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Sleep disturbances during the menopausal transition: the role of sleep reactivity and arousal predisposition

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Abstract

Background: Sleep disturbances are common during the menopausal transition and several factors can contribute to this increased incidence. This study examined the association between sleep reactivity, arousal predisposition, sleep disturbances and menopause.

Methods: Data for this study were derived from a longitudinal, population-based study on the natural history of insomnia. A total of 873 women (40-60 years) were divided into two groups according to their menopausal status at baseline: reproductive (n=408) and postmenopausal (n=465). Participants were evaluated annually throughout the five-year follow-up period. Four questionnaires were used to examine sleep quality, insomnia severity, sleep reactivity, and arousal predisposition. The data were analysed using two approaches: cross-sectional with a multivariate analysis and binary regression, and longitudinal with a linear mixed models using a menopausal groups (3) x time (5) design.

Results: Cross-sectional analyses showed that postmenopausal women reported significantly more severe insomnia and poorer sleep quality than reproductive women. Sleep reactivity and arousal predisposition were significant predictors of sleep disturbances. Longitudinal analyses revealed increased sleep disturbances in the two years before and after the menopausal transition. Sleep reactivity and arousal predisposition did not moderate the temporal relationships between menopausal transition and sleep disturbances.

Conclusion: More sleep disturbances were reported during the menopausal transition, but those difficulties were not explained by sleep reactivity and arousal predisposition. These results suggest the involvement of other psychophysiological factors in the development of sleep disturbances during the menopause.

Introduction

Sleep disturbances are common in the general population, especially insomnia symptoms whose prevalence rates can reach 30% to 35% across countries (Ohayon, 2002). Nevertheless, the pathophysiology of insomnia has not been fully unravelled. In the "three-factor" model of insomnia (Spielman, Saskin, & Torpy, 1987), hyperarousal and stress are proposed to be predisposing and precipitating factors, respectively. During a stressful event, an individual generates a stress response, which includes a physiological (e.g., increased heart rate), a cognitive (e.g., rumination) and an emotional (e.g., anxiety) component, thereby increasing the likelihood of an acute episode of insomnia (Harvey, Gehrman, & Espie, 2014). For most people, acute insomnia resolves itself when the initial triggering factor fades away. Nevertheless, some individuals, probably those more vulnerable to experience sleep difficulties after a stressful event (also called sleep reactivity), will be more likely to develop chronic insomnia, sustained by hyperarousal (Drake, Pillai, & Roth, 2014; Harvey et al., 2014). In this context, hyperarousal represents a trait predisposition, which refers to a general tendency to activate, under several stressful situations, whereas sleep reactivity refers to a tendency to experience sleep disturbances when exposed to stressful situations. The two constructs are intertwined.

Other factors increase the risk to develop sleep disturbances as well. For instance, insomnia is twice as common in older adults as it is in younger adults (Ohayon, Carskadon, Guilleminault, & Vitiello, 2004). Moreover, women are 1.3 to 1.8 times more likely to develop insomnia and 1.41 times more likely to report sleep disturbances compared with men (Krystal, 2003; Zhang & Wing, 2006). Not surprisingly, the prevalence of sleep disturbances increases from 12 to 40% in women aged 40 to 54 years, a period in line with the typical age of menopause (Kravitz & Joffe,

2011). Biological (e.g., hormone, hot flashes) changes that occur during menopause are also recognized as the main factors accounting for sleep disturbances during this life transition (Kravitz & Joffe, 2011; Polo-Kantola, 2008).

The age range of menopause in healthy women is relatively wide (42 to 58 years) and seem to be highly variable across women (Soules et al., 2001). The main criterion to define natural menopause is a twelve-month period of amenorrhea (absence of menstruation) that cannot be attributed to a medical condition (Soules et al., 2001). Sleep disturbances may appear even during perimenopause and can be the primary symptoms of the menopausal transition, along with irregular menstruations (Polo-Kantola, 2008). Indeed, the prevalence of sleep disturbances was 1.3 and 1.6 times higher in perimenopausal and postmenopausal women, respectively, compared to reproductive women (Kravitz et al., 2003). With regard to insomnia, 56.6% perimenopausal and 50.7% postmenopausal women report chronic insomnia in comparison to 36.6% in reproductive women (Ohayon, 2006); insomnia becomes especially frequent in the later stage of perimenopause relative to the earlier stage (odd ratio = 1.3) (Ciano, King, Wright, Perlis, & Sawyer, 2017). These symptoms can last for several years after menopause (Berecki-Gisolf, Begum, & Dobson, 2009) and can have a negative impact on quality of life (Ledesert, Ringa, & Breart, 1994).

