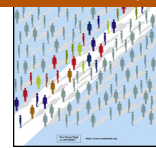




Maturitas

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

The role of depressive symptomatology in peri- and post-menopause

Erika Borkoles^a, Nick Reynolds^{a,b}, David R. Thompson^b, Chantal F. Ski^b, Lily Stojanovska^c, Remco C.J. Polman^{a,d,*}^a Institute of Sport, Exercise and Active Living, Victoria University, Melbourne, Australia^b Centre for the Heart and Mind, Australian Catholic University, Melbourne, Australia^c College of Health and Biomedicine, Centre for Chronic Disease Prevention and Management, Victoria University, Melbourne, Australia^d Psychology Department, University of Bournemouth, Poole BH12 5BB, Dorset, United Kingdom

ARTICLE INFO

Article history:

Received 23 February 2015

Accepted 10 March 2015

Keywords:

Menopause

Depression

Vasomotor symptoms

Somatic symptoms

ABSTRACT

Objectives: There is evidence that menopausal symptoms manifested at peri-menopause occur less frequently when compared to the symptoms experienced at post-menopause. The aim of this study was to investigate this and to test the hypothesis that depressive symptomatology mediates the relationship between menopausal stage and symptom frequency.

Methods: This cross-sectional study included 213 women (M age = 52 years), of whom 125 were peri- and 88 post-menopausal. Measures comprised the Center for Epidemiologic Studies-Depression scale (CES-D) and the Women's Health Questionnaire (WHQ) vasomotor symptoms and somatic symptoms subscales.

Results: Multiple mediated regression analyses provided evidence that somatic symptoms and vasomotor symptoms were less frequent at post- compared to peri-menopause, and that these differences were mediated by depressive symptomatology. Multivariate effect sizes ranged from small to moderate, and univariate effect sizes were uniformly small with wide confidence intervals.

Conclusions: The frequency of vasomotor and somatic symptoms appears to increase with depressed affect. The management of symptoms could include interventions of a psychotherapeutic nature, which may offset this effect, particularly in women for whom depressive symptoms are a feature of the climacteric syndrome. The extent to which depression and the climacteric syndrome may be causally related to one another remains unclear and longitudinal research should further examine the mechanisms of this association.

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1. Introduction

Depression is the single greatest cause of disability worldwide and women are almost twice as likely as men to suffer major depressive disorders (odds ratio 1.7, 95% confidence interval 1.5–2.0) [1,2]. A possible explanation for the gender difference in vulnerability for depression between men and women are varying levels of the gonadal hormones estrogen and progesterone [3–5]. Reproductive cycle events, like the menopausal transition, have also been implicated as windows of vulnerability for depression in women [6]. During menopause women are more likely to experience somatic/physical (e.g., insomnia, headaches, paresthesia)

and vasomotor (e.g., hot flashes, night sweats) symptoms caused by serotonergic and non-adrenergic fluctuations [7]. In particular vasomotor symptoms (VSM) have been associated with depressive symptoms (domino hypothesis [8]). Together with psychosocial and behavioural factors (e.g., social support, loss of interest in sex, stressful events) women transitioning into menopause might be particularly susceptible to mood disturbances in general and depressive symptomatology in particular.

Mood disturbances are reported by 75% of peri-menopausal women [9] and are routinely assessed in surveys examining menopausal symptomatology (e.g., depression, anxiety and irritability). There is currently no consensus whether depression or depressive symptoms constitute core menopausal symptoms [10]. Some researchers have excluded depression from the diagnostic criteria for reproductive related disorder [11], whereas others have shown in longitudinal studies that in particular the peri-menopausal period is associated with a changing hormonal milieu and increased occurrence (up to 2 to 14 fold) of depressive symptomatology compared to pre-menopause [12–14].

* Corresponding author. Tel.: +44 1202 966671.

