave the path to comparability of studies on this topic.

Although the majority of women do not experience negative mood consequences during menopausal transition, the risk to develop a (major) depression or depressive symptoms during perimenopause is higher than in the premenopausal stage (Bromberger et al., 2011; Soares and Zitek, 2008). However, estimates from individual studies are heterogeneous and hence the true risk estimate is unknown.

The aim of this study is to determine the risk of depression and depressive symptoms during the perimenopause compared to the pre- and postmenopause by meta-analysis. A secondary objective is to determine if vasomotor symptoms and depression are related during the perimenopause. In our analyses the strict STRAW menopausal criteria (Soules et al., 2001) will be followed in order to obtain as much uniformity as possible.

## 2. Methods

We used the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement as a guideline for this study (Moher et al., 2009).

The database of Pubmed, Web of Science and Cochrane library have been systematically searched for published papers, or papers that were published advance online before up to July 2015.

Combinations of search terms 'depression' and 'depressive disorder' with 'climacteric, 'perimenopause', 'menopause', 'female hormones' and 'gonadal steroids' have been used. Exclusion terms as 'bipolar disorder', 'drug abuse', 'premature ovarian failure' and 'breast neoplasm' were applied with the restriction 'human' and 'female'. The search was performed by two independent researchers. In case of uncertainty or incongruences the researchers discussed the concerning paper and agreed at all times.

A total of 2495 articles have been found (see Fig. 1 for the flow chart). In order to be included, studies had to: (1) apply the STRAW criteria (Soules et al., 2001) to define menopausal status, (2) use a (semi-) structured interview for a depression diagnosis (captured by a DSM diagnosis (APA, 2000)), standardized questionnaires for depressive symptoms or symptom severity and (3) to report sufficient data to perform a meta-analysis. In case of (partly) overlapping study populations among papers, we chose to stay with the largest *N* or the longest follow-up. In case of lack of usable data, the corresponding authors were asked by email to provide the necessary information.

Comprehensive Meta-Analysis (CMA) software (Borenstein et al., 2006) was utilized to perform the meta-analysis. Random Effect models were used to estimate the overall summarized (log) odds ratios and 95% Confidence Interval (CI) on a diagnosis of depression or an above cut-off depressive symptom score as a function of menopausal status. Hedges' g was used as effect-size estimate for potential differences in continuous depressive symptom severity scores among the different menopausal phases. Possible heterogeneity was assessed by the $I^2$ and assessed for statistical significance using the Q statistic (Higgins et al., 2003). The potential moderators age, depression questionnaire and duration of study were related to outcome. Results were considered statistical significance at $P < 0.05$. There were no patients or direct patient data involved in this study. Yet, the objective to study this topic is driven by questions from patients in the target population on their odds on perimenopausal depression.

Eleven studies met the inclusion criteria and were evaluated in this analysis. In 2 publications (Bromberger et al., 2010; Woods et al., 2008) perimenopausal data were split according to early and late perimenopausal phase. Outcomes were pooled to obtain data about the perimenopausal stage as a whole for the second mentioned publication (Thierney et al., 2007). For the study of Bromberger et al. (2010), this was not possible due to lack of data on the number of subjects that were either in the early or the late perimenopausal phase. The results of this particular study on presence of depressive symptoms were entered in CMA twice as perimenopausal versus early and late premenopausal.

## 3. Results

Table 1 shows a summary of the studies that have been included. The number of women included in the studies ranged from 138 to 3296 subjects, with comparable mean ages at baseline. There were 5 studies with a longitudinal design, 6 studies were cross sectional. The time interval for measurements in longitudinal studies differed between studies: from every 6 months (Cohen et al., 2006) to annually (Bromberger et al., 2010). Only one study published the data on women without a history of depression (Cohen et al., 2006).