In addition to the biological changes associated with menopausal transition (Kravitz & Joffe, 2011), middle-age women may present other risk factors of developing sleep disturbances due to various stressful life events (Cuadros et al., 2012) and psychosocial factors (e.g., beliefs, attitudes) linked to menopausal experience (Hunter, 2003). For example, psychological distress, maladaptive coping strategy or misperceptions regarding menopausal symptoms could have a negative impact on sleep. Several studies have examined risk factors of menopausal insomnia (e.g., hot flashes,

age) (Q. Xu, Lang, & Rooney, 2014), but only one has investigated whether some premorbid personality traits increase the risks of sleep disturbances during perimenopause (Sassoon, de Zambotti, Colrain, & Baker, 2014). Although, a few cross-sectional studies have investigated the possible association of sleep disturbances with stress and hyperarousal in middle age women (Bertisch et al., 2019; de Zambotti, Sugarbaker, Trinder, Colrain, & Baker, 2016; Hall et al., 2015), none of those studies has investigated the presence of sleep reactivity and arousal predisposition as potential risk factors. Examining moderators is also important to identify potential factors that contribute to perpetuating sleep difficulties, but no longitudinal studies has investigated the influence of these factors on sleep difficulties during the menopausal transition.

The present study evaluated sleep disturbances (i.e., sleep quality and insomnia severity) during the menopausal transition using cross-sectional (objectives 1 and 2) and longitudinal (objectives 3 and 4) approaches. The first and second objectives were to compare sleep disturbances in reproductive and postmenopausal women (with or without replacement hormone therapy) and investigate whether such sleep disturbances could be predicted by sleep reactivity and arousal predisposition. The third and fourth objectives were to examine temporal changes of sleep disturbances during the menopausal transition and to evaluate whether sleep reactivity and arousal predisposition were moderators of the onset of new sleep disturbances during the transition to menopause. It was hypothesized that postmenopausal women would report more sleep disturbances compared with reproductive women, and these sleep disturbances would be explained by higher levels of arousal predisposition and sleep reactivity. We also hypothesized that the onset of the menopause would be associated with more sleep disturbances, and that sleep reactivity and arousal predisposition would be moderating factors of sleep disturbances during the menopausal transition.

Methods

Context of the Parent Epidemiological Study

This study was based on secondary analyses of data derived from a longitudinal, prospective, population-based survey of the natural history of insomnia in Canada. That study included a total of 3,419 participants and investigated the incidence, persistence, and remission of insomnia over a 5-year period treatment (Morin et al., 2020). Initially, telephone interviews were conducted to determine the prevalence of insomnia and to inquire whether individuals were willing to participate in the longitudinal, five-year study. Baseline assessment was conducted one month after the telephone interview (T1), and follow-up assessments were conducted at 6, 12, 24, 36, 48, and 60 months (T2 to T7) after the initial assessment. Data from all these assessments were included in this paper. Ethical approval was obtained from Laval University Ethics Board and all participants provided informed consent.

Participants

To achieve the first and second objectives (cross-sectional perspective), baseline data from an initial sample of 873 women aged 40 to 60 years old from the complete dataset were analyzed. Based on their responses to two questions on menopause and use of replacement hormone therapy (HRT), participants were divided into two groups according to menopausal status: 408 reproductive women and 465 postmenopausal women. In the postmenopausal group, 90 of the women were taking HRT.