E-mail addresses: Erika.borkoles@vu.edu.au (E. Borkoles),

Nick.Reynolds@acu.edu.au (N. Reynolds), David.Thompson@acu.edu.au

(D.R. Thompson), Chantal.Ski@acu.edu.au (C.F. Ski), Lily.Stojanovska@vu.edu.au

(L. Stojanovska), rpolman@bournemouth.ac.uk (R.C.J. Polman).

The equivocal findings with regard to depressive episodes in menopause are partly due to methodological (e.g., epidemiological vs. clinical studies), diagnostic (assessment of depression; self-report vs. clinical assessment), and menopausal status differences [15]. For example, epidemiological studies have generally found no increase in depressive symptoms in menopause, whereas clinical studies have found higher prevalence rates [16]. In addition, differences exist in regard to menopausal symptom severity during the peri- vs. post-menopausal periods [17]. More recently, Freeman et al. [18] identified higher risk of depressive symptoms leading up to the final menopausal period and lower risk thereafter. However, for women with a history of depression the risk significantly increased both before and after menopause.

A number of risk factors have been identified, which might result in menopausal women experiencing more or less depression or depressive symptoms. These include VMS [19], hormonal vulnerability [20], socioeconomic status (SES), education and achievement (higher SES, education and income resulting in less depressive symptoms), smoking, exercise, body mass index (BMI), social support and partner status, coping, attitude, stressful life events and past history of mood disorder [21].

Elucidation of the role of depression during different stages of menopause (peri- vs. post) is of clinical relevance given its serious consequences for health and cognition. Menopausal symptoms including depression greatly influences well-being and quality of life [22]. In addition, depression is associated with other chronic diseases including metabolic syndrome, osteoporosis, cardiovascular disease [18] and reduced cognitive functioning [23]. Therefore, the present study examined whether depressive symptomatology mediates the hypothesized association between menopausal status and menopausal symptoms.

2. Methods

2.1. Participants

The study included 213 participants (M age = 52.2 years, SD = 5.9) of which 125 were classified as peri-menopausal (58%; M age = 50 years, SD = 4.2) and 88 post-menopausal (42%; M age = 54.2 years, SD = 5.9). The sample included 17 participants who had undergone a surgical procedure that might affect their experience of menopause. Two post-menopausal women had each undergone a hysterectomy with bilateral oophorectomy, and 15 peri-menopausal participants had undergone a hysterectomy (n = 8) or hysterectomy with unilateral oophorectomy (n = 7). The sample contained no reports of chronic and debilitating illness and no psychoactive substance use was reported. Over 70% of participants were of Anglo-Celtic origin, most were employed on a full- or part-time basis, possessed a tertiary qualification, and had one or more children (see Table 1). Ethical approval for the study was provided by Victoria University Human Research and Ethics Committee.

2.2. Procedure

A cross-sectional study of menopause and depressive symptoms was undertaken with female volunteers recruited at peri-menopause (defined as the period from the commencement of menstrual irregularity to one year after the cessation of menstrual periods) and post-menopause (defined as one year or more after the cessation of menstrual periods) [24]. Participants were recruited via advertisements displayed in print media of the Queensland Menopause Society, advertisements displayed on the website of the Australian Menopause Society,

Table 1
Demographic characteristics (n = 223).

| Variables | n | (%) |
|------------------------|-----|--------|
| Ethnicity | | |
| Anglo-Celtic | 157 | (70.2) |
| European | 42 | (18.8) |
| Asian | 12 | (5.0) |
| Other | 12 | (5.0) |
| Education level | | |
| Secondary | 31 | (14.0) |
| Trade or diploma | 45 | (20.3) |
| University degree | 67 | (30.1) |
| Post-graduate degree | 79 | (35.6) |
| Employment status | | |
| Full time | 105 | (70.5) |
| Part time | 32 | (21.5) |
| Not in paid employment | 12 | (8.0) |
| Parity | | |
| Nil | 52 | (23.3) |
| One | 28 | (12.6) |
| Two | 94 | (42.2) |
| ≥Three | 49 | (22.0) |
| Relationship status | | |
| Married | 96 | (64.0) |
| Separated or divorced | 29 | (19.4) |
| Single | 24 | (16.1) |
| Current smoker | 25 | (11.2) |

and leaflets distributed at support organisation (e.g. Women's Wellness West). Consenting participants provided demographic information, including age, income, paid employment, parity and cigarette smoking and completed a questionnaire pack containing measures of depressive symptomatology and menopausal symptoms. Hard-copy and digital forms of the questionnaire pack were accessed via web-link and required between 25 and 30 min to complete.