### 3.1. Clinical depression

Two longitudinal studies described the odds to develop a depression during the perimenopause compared to the premenopause (total N=874) (Cohen et al., 2006; Freeman et al.,

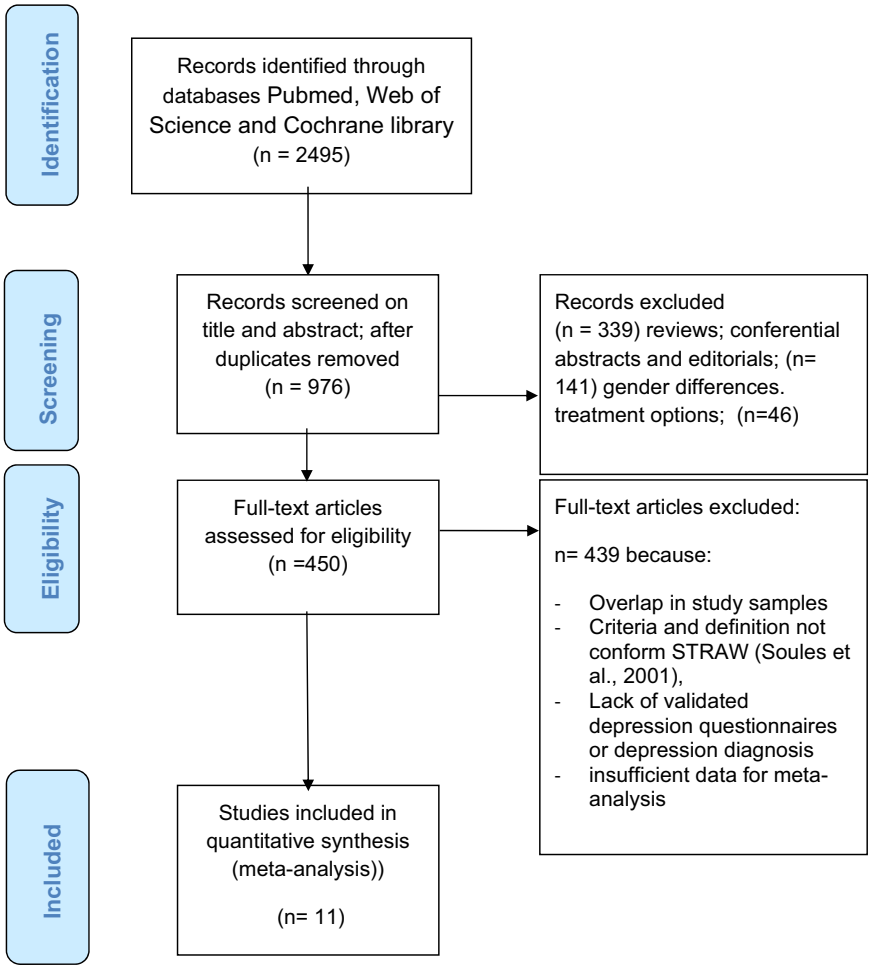



**Fig. 1.** Flow Chart: inclusion of studies.

2006). The odds were not significantly increased during the perimenopause (OR 1.78, 95% CI=0.99-3.2, $p=0.054$). No between-study heterogeneity was found ($p=0.78$) and thus moderator analyses were not performed. None of the longitudinal studies compared the perimenopause to the postmenopause.

### 3.2. Depressive symptoms

The odds on the occurrence of depressive symptoms during the perimenopause were reported in 9 studies. The numbers of women included in the studies ranged from 138 to 3296 subjects (Table 1) with a total of 8103 subjects. All 9 studies measured depressive symptoms with different validated depression questionnaires. The cut off scores for significant depressive symptoms were similar for most studies (Cusin et al., 2010), indicating clinically significant depressive symptoms, except in two publications (Chedraui et al., 2009; Joffe et al., 2002). Joffe et al. (2002) used the Center for Epidemiologic Studies for Depression scale (CESD) with a cut off of 24 and this indicates severe depressive symptoms. The second study of Chedraui et al. (2009) measured depressive symptoms with the Hamilton Depression Rating Scale (HDRS) and used a cut off of $>$ 8, indicating mild depressive symptoms. Six studies compared the occurrence of depressive symptoms in the perimenopausal stage and the premenopausal stage (Bromberger et al., 2010; Brown et al., 2014; Chedraui et al., 2009;Freeman et al., 2006; Joffe et al., 2002; Juang et al., 2005). The odds on the presence of depressive symptoms (Fig. 2) during the perimenopause were doubled when compared to the premenopause (OR=2.0, 95% CI=1.47-2.71, $p<0.001$). Significant between-study heterogeneity among studies was detected ($I^2=65.96$, Q=17.63, $p=0.007$). The heterogeneity was unrelated to the mean age of the participants or the questionnaire that was used. Six studies compared the occurrence of depressive symptoms in the perimenopause versus that in the postmenopause (Brown et al., 2014; Chedraui et al., 2009; Dennerstein et al., 2004; Joffe et al., 2002; Juang et al., 2005; Nappi et al., 2010). The odds on depressive symptoms in the perimenopause were not significant and were not comparable to those during the postmenopause (OR=1.07, 95% CI=0.74–1.57; $p=0.70$). In this analysis, there was no significant between-study heterogeneity ($I^2=40.26$, Q=8.37, $p=0.14$) and hence, moderator analysis was not performed.