To achieve the third and fourth objectives (longitudinal perspective), participants were separated into three groups according to their menopausal stage during the five years of the study (which included seven measurement times): women already menopausal at time 1 (n = 465 - postmenopausal women), women who were reproductive throughout the study (n = 206 – reproductive women), and women who

entered the menopausal transition phase during the five-year period (n = 202 - perimenopausal women). The menopausal status (groups) of participants in each phase of the study was determined by their answer to the questions: "Are you menopausal?" and "Do you use replacement hormone therapy for menopause?". Perimenopausal stage was therefore defined as the first phase in which the participant answered "yes" to these questions, having answered "no" in the previous phase(s). For example, a participant who answered "no" from T1 to T3 and "yes" from T4 to T7 was included in the perimenopausal group. Women who answered "no" or "yes" from T1 to T7 were included in the reproductive and postmenopausal groups, respectively. Inconsistent data were adjusted. For example, if a woman was considered postmenopausal at T3 and T5 but not at T4, the variable was adjusted to fit with responses on the two other surveys.

Outcomes measures

Several validated self-report questionnaires were completed by participants and covered sleep, mood, life events, and health-related quality of life domains. Questionnaires assessing sleep disturbances (e.g., sleep quality and severity of insomnia), arousal predisposition and sleep reactivity were administered at each of the assessment points (T1 to T7). Other data, such as age, medical and psychological (e.g., depression, anxiety) conditions, sleep medication and HRT use were also examined to determine whether they interacted with the dependent variables.

Sleep disturbances

Insomnia Severity. The *Insomnia Severity Index* consists of seven items that assess insomnia severity over the last month (initial, middle and late insomnia, satisfaction with sleep, perceived daytime impairments and consequences). Each item is assessed on a scale of 0 to 4 (0 = none to 4 = very severe), with total scores ranging between 0 and 28. A result greater than seven suggests the presence of clinical

insomnia. The ISI has good internal consistency, test-retest reliability (Cronbach's alpha = 0.83), and convergent validity (r = 0.65 when compared with a sleep diary) (Morin, Belleville, Belanger, & Ivers, 2011).

Sleep Quality. The *Pittsburgh Sleep Quality Index* is a questionnaire that assesses sleep quality and habits over the past month. It consists of 19 items grouped into seven categories: quality, latency, duration, efficacy, sleep disturbance, daily dysfunction, and use of medication to promote sleep. Scores for each subcategory (from 0 to 3) are summed to give a total score of between 0 and 21. A result greater than five suggest the presence of clinically important sleep disturbances. The psychometric properties of the PSQI are well recognized and support its utility both in clinical practice and in research activities. Its sensitivity and specificity to detect clinical insomnia are 89.6% and 86.5%, respectively (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989).

Sleep Reactivity

The *Ford Insomnia Response to Stress Test* is a nine-item questionnaire used to assess the likelihood of individual experiencing sleep disturbances in response to stressful situations. Each item is evaluated on a four-point scale (1 = not likely to 4 = very probable), with total scores ranging between 9 and 36. A median of 20 has been validated in the literature, with a score below 20 indicating low sleep reactivity and a score above 20 indicating high sleep reactivity (Drake, Richardson, Roehrs, Scofield, & Roth, 2004). The FIRST has high internal consistency (Cronbach's alpha = 0.83) and good test-retest reliability (r coefficient = 0.92) (Drake et al., 2004).

Arousal Predisposition

The *Arousal Predisposition Scale* consists of 12 items measuring emotional and cognitive arousal (reactivity) in response to different situations. Each item is rated on a five-point scale (0 = not in agreement to 4 = completely in agreement) and summed to

give a total score of between 1 and 48. A median score of 30 has been validated to separate individuals with low arousal predisposition from those with high arousal predisposition (Altena et al., 2017). The APS has good predictive validity and internal consistency (Cronbach's alpha = 0.84) (Coren & Mah, 1993).

Psychological conditions

Depression symptoms. The *Beck Depression Inventory* (BDI) is a 21-item questionnaire assessing the severity of depressive symptoms during the last 2 weeks. Each item is rated on a 4-point Likert scale, and the total score varies between 0 and 63. A high score suggests a greater level of depression. Both its internal consistency (Cronbach's alpha = 0.91) and test-retest reliability (r = 0.93) are excellent (Beck, Steer, & Brown, 1996).