2.3. Materials

2.3.1. The Center for Epidemiologic Studies of Depression Scale (CES-D)

This widely-used 20-item CES-D [25] questionnaire asks participants to indicate the frequency of depressive symptoms experienced during the preceding week. Participants respond to items using a 4 point Likert scale, which ranges from 0 ("rarely or none of the time") to 3 ("most or all the time"). The CES-D yields a total score, which ranges from 0 to 60. Participants who score ≥ 16 are considered likely to be at risk of depression [25,41]. The internal consistency of the CES-D for the present sample was high (α = 0.92) and comparable to that obtained from previous samples [26].

2.3.2. The Women's Health Questionnaire (WHQ)

This 36-item WHQ questionnaire [27] assesses the frequency of menopausal symptoms over the preceding few days. Participants respond using five point scale with a range from 1 ("Yes, definitely") to 5 ("No, not at all"). The subscales of the WHQ comprise self-perceived attractiveness, depression, anxiety, sleep disturbance, sexual dysfunction, menstrual symptoms, VMS and somatic symptoms. Responses to items within each subscale are summed and re-scaled to range from 0 to 1, with higher scores corresponding to greater symptom frequency. The reliability of the vasomotor symptoms subscale (α = 0.83) and the somatic symptoms subscale (α = 0.79) ranged from adequate to good in the present sample.

2.4. Analysis strategy

The data were analysed with IBM Statistical Package for the Social Sciences (SPSS) version 22 and PROCESS [28]. A preliminary analysis used odds ratios to test differences in symptom prevalence as a function of menopausal status and CES-D high- and low depression risk categories. The outcome variables were dichotomized such that 0 denoted symptom absent and 1 denoted symptom present.

Mediated multiple regression models were constructed to predict symptom frequency as a direct function of menopausal status and symptom frequency as an indirect function of menopausal status through depression, controlling for income, smoking status, and parity. The indirect effect was estimated with bootstrap bias-corrected and accelerated (BCa) confidence intervals that were generated from 5000 samples [29].

Bootstrap BCa CI point estimates are reported and unstandardized regression coefficients for path a (X (menopausal status) to M (depression)), controlling for covariates income, parity, smoking), path b (M to Y (vasomotor or somatic symptoms)) controlling for X , and path c' (X to Y controlling for M and covariates). In addition, two indices of explained variance are reported. The coefficient of determination (R^2) and Kappa-squared (K^2), which is the indirect effect expressed as a proportion of the maximum possible indirect effect based on the variances of X , M , and Y and their inter-correlations [30].

The product of coefficients method was used to estimate the sample size required for 80% power to detect an indirect effect (ab) and assumed medium sized effects at paths a and b . A sample of 71 participants provided sufficient power using the bootstrap bias-corrected method at α of 0.05 [31].

3. Results

A square root transformation of the CES-D normalized its error distribution and brought several outlying values within a more probable range of the distribution's mean. Missing values, 3% of cases, were regarded as missing at random and excluded from the analyses. There were otherwise no substantive violations of the multivariate assumptions.

3.1. Symptom prevalence

Sixteen percent of participants who reported no somatic symptoms, while 36% reported no VMS. There was a higher likelihood of experiencing VMS given peri-menopausal status (OR: 1.95; [95% CI: 1.11 to 3.39], $p < 0.001$), whereas the prevalence of somatic symptoms did not significantly differ between menopausal groups. Prevalence was positively correlated with CES-D depression risk categories. Participants in the high risk group were more likely to experience VMS (OR: 3.01; [95% CI: 1.68 to 5.36]) and somatic symptoms (OR: 14.58; [95% CI: 3.36 to 63.27]) relative to participants who scored 15 or less on the CES-D. Table 2 displays the means and standard deviations of VMS and somatic symptoms according to menopausal and depressive symptomatology status.