### 3.3. Severity of depressive symptoms

Seven studies (Brown et al., 2014; Chedraui et al., 2009; Cheng et al., 2008; Dennerstein et al., 2004; Juang et al., 2005; Nappi et al., 2010; Woods et al., 2008) reported on mean severity of depressive symptoms as a function of menopausal status (Fig. 3). On average, perimenopausal women scored higher on depressive symptoms when compared to premenopausal women (g=0.36, 95% CI=0.11-0.60, $p=0.005$). No significant difference in mean depression severity was found between peri- and postmenopausal women (g=0.44, 95% CI=0.15–1.0, $p=0.14$). Significant between study heterogeneity was found in both analyses (Q=25.91; $I^2=84.56$; $p<0.001$ and Q=186.98; $I^2=96.79$; $p<0.001$ respectively). The observed between study heterogeneity was unrelated

**Table 1**
A summary of demographic and methodological variables of the included studies.

| Author | Study (duration) | Reference group | N | Age | Measurement of depression, cut off | History of depression | Measurement of vasomotor complaints in perimenopause |
|---|---|---|---|---|---|---|---|
| Dennerstein et al., 2004 | Longitudinal study (10 years) | Peri vs post | 314 | 45–55 | CESD (10 item) > 10 | Unknown | No |
| Cohen et al., 2006 | Longitudinal study (6 years) | Peri vs pre | 643 | 36–45 | DSM (SCID) | No history | Yes |
| Freeman et al., 2006 | Longitudinal study (8 years) | Peri vs pre | 231 | 35–47 | DSM (PRIME-MD) | Unknown | No |
| Freeman et al., 2006 | Longitudinal study (8 years) | Peri vs pre | 231 | 35–47 | CESD > 16 | Unknown | Yes |
| Woods et al., 2008 | Longitudinal study (6 years) | Peri vs pre | 320 | 35–55 | CESD | Unknown | Yes |
| Bromberger et al., 2010 | Longitudinal study (8 years) | Peri vs early and late pre | 3296 | 42–52 | CESD > 16 | Unknown | No |
| Joffe et al., 2002 | Cross-sectional | Peri vs pre and post | 584 | 40–60 | CESD > 24 | Unknown | Yes |
| Juang et al., 2005 | Cross-sectional | Peri vs pre and post | 1497 | 40–54 | HADS > 8 | Unknown | Yes |
| Cheng et al., 2008 | Cross-sectional | Peri vs pre and post | 1113 | 43–57 | HADS | Unknown | No |
| Chedraui et al., 2009 | Cross-sectional | Peri vs pre and post | 404 | 40–59 | HDRS > 8 | Unknown | No |
| Nappi et al., 2010 | Cross-sectional | Peri vs post | 138 | 40–60 | Zung > 50 | Unknown | No |
| Brown et al., 2014 | Cross-sectional | Peri vs pre and post | 206 | 40–60 | CESD > 16 | Unknown | No |

Abbreviations. CESD: Center for Epidemiologic Studies for Depression scale; DSM: Diagnostic and Statistical Manual of Mental Disorders; HADS: Hospital Anxiety and Depression Scale; HDRS Hamilton Depression Rating Scale; peri: perimenopausal; pre: premenopausal; post: postmenopausal; PRIME-MD: Primary Care Evaluation of Mental Disorders; SCID: Structured Clinical Interview for DSM-IV; Zung: Zung self rating depression scale

to mean age of the sample, duration of study and the depression severity measure that was used.