Anxiety symptoms. The State-Trait Anxiety *Inventory (Trait Subscale) (STAI)* is a 20-item questionnaire assessing anxiety as a personality trait. Each item is rated on a 4-point Likert scale (1 = not at all to 4 = a lot), and the total score varies between 20 and 80. A high score indicates a greater level of trait anxiety. Both its internal consistency (Cronbach's alpha = 0.86 to 0.95) and test-retest reliability are good (r = 0.65 to 0.75) (Spielberger, Gorsuch, & Lushene, 1983).

Medical and health conditions

Medical conditions, sleep medication, HRT, and use of cigarettes or alcohol are measured with the following questions: "Currently, do you suffer from one or more of the following health problems? Check all that apply." (e.g., diabetes, cancer, chronic pain), "During the last month, how many nights per week have you used prescribed or natural product medication to sleep? Specify which one.", "Do you use replacement hormone therapy for menopause?"(yes/no), "Do you smoke cigarettes, cigars, or pipes? (yes/no) How many per day?" and "How many drinks of alcohol do you take in a day or

in a week?" respectively.

Statistical Analyses

Data analyses were conducted using SPSS with standard alpha of 5%. Data distributions were checked for normality and outliers. Missing values were not imputed. Descriptive statistics were obtained for sociodemographic variables. Variables potentially influencing sleep disturbances and menopause (i.e., age, replacement hormone therapy, sleep medication, depression and anxiety, medical conditions, and use of cigarettes or alcohol) were analyzed using Chi-square (categorical), Student's T-test (continuous/categorial) and Pearson's correlation (continuous). Variables showing a significant relationship with sleep and menopause were included as covariates in the analyses. However, due to their strong bidirectional relationships with sleep disturbances (Benca, Obermeyer, Thisted, & Gillin, 1992), depression and anxiety symptoms were examined with sensitivity analyses. All main analyses were completed twice (with and without inclusion of anxiety and depression as covariates) and comparisons were made to investigate the robustness of the main findings.

To verify the first and second hypotheses, two analyses were carried out on baseline data. First of all, two multivariate analyses of variance (MANOVAs) were performed on measures of sleep quality and insomnia severity, controlling for age. Independent variables were menopausal groups and use of replacement hormone therapy (two levels for each). In total, four MANOVAs were conducted on the variables described above: two MANOVAs between postmenopausal (n = 465) and reproductive (n = 408) women and two MANOVAs between postmenopausal women with (n = 90) and without replacement hormone therapy (n = 375). Then, two binary logistic regression analyses were performed to examine the predictive power of sleep reactivity

and arousal predisposition in predicting clinical levels of insomnia severity (ISI ≥ 8) and sleep quality (PSQI >5) in reproductive and postmenopausal women.

Method used modified and standardized with longitudinal results (cf. results). To verify the third and fourth hypotheses, two analyses were carried out on the longitudinal data. Firstly, linear mixed models using a split-plot 3 (groups) x 5 (time) design were performed on sleep quality and insomnia severity scores in the three groups. Because of the observational design (i.e., reproductive women could become postmenopausal at any time of the study = perimenopausal group), the time variable was (Singer & Willett, 2003): the assessment when transition to menopause was observed was set at centered time = 0 so that the menopausal transition coincided for all women reaching that status. The assessments before the transition were represented by negative values (from -1 to -3 assessments before transition) and the assessments after the transition were represented by positive values (+ 1 to + 2 assessments after transition). In order to reduce pre-existing differences between conditions, each transitioning participant was matched (whenever possible) with one woman in each of the other two conditions, i.e., women who remained postmenopausal and non-menopausal (reproductive) during the five years. Matching was done according to age at baseline, the study initiation phase and the number of participation phase. In the end, all 202 perimenopausal women were matched with at least 154 postmenopausal women or 119 reproductive women.