3.2. The frequency of VMS

The parameters of the mediation analyses are shown in Table 3a. The multiple regression model with covariates explained 11% of the variance in VMS scores as a function of depression and menopausal status ($R^2 = 0.11$ [95% CI: 0.03 to 0.18]). The effect sizes of path a (Cohen's $d = 0.30$) and path b ($\eta^2 = 0.04$) were small according to conventional guidelines. There were fewer symptoms of depressed affect at post- than peri-menopause ($a = -0.41$ [95% CI: -0.87 to -0.08]) and participants with elevated depressive symptoms

tended to report more frequent VMS ($b = 0.06$ [95% CI: 0.01 to 0.10]) holding the covariates constant at both paths and controlling for the effect of menopausal status at path b .

There was a direct effect of menopausal status on VMS ($c' = -0.15$ [95% CI: -0.30 to -0.05]). The BCa CI of the indirect effect excluded zero and the point estimate indicated a reduction in the frequency of VMS through depression ($ab = -0.023$ [95% CI: -0.063 to -0.002]). The indirect effect explained 3% of the maximum possible indirect effect based on the model without covariates ($K^2 = 0.033$; $SE = 0.01$ [95% CI: 0.006 to 0.075]).

3.3. The frequency of somatic symptoms

The multiple regression model with covariates explained 27% of variance in somatic symptom scores as a function of the antecedent and mediator variables ($R^2 = 0.27$ [95% CI: 0.16 to 0.37]) (Table 3b). The effect size at path b was large ($\eta^2 = 0.24$) and the unstandardized coefficient indicated that somatic symptoms increased with depressive symptoms ($b = 0.08$ [95% CI: 0.06 to 0.10]) controlling for the covariates and menopausal status. The BCa CI of the indirect effect excluded zero and indicated fewer somatic symptoms at post- relative to peri-menopause through depression scores ($ab = -0.03$; $SE = 0.01$ [95% CI: 0.069 to 0.005]). The indirect effect explained 8% of the maximum possible effect based on the proposed model without covariates ($k^2 = 0.08$ [95% CI: 0.01 to 0.15]).

4. Discussion

Menopausal symptoms may vary from peri- to post-menopause transition as an indirect function of depressive symptomatology and the present findings provide support for this hypothesis. From peri- to post-menopause, depressed affect mediated a decline in the frequency of VMS and somatic symptoms, controlling for the effects of income, parity, and tobacco use.

The prevalence of VMS and somatic symptoms in the present sample was not dissimilar to that obtained in other women in Western cultures [13,27]. In addition, our findings support the notion that peri-menopausal women experience a higher frequency of symptoms than post-menopausal women. In particular, VMS prevalence is higher in the years before the final menstrual period (FMP) and peaks at approximately 1 year after [32].

Our study found a difference of one unit on the WHQ response scale from peri- to post-menopause, which reflects a substantive or 'clinically significant' degree of change [33]. Part of this overall effect was directly attributable to menopausal status and a portion was due to the mediator depression (partial mediation). In particular, menopausal status predicted fewer depressive symptoms among postmenopausal participants, which corresponded to reports of less frequent VMS in this group. The findings are broadly compatible with neuro-cognitive theories which attribute symptom change to the machinations of biological, behavioural, or psychological entities [34]. There is some evidence that the frequency of hot flushes and night sweats peak at peri-menopause and then declines in concert with hormonal changes during this period [35]. The changing hormonal milieu may also affect depressive symptomatology thereby reducing the frequency of vasomotor symptoms [36].