### 3.4. Vasomotor symptoms and depressive symptoms during perimenopause

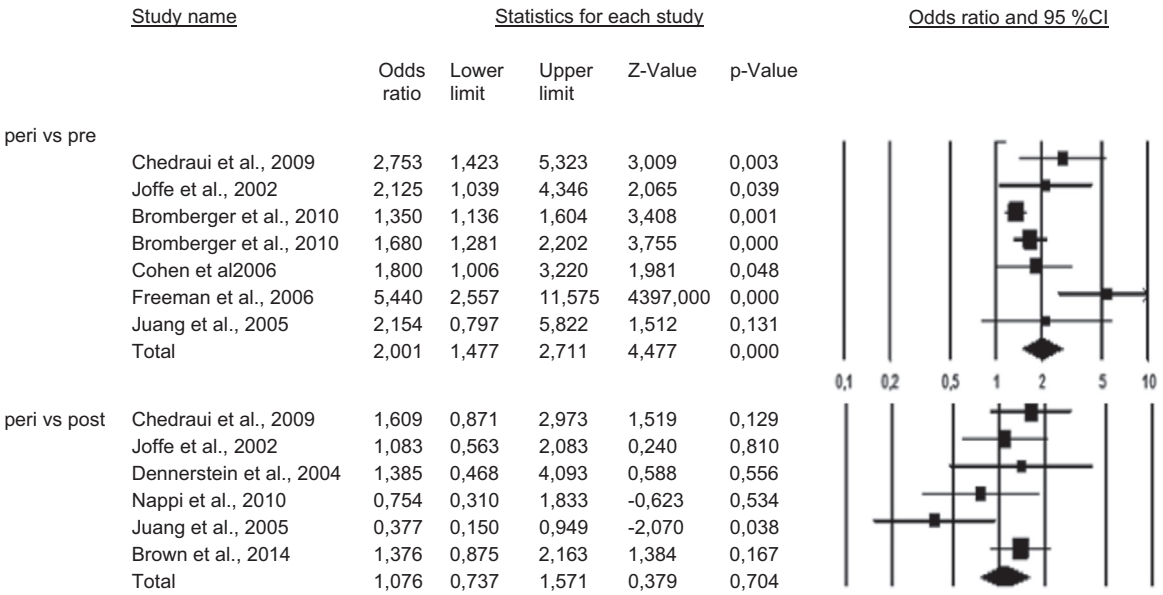
Seven studies published about the relation between vasomotor symptoms and depressive symptoms (Bromberger et al., 2010; Brown et al., 2014; Cohen et al., 2006; Freeman et al., 2006; Joffe et al., 2002; Juang et al., 2005; Woods et al., 2008). The studies of Bromberger et al. (2010), Brown et al. (2014), Juang et al. (2005) and Woods et al. (2008) were not taken into the meta-analysis because of lack of information on odds on the relation between vasomotor and depressive symptoms during the perimenopause. Overall, women who experiences vasomotor symptoms in the perimenopausal phase were more likely to report depressive symptoms (OR = 2.15, 95% CI = 1.14-3.35; $p < 0.001$), with the presence of between-study heterogeneity in outcome ($I^2 = 0.2$, $X^2 = 0.43$, $P = 0.81$).

## 4. Discussion

In this study we show that the odds for the occurrence of *clinical depression* are not significantly increased (trend) for women in the perimenopause compared to the premenopause. The odds on *depressive symptoms* in perimenopause are doubled when compared to the premenopause and similar when compared to the postmenopause. Additionally, during the perimenopausal phase women report a higher level of *depressive symptom severity* when compared to the premenopause but not to the postmenopause. Furthermore, there are indications for a positive relationship between vasomotor complaints and depression during the perimenopause.

One earlier meta-analysis (Weber et al., 2013) on depression and depressive symptoms during the perimenopause has been performed. This publication included two longitudinal studies that reported on depressive symptoms and two on the presence of a depression diagnosis. Although it is not clear which criteria for defining menopausal stages have been used in this particular study, they found an odds ratio of 2 on depression diagnosis in the perimenopause when compared to the premenopause. For depressive symptoms the odds increased 1.3 times in early perimenopause and 1.8 times in late perimenopause with the premenopausal phase as reference. The odds for depression or depressive symptoms during the perimenopause as compared to the postmenopause were not calculated in this particular paper. We included more studies and applied strict STRAW criteria (Soules et al., 2001) and find similar results on depressive symptoms but not on clinical depression. What we add, based on a larger pool of studies, is that also the odds on the occurrence of depressive symptoms in the perimenopause were comparable to the postmenopause and that the symptoms of depression are more severe during perimenopause than during premenopause.