Method used modified and standardized with longitudinal results (cf. results). Secondly, the moderating effect of sleep reactivity and arousal predisposition were tested on the relationship between menopausal groups and continuous scores of insomnia severity and sleep quality for the longitudinal component. A total of 3 (conditions: reproductive, peri- and postmenopausal) x 2 (reactivity or arousal: low or

high) groups of women were included in mixed model analysis (cf. *outcome measures*) (Altena et al., 2017; Drake et al., 2004).

Results

Sample Descriptive Statistics

Participants were 873 women aged between 40 and 60 years (mean = 50.6 ± 5.9). Most of them had completed at least a high school (27.6%) or a junior college degree (56.2%), they were married or living with a partner (58.6%), and were working full-time (55.9%). In addition, 95.3% were White women and fewer than 20.0% reported having an active medical condition (e.g., diabetes, hypertension). They reported mild depressive symptoms (mean BDI score = 9.0 ± 9.1) and anxiety symptoms (mean STAIT score = 37.7 ± 11.1). At baseline (T1), 408 women were classified as reproductive (mean age = 45.8 ± 3.8) and 465 postmenopausal (mean age = 54.8 ± 4.0). A total of 27.8% of reproductive and 29.4% of postmenopausal women were taking medication (with and without a prescription) for sleep; 13.0% of reproductive women were taking medication three or more times a week (vs 10.8% postmenopausal), 5.0% less than once a week (vs 7.0% postmenopausal), and 9.8% once or twice a week (11.6% post). Among postmenopausal women, 19.4% were taking HRT.

Comparisons with Covariates

The first set of analyses involved covariates that could potentially have an impact on sleep and menopause (e.g., age, medical and psychological conditions, caffeine, tobacco and alcohol use, sleep-promoting medications, and replacement hormone therapy). Only age and the use of replacement hormone therapy were significantly different between the two groups, with postmenopausal women being older and with more women in that group being on HRT than among reproductive women, F (1, 873) = 1134.33, $p < .001$, $\eta^2 = .57$ and χ^2 (1, 873) = 88.04, $p < .001$, respectively.

Comparison of sleep disturbances in reproductive and postmenopausal women (with or without HRT).

Means and standard deviations of the insomnia severity, sleep quality, sleep reactivity and arousal predisposition are described in *Table 1*. The MANOVA showed a main effect of menopause on sleep disturbances, F (2, 866) = 14.82, p <.001, η^2= .03. Average sleep quality scores on the PSQI exceeded five in both groups, which is the typical cut-off score indicating poor sleep quality; 55.1% of reproductive women and 70.1% of postmenopausal women exceeded that score. However, as expected, postmenopausal women reported significantly poorer sleep quality than that reported by reproductive women, F (1, 867) = 28.57, p <.001, η^2= .03. The average severity of insomnia was also significantly higher in postmenopausal women than in reproductive women, F (1, 867) = 15.08, p <.001, η^2 = .02, although both groups exceeded the typical cut-off score of "no insomnia" (i.e., ISI ≥ 8 for 47.5% of reproductive and 60.4% of postmenopausal women).

Moreover, no significant difference was found on insomnia severity or sleep quality between postmenopausal women with and without HRT, F (2, 866) = 1.92, p = .147, η^2= .04. Although the postmenopausal women were older than the reproductive women, age made no significant contribution to the variance of either sleep variables, F (2, 866) = 0.01, p = .987, η^2 = .001. An exploratory MANOVA (sensitivity analysis) with depression and anxiety included as covariates revealed that (a) depression and anxiety covariate had a highly significant contribution to sleep disturbances, F (2, 843) = 40.16, p = .000, η^2 = .09 and F (2, 843) = 27.24, p = .000, η^2 = .06, but (b) menopause still had a significant effect on sleep, F (2, 843) = 7.78, p <.001, η^2= .02, even after controlling for anxiety and depression.