The findings are also compatible with behavioural explanations, particularly as they pertain to complex patterns of overt behaviour. For example, there is evidence that VMS do not decline but instead are under-reported at post-menopause. This may indicate that women grow more tolerant of symptoms or become increasingly proficient at managing their effects during this period. It is conceivable that the indirect effect signifies an increased capacity to cope

Table 2
Symptom frequency according to menopausal status and CES-D risk category (mean (±SD)).

| | Menopausal status | | Depressive symptomatology | |
|--------------------|-------------------|-------------|---------------------------|-------------|
| | Peri | Post | CES-D < 15 | CES-D ≥ 16 |
| Vasomotor symptoms | 0.61 (0.45) | 0.44 (0.44) | 0.49 (0.46) | 0.65 (0.42) |
| Somatic symptoms | 0.40 (0.28) | 0.38 (0.27) | 0.34 (0.26) | 0.50 (0.26) |

Table 3a
Regression pathways of the mediation model of vasomotor symptom frequency with covariates at paths *a* and *c'*.

| Antecedent | | Depressive symptomatology (M) | | | | <i>c'</i> | Vasomotor symptoms (Y) | | | |
|--------------------------------|-----------------|---|------------|-----------------------|-------------|------------------|---|-------------|-----------------------|-------------|
| | | <i>B</i> | SE | 95% CI | <i>p</i> | | <i>B</i> | SE | 95% CI | <i>p</i> |
| Menopausal status (X) | <i>a</i> | -0.48 | 0.2 | -0.87 to -0.08 | 0.01 | <i>c'</i> | -0.13 | 0.06 | -0.26 to -0.01 | 0.03 |
| <i>M</i> | | - | - | - | - | <i>b</i> | 0.06 | 0.02 | 0.01 to 0.10 | 0.01 |
| <i>C</i> ₁ (parity) | | -0.10 | 0.08 | | 0.220 | | -0.01 | 0.02 | | 0.59 |
| <i>C</i> ₂ (income) | | -0.17 | 0.03 | | <0.000 | | -0.02 | 0.01 | | 0.04 |
| <i>C</i> ₃ (smoke) | | -0.72 | 0.32 | | 0.020 | | 0.00 | 0.09 | | 0.99 |
| Constant | | 6.42 | 0.70 | | <0.000 | | 0.61 | 0.26 | | 0.01 |
| | | <i>R</i> ² = 0.136 | | | | | <i>R</i> ² = 0.104 | | | |
| | | <i>F</i> (4, 199) = 7.83, <i>p</i> < 0.0001 | | | | | <i>F</i> (5, 198) = 4.62, <i>p</i> < 0.0005 | | | |

C: covariate. *B*: unstandardized regression coefficient. SE: standard error. CI: confidence intervals.

at post-menopause on average, which manifests in fewer or less bothersome VMS.

There was no support that somatic symptoms differed as a function of menopausal status either before or after controlling for the indirect effect of depression. However, menopausal status predicted fewer somatic symptoms at post-menopause through depression.

The major strength of this study is the clarification that leading up to menopausal transition women are much more likely to be at risk of having depressive symptoms than those who reached the FMP, and those with a previous history of depression having even greater risk. In addition, peri-menopause is also a time when the frequency of some menopausal symptoms may peak. The present study postulated that menopausal status and menopausal symptoms are causally related via depression. The mediated regression analyses of these observational data were consistent with this notion. Depressive symptoms were less frequent at post-menopause and this reduction was correlated with fewer reported vasomotor and somatic symptoms.

However, it is still unclear what is the association between depressive and vaso-motor symptoms and whether it is due to a common physiological mechanisms or not and what their psychological and social impact are on women. Freeman et al. [37] found that greater variability in FSH (follicle-stimulating hormone) and estradiol was significantly associated with depressive symptoms in the menopause transition. Those with a faster rate of change in FSH before the FMP had lower risk of depressive symptomatology than those with or without history of depression after the FMP. Strauss [38] examined possible underlying mechanisms in 986 women over a 9-year follow-up. She found that initial levels of depressive

symptoms predicted future menopausal symptoms, and vice versa, initial levels of menopausal symptoms also predicted depressive symptoms. This suggests that more than one mechanism influences the relationship between menopausal symptoms and depression.