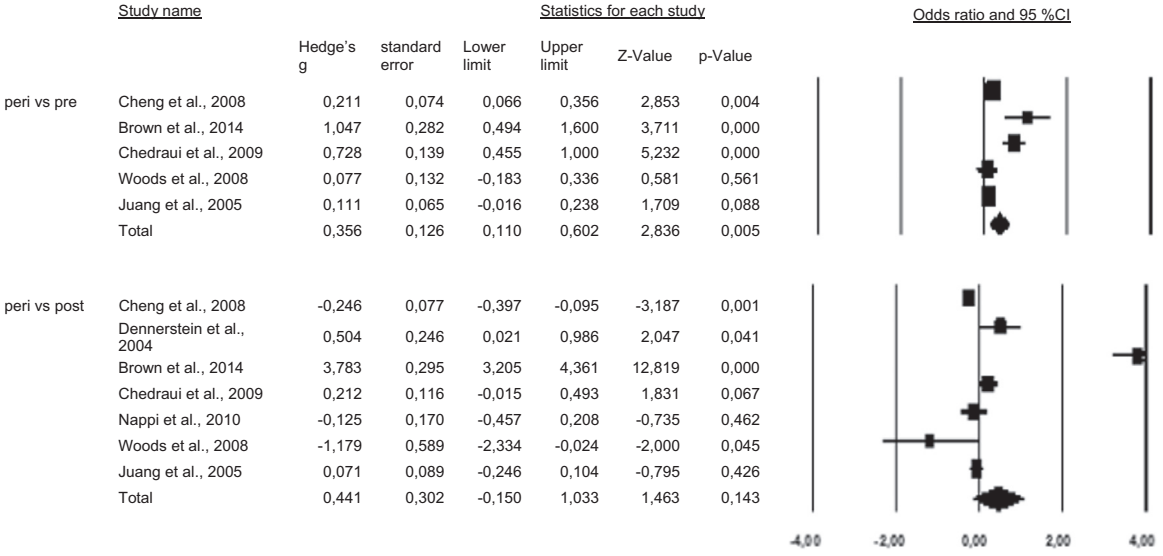
There is not a significant increased risk on depression during the perimenopause. The analyses included only 2 studies and shows a trend towards an increased risk during the perimenopause compared to the premenopause. Probably more studies are needed in which the STRAW criteria for defining menopause are applied (Soules et al., 2001), to draw a more final conclusion about the true risk of a clinical depression during perimenopause. The increased risk of depressive symptoms during the menopausal transition is due to multifactorial reasons. Earlier depression is a predictor for depression during the perimenopause (Freeman et al., 2014; Gibbs et al., 2013). Also stressful life events (Bromberger et al., 2011; Gibbs et al., 2013), health and lifestyle factors (Gibbs et al., 2013), and a history of premenstrual dysphoric



| | Study name | Odds ratio | Lower limit | Upper limit | Z-Value | p-Value |
|---|---|---|---|---|---|---|
| peri vs pre | | | | | | |
| | Chedraui et al., 2009 | 2,753 | 1,423 | 5,323 | 3,009 | 0,003 |
| | Joffe et al., 2002 | 2,125 | 1,039 | 4,346 | 2,065 | 0,039 |
| | Bromberger et al., 2010 | 1,350 | 1,136 | 1,604 | 3,408 | 0,001 |
| | Bromberger et al., 2010 | 1,680 | 1,281 | 2,202 | 3,755 | 0,000 |
| | Cohen et al2006 | 1,800 | 1,006 | 3,220 | 1,981 | 0,048 |
| | Freeman et al., 2006 | 5,440 | 2,557 | 11,575 | 4397,000 | 0,000 |
| | Juang et al., 2005 | 2,154 | 0,797 | 5,822 | 1,512 | 0,131 |
| | Total | 2,001 | 1,477 | 2,711 | 4,477 | 0,000 |
| peri vs post | Chedraui et al., 2009 | 1,609 | 0,871 | 2,973 | 1,519 | 0,129 |
| | Joffe et al., 2002 | 1,083 | 0,563 | 2,083 | 0,240 | 0,810 |
| | Dennerstein et al., 2004 | 1,385 | 0,468 | 4,093 | 0,588 | 0,556 |
| | Nappi et al., 2010 | 0,754 | 0,310 | 1,833 | -0,623 | 0,534 |
| | Juang et al., 2005 | 0,377 | 0,150 | 0,949 | -2,070 | 0,038 |
| | Brown et al., 2014 | 1,376 | 0,875 | 2,163 | 1,384 | 0,167 |
| | Total | 1,076 | 0,737 | 1,571 | 0,379 | 0,704 |