Sleep reactivity and arousal predisposition as predictors of sleep disturbances

The results of the binary logistic regressions are described in *Table 2.* They showed the models to have good classification capacity for sleep quality (65.9-70.1%) and for insomnia severity (67.3-69.4%), reflecting a higher sampling of reproductive and postmenopausal women with sleep difficulties. The specificity and sensitivity of two questionnaires were on average 49.9% and 82.6%, respectively for postmenopausal women, and for 72.8% and 59.6%, respectively for reproductive women. Sleep reactivity and arousal predisposition were significant predictors ($p < .001$) of poorer sleep quality and greater insomnia severity. For example, postmenopausal with high sleep reactivity had 1.10 (95% CI = 1.06-1.14) and 1.07 (95% CI = 1.05-1.14) times greater risk of reporting poor quality of sleep and greater insomnia severity than the postmenopausal women with low sleep reactivity. Similarly, postmenopausal women with high arousal predisposition were 1.05 (95% CI = 1.02-1.09) and 1.09 times (95% CI = 1.05-1.13) more likely to have poor sleep quality and greater insomnia severity than the women with low arousal predisposition. Similar results were found in reproductive women, and no significant difference was noticed between the two groups.

Examination of the temporal changes of sleep disturbances during the menopausal transition

The longitudinal analyses showed significant effects of transition stage (i.e. timing) and menopausal groups on sleep disturbances, on both insomnia severity F (5, 1763) = 5.93, $p < .001$, $\eta^2 = .02$ and F (2, 473) = 6.48, $p =. 002$, $\eta^2 = .03$, respectively, and sleep quality, F (5, 1779) = 3.20, $p = .007$, $\eta^2 = .01$ and F (2, 477) = 13.48, $p < .001$, $\eta^2 = .05$, respectively. A significant interaction was also observed between stage and menopausal groups for insomnia severity, F (10, 1762) = 1.78, $p = .05$, $\eta^2 = .01$ and for sleep quality, F (10, 1778) = 2.02, $p = .028$, $\eta^2 = .01$. In order to determine the direction of the

interaction effects, four simple effect tests were performed. As seen in *Figures 1 and 2,* the results showed menopausal groups to have a significant time effect from stages -3 to 2 (p <.05, except at stage 1 where p = .09; $\eta^2 \leq .01$) on insomnia severity, and at each stage of the transition (p <.01; $\eta^2 \leq .03$) on sleep quality. The results also showed that for all five transition stages, reproductive women had significant changes of insomnia severity (p = .001; η^2= .01) and postmenopausal women had significant changes of sleep quality (p =. 001; η^2 = .01) and insomnia severity (p =. 004; η^2= .01).

Sensitivity analyses revealed that depression and anxiety both had a significant covariate effect on insomnia severity (p = .000, η^2 = .05 and p = .000, η^2= .03), and sleep quality (p = .000, η^2 = .04, and p =.000, η^2 = .01), while the unique contribution of menopause was still significant for insomnia severity, F (2, 460) = 6.20, p = .002, η^2 = .03, and for sleep quality, F (2, 458) = 14.77, p = .000, η^2= .06. However, main effect of the transition stage and stage x menopausal interaction failed to reach significance for insomnia severity (p = .336 and p = .446, respectively) and sleep quality (p = .684 and p = .312, respectively).

Moderating role of sleep reactivity and arousal predisposition

Results on the moderating role of sleep reactivity and arousal predisposition are reported in *Tables 3 and 4,* respectively. The analyses showed that sleep reactivity and arousal predisposition had a significant effect on insomnia severity (p <.001; η^2 = .11 and η^2 = .12) and sleep quality (p <.001; η^2= .08 and η^2 = .09), regardless of transition stages and menopausal groups. However, no significant difference for sleep reactivity was found with groups, stages, and the interaction (= moderation) between transition stage and menopausal groups for insomnia severity (p = .733, p = .632, and p = .489, respectively) or sleep quality (p = .125, p = .971, and p = .962, respectively). For arousal predisposition, no significant difference was observed for the transition groups,

stages and interaction (= moderation) between stage and menopausal groups neither for insomnia severity (p = .439, p = .355, and p = .781, respectively) nor for sleep quality (p = .305, p = .469, and p = .313, respectively).

Discussion

The cross-sectional data documented the higher rates of sleep disturbances (i.e., poor sleep quality and insomnia severity) during menopause, which was partially explained by higher levels of arousal predisposition and sleep reactivity. Longitudinal data showed that sleep disturbances increased around the menopausal transition (three years before and two years after), although sleep reactivity and arousal predisposition did not moderate this temporal relationship.