Our results are clinically important, because depression is strongly associated with poorer quality of life and health limiting conditions, such as cardiovascular disease. It is a standard practice for many healthcare professionals to assess clients for depression and other psychiatric syndromes that are known to affect health outcomes. A comprehensive process of assessment may be especially pertinent in those with complex syndromal conditions, such as menopausal symptom clusters.

Psychotherapy could benefit women who require medical support during the climacteric if depressed affect compounds menopausal symptoms in the manner described. Applied relaxation, for instance, has been shown to reduce the frequency of vasomotor symptoms [39] and the beneficial effects of this and other psychotherapeutic interventions may be especially pronounced in groups of women for whom depressed affect is a feature of the climacteric.

The mediation models were constructed based on a postulated mechanism and it remains unclear whether the models were correctly specified. In addition, epiphenomenal associations may compromise these findings despite the models' inclusion of covariates [28]. This is especially likely given the use of menopausal status as a proxy for complex biological and psychosocial processes, and the study's reliance on questionnaire measures which provide raw scores rather than the measurements essential for parametric statistical analysis [40]. For example, the CES-D with a cut-off point of ≥16 or higher may not indicate a clinical diagnosis

Table 3b
Regression pathways of the mediation model of somatic symptom frequency with covariates at paths *a* and *c'*.

| Antecedent | | Depressive symptomatology (M) | | | | <i>c'</i> | Somatic symptoms (Y) | | | |
|--------------------------------|-----------------|---|------------|-----------------------|-------------|------------------|---|-------------|----------------------|------------------|
| | | <i>B</i> | SE | 95% CI | <i>p</i> | | <i>B</i> | SE | 95% CI | <i>p</i> |
| Menopausal status (X) | <i>a</i> | -0.48 | 0.2 | -0.87 to -0.08 | 0.01 | <i>c'</i> | 0.005 | 0.03 | -0.06 to 0.07 | 0.87 |
| <i>M</i> | | - | - | - | - | <i>b</i> | 0.08 | 0.01 | 0.06 to 0.10 | <0.001 |
| <i>C</i> ₁ (parity) | | -0.10 | 0.08 | | 0.22 | | 0.001 | 0.02 | | 0.91 |
| <i>C</i> ₂ (income) | | -0.17 | 0.03 | | <0.001 | | -0.02 | 0.01 | | 0.03 |
| <i>C</i> ₃ (smoke) | | -0.72 | 0.32 | | 0.02 | | -0.02 | 0.09 | | 0.65 |
| Constant | | 0.27 | 0.14 | | <0.001 | | 0.27 | 0.14 | | 0.05 |
| | | <i>R</i> ² = 0.136 | | | | | <i>R</i> ² = 0.255 | | | |
| | | <i>F</i> (4, 199) = 7.83, <i>p</i> < 0.0001 | | | | | <i>F</i> (5, 198) = 13.59, <i>p</i> < 0.001 | | | |

C: covariate. *B*: unstandardized regression coefficient. SE: standard error. CI: confidence intervals.

of depressive disorder. Depressive symptoms are also time limited. Further studies are warranted to confirm our findings with regards to risk of depressive symptoms associated with this important phase of women's lives.

Future investigation may consider implementing prospective designs and substantially larger sample sizes to elucidate the relationship, causal or otherwise, between depressed affect menopausal symptoms.

Conflict of interest statement

None.

Contributors

EB: Study design, data collection, data interpretation, and manuscript preparation.

NR: Data analysis, data interpretation and manuscript preparation.

CFS: Data interpretation and manuscript preparation.

LS: Study design and data collection.

DRT: Data interpretation and manuscript preparation.

RCJP: Study design, data analysis, data interpretation and manuscript preparation.

Competing interest

The authors have no financial or other competing interest.

Funding

The authors did not receive any funding to complete this study.

Acknowledgement

We would like to thank all the women who participated in this study.

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