**Fig. 2.** Odds on depressive symptoms in the perimenopausal phase versus the premenopausal and postmenopausal phase.



| | Study name | Hedge's g | standard error | Lower limit | Upper limit | Z-Value | p-Value |
|---|---|---|---|---|---|---|---|
| peri vs pre | Cheng et al., 2008 | 0,211 | 0,074 | 0,066 | 0,356 | 2,853 | 0,004 |
| | Brown et al., 2014 | 1,047 | 0,282 | 0,494 | 1,600 | 3,711 | 0,000 |
| | Chedraui et al., 2009 | 0,728 | 0,139 | 0,455 | 1,000 | 5,232 | 0,000 |
| | Woods et al., 2008 | 0,077 | 0,132 | -0,183 | 0,336 | 0,581 | 0,561 |
| | Juang et al., 2005 | 0,111 | 0,065 | -0,016 | 0,238 | 1,709 | 0,088 |
| | Total | 0,356 | 0,126 | 0,110 | 0,602 | 2,836 | 0,005 |
| peri vs post | Cheng et al., 2008 | -0,246 | 0,077 | -0,397 | -0,095 | -3,187 | 0,001 |
| | Dennerstein et al., 2004 | 0,504 | 0,246 | 0,021 | 0,986 | 2,047 | 0,041 |
| | Brown et al., 2014 | 3,783 | 0,295 | 3,205 | 4,361 | 12,819 | 0,000 |
| | Chedraui et al., 2009 | 0,212 | 0,116 | -0,015 | 0,493 | 1,831 | 0,067 |
| | Nappi et al., 2010 | -0,125 | 0,170 | -0,457 | 0,208 | -0,735 | 0,462 |
| | Woods et al., 2008 | -1,179 | 0,589 | -2,334 | -0,024 | -2,000 | 0,045 |
| | Juang et al., 2005 | 0,071 | 0,089 | -0,246 | 0,104 | -0,795 | 0,426 |
| | Total | 0,441 | 0,302 | -0,150 | 1,033 | 1,463 | 0,143 |



**Fig. 3.** Hedges'g of depressive symptoms severity in the perimenopausal phase versus the premenopausal and postmenopausal phase.

disorder (PMDD) (Becker et al., 2007; Flores-Ramos et al., 2010) are related to depressive symptoms and depression during the menopausal transition. Besides, psychological factors as interpersonal relations, role and sociocultural factors are described as predictors for depression during menopause (Deeks, 2003). There is evidence that negative attitudes about the menopause, before the menopause are associated with more distress during the perimenopause (Ayers et al., 2010). Some studies suggest that there is a bi-directional relationship between vasomotor symptoms and depressive symptoms (Worsley et al., 2014). Our study included three studies that reported on both vasomotor- and depressive symptoms during the perimenopause, supporting this hypothesis. The included studies use different definitions to determine vasomotor complaints. Freeman et al. (2006) only asked for the presence of hot flashes, while Joffe et al. (2002) considered vasomotor symptoms as present when daytime hot flushes or night sweats arose during the past month. The cautious conclusion of this meta-analysis includes the correlation between the presence of any vasomotor symptoms with depressive symptoms during perimenopause.

Other serious health issues are described in the perimenopause and hereafter, including cardiovascular disease (Cagnacci et al., 2015), musculoskeletal disorders, cancer, cognitive decline and dementia, chronic obstructive pulmonary disease, diabetes mellitus, metabolic syndrome, sleep disturbances and migraine (van Dijk et al., 2015). Bromberger et al. (2015) suggest that having a chronical medical condition prior to midlife and role limitations due to physical health problems during several years are predictors of a first onset major depression during midlife. More traditional psychiatric illness histories and psychological symptoms are possible risk factors for recurrence of major depression in the perimenopause. Due to lack of data, this could not be studied in the current paper.