Consistent with previous studies (Kravitz & Joffe, 2011; Ohayon, 2006; Young, Rabago, Zglerska, Austin, & Laurel, 2003), our results showed that postmenopausal women reported worse sleep quality and higher insomnia severity compared with reproductive women, and these findings were independent of age, depression and anxiety symptoms. The results also indicated that more 60% of postmenopausal women reported clinical levels of insomnia (ISI ≥ 8) and poor sleep quality (> 5), confirming the high incidence of sleep disturbances during menopause. Our results also showed that postmenopausal women taking replacement hormone therapies (HRT) did not sleep better than those not using HRT. Previous studies have reported conflicting results about the effects of HRT for sleep disturbances during menopause (Diem et al., 2006; Hachul et al., 2008; Kalleinen, Polo, Himanen, Joutsen, & Polo-Kantola, 2008; M. Xu et al., 2011), with some suggesting sleep improvements while others reporting no significant benefits. The results need to be interpreted cautiously as the lack of significant findings could be accounted for by lack of statistical power. Some methodological differences with other studies may also explain these results (Cintron et

al., 2017), such as heterogeneity of samples and instruments used to assess sleep disturbances, as well as the lack of information on severity of vasomotor symptoms, and formulations, doses, and duration of HRT.

Our results showing that women with a high level of sleep reactivity or arousal predisposition are at higher risk of poor sleep quality and more severe insomnia relative to those with low levels of reactivity or arousal predisposition are consistent with other studies linking insomnia to psychological factors (Drake et al., 2004; Fernandez-Mendoza et al., 2010; Jarrin, Chen, Ivers, Drake, & Morin, 2016). One other study conducted in the general population demonstrated that sleep reactivity increased over time such that 68% of individuals with insomnia and low sleep reactivity at baseline had to be reclassified as having high sleep reactivity at a later assessment point (Kalmbach, Pillai, Arnedt, Anderson, & Drake, 2016). This evidence may suggest that arousal and sleep reactivity are premorbid characteristics, which might predict future occurrence of sleep disturbances (Drake et al., 2014; Fernandez-Mendoza et al., 2010). Greater sleep reactivity and arousal predisposition may play a critical role in the increased incidence of insomnia in women (Drake, Friedman, Wright, & Roth, 2011), especially during the menopause.

The longitudinal data are consistent with those of several previous studies also showing significant increase of sleep disturbances during the menopausal transition (Berecki-Gisolf et al., 2009; Dennerstein, Lehert, Guthrie, & Burger, 2007; Tom, Kuh, Guralnik, & Mishra, 2010). At any time during the five years of our study, peri and postmenopausal women reported poor sleep quality and insomnia, independent of the presence or absence of concomitant depressive symptoms. The menopausal transition is most likely associated with several biological (e.g., hormonal, hot flashes), psychosocial (e.g., beliefs, anxiety) and demographic (ethnicity) factors (Hunter, 2003; Kravitz &

Joffe, 2011), which is turn can be conceptualized as a major precipitating factor of sleep disturbances during this transition. Sleep reactivity, which has been shown to have a critical influence on the progression of insomnia in the general population (Drake et al., 2004; Petersen, Kecklund, D' Onofrio, Nilsson, & Åkerstedt, 2012), may also influence the impact of some menopausal symptoms on the sleep system (Kalmbach et al., 2019).

Contrary to our hypothesis, we did not find that sleep reactivity or arousal predisposition played a moderating role of the association between sleep disturbances and menopausal transition. One possible explanation is that sleep reactivity and arousal predisposition are viewed as predisposing factors which, by definition, are pre-existing and remain stable over time (Altena et al., 2017; Jarrin et al., 2016). Although sleep reactivity may act as a moderator of stressful life events on the risk of experiencing insomnia (Kalmbach et al., 2016), it could be that the change in menopausal status is a gradual process and may not be a sufficient stressor to produce or perpetuate sleep problems. Other factors, such as vasomotor symptoms (e.g. hot flashes), psychological (e.g., anxiety, worries), moderate sleep during menopause (Ford, Sowers, Crutchfield, Wilson, & Jannausch, 2005; Hunter, 2003; Pien, Sammel, Freeman, Lin, & Deblasis, 2008; Pinkerton, Abraham, Bushmakin, Cappelleri, & Komm, 2016). Also, since no information on such variables as hot flashes was available in the current study, it remains unclear the extent to which such symptoms contributed to increasing sleep disturbances during menopausal transition.