There is doubt about the impact of the changes in female hormones in the etiology of depressive symptoms during menopausal transition. Although some studies conclude that there is no relation between fluctuation of female hormones and depression in menopausal transition (Flores-Ramos et al., 2014; Bromberger et al., 2010), other studies provide evidence in the opposite direction (Freeman et al., 2006; Gordon et al., 2015; Słopień et al.,

2015). The results of a recent meta-analysis support the hypothesis of a relation between fluctuating hormones and depression by showing that the risk of depression in postmenopausal women is associated with age at menopause and the duration of the reproductive period (Georgakis et al., 2016). They stated that a longer exposure to endogenous hormones, reflecting a longer reproductive period and a late postmenopausal phase, was associated with a lower risk of depression in postmenopause. The underlying mechanism explaining this relation is not clear. Several studies discuss the influence of estrogen on affective regulation. Estrogen is thought to influence the regulation of hypothalamic-pituitary-adrenal (HPA) axis activity (Toufexis et al., 2014). It exerts neuroprotective action in the brain by inducing the synthesis of brain derived neurotrophic factor (Pluchino et al., 2013). Besides, it is believed that estrogen regulates the synthesis and metabolism of the neurotransmitters that are classically implicated in depression as serotonin and noradrenalin (Shors and Leuner, 2003).

The results of this meta-analysis indicate that in the perimenopause, the risk on occurrence of depressive symptoms is comparable to that in the postmenopause. The severity of depressive symptoms is also comparable in both phases. A possible explanation is that the menopausal transition may be seen as the straw that breaks the camel's back or as described earlier by Soares and Zitek (2008) 'The window of vulnerability' for the development of depression in later life. It is possible that the symptoms of depression start during the vulnerable period of perimenopause and are continued in the postmenopause. An additional explanation can be found in the relation between vasomotor symptoms and depressive symptoms. In the study of Cohen et al. (2006) a possible domino effect is described: the presence of mood problems during the perimenopause could be secondary to vasomotor complaints and sleeping problems. Since vasomotor complaints also occur during the postmenopausal phase (Harlow et al., 2012), the same domino effect is applicable in this phase, possibly leading to the occurrence of depressive symptoms.

The trend of increased risk on depression and the increased risk on depressive symptoms during the perimenopause together with the possible consequences of depression on women's physical health during midlife does point out the importance of an early recognition of a depressive disorder (Clayton and Ninan, 2010). Close monitoring of complaints and identification of possible risk factors of depression during perimenopause can play a role in the early recognition of depression – and the treatment of it - during this phase (Clayton and Ninan, 2010; Santoro et al., 2015).

## 5. Limitations

There are several considerations to be made when interpreting the results of this study. First, the included studies applied a different time interval regarding the measurement of the depressive symptoms during the different menopausal phases. Longer intervals of annual assessments possibly give a misperception or an underestimation of the occurrence of depressive complaints (de Kruif et al., 2015; Schmidt et al., 2006). A second remark is that the distinction between menopausal symptoms and depressive symptoms can be very difficult (Llaneza et al., 2012; Soares and Taylor, 2007). The symptoms of depression and menopause often overlap. Loss of concentration, low energy and sleep problems for instance can be regarded both as depressive symptoms as well as symptoms of menopausal transition (Soares and Taylor, 2007). This can lead to higher scores on depression questionnaires. A third consideration is that none of the included studies compared the odds of the perimenopausal occurrence of *clinical depression* to the postmenopausal phase. A last remark is that the number of studies included is too small to draw extensive conclusions about clinical depression during perimenopause and vasomotor symptoms because of possible selective reporting bias.

## 6. Conclusion

This meta-analysis, performed under strict definitions of menopausal stages, shows that there is not a significant increased risk on depression during the perimenopause. The analyses shows a trend towards an increased risk during the perimenopause compared to the premenopause. The odds to develop depressive symptoms during the perimenopause and the severity of depressive symptoms are increased when compared to the premenopause. There are indications that vasomotor complaints are positively related to depressive symptoms during perimenopause. Close monitoring of complaints and identification of factors associated with depression during the perimenopause can lead to early recognition of depression and give the possibility of early interventions that may favor its course.

## Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## Contributors

All authors have materially participated in the research and/or article preparation: M de Kruif research and article preparation; A. Spijker: article preparation; M.L Molendijk: research and article preparation.

#### Acknowledgements

None.

## Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.jad.2016.07.040.

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