This study has some limitations. For instance, there was no formal evaluation of diagnosis of insomnia and the data were all based on self-report measures, which could be problematic for sleep and insomnia given the well-known discrepancies between subjective and objective measurements. The sample was fairly homogeneous and may not have been representative of the minority/ethnic groups in Canada. With regard to

this last issue, previous studies have shown that beliefs and perceptions of some menopausal symptoms may vary as a function of several biopsychosocial and cultural differences (Davis & Wellons, 2013; Hunter, 2003), which may have affected our participants' response to the question about their menopausal groups. A related issue was the use of a single question to determine menopausal groups, which may have yielded some false-negatives. Our survey did not include clinical information on menopause and some of its prominent symptoms such as hot flashes. Most of these limitations are essentially the result of conducting secondary analyses from a study that was not initially designed to answer the research questions addressed in the current study. Future prospective studies should use recommended standard assessment procedures (STRAW) based on biological parameters (menstrual cycles, hormones) to validate menopausal status (Soules et al., 2001). Despite these limitations, our study has several strengths including its large, population-based sample, the inclusion of well-validated measures to capture key constructs related to sleep/insomnia, and the repeated assessments over a 5-year period. In addition, the combination of both a cross-sectional and a longitudinal perspectives lends further value to our study.

In conclusion, the findings document the increasing incidence of sleep disturbances during menopausal transition and potential risk factor such as hyperarousal and sleep reactivity. Additional research is warranted to delineate further the relative contribution of pre-existing psychosocial characteristics (e.g., sleep reactivity and arousal) and biological (e.g., hot flashes) factors, and their interaction, in explaining this increased incidence of sleep disturbances. Monitoring these biopsychological changes prospectively during the different menopausal stages in a large cohort of women would provide a better understanding of these relationships between sleep and menopause. In

addition to a better theoretical understanding, such studies would also provide useful information for improving the screening and treatment of menopausal insomnia.

Table 1. Means and standard deviation of the baseline on insomnia severity (ISI), sleep quality (PSQI), sleep reactivity (FIRST) and arousal predisposition (APS) according to the reproductive and postmenopausal women.

	Reproductive	Postmenopausal	p	η^2
	M (ET)			
ISI	8.16 (5.78) [a]	9.75 (6.25) [b]	.001	.02
PSQI	5.96 (8.82) [a]	7.45 (4.35) [b]	.001	.03
FIRST	23.20 (6.31)	24.03 (6.88)	.066	.00
APS	30.89 (7.33)	31.05 (7.25)	.750	.00

Note. Averages that do not share the same letters in higher indices are significantly different from each other ($p < .001$) (MANOVAs).
Effect size: $\eta^2 = .01$ (small), $\eta^2 = .06$ (moderate), $\eta^2 = .14$ (large).

Table 2. Binary logistic regression analysis predicting sleep reactivity (FIRST) and arousal predisposition (APS) in sleep disturbances.

		Reproductive		Postmenopausal	
		β^1	*95% C.I.*[2]	β^1	*95% C.I.*[2]
ISI	FIRST	1.09***	[1.05 ; 1.14]	1.07***	[1.04 ; 1.11]
	APS	1.08***	[1.04 ; 1.12]	1.09***	[1.05 ; 1.13]
PSQI	FIRST	1.10***	[1.05 ; 1.14]	1.10***	[1.06 ; 1.14]
	APS	1.05**	[1.02 ; 1.09]	1.05**	[1.02 ; 1.09]

Note. [1]Standardized coefficient and [2]Confidence Interval.
Significant **$p < .01$; ***$p < .001$
Effect size: $R^2 = .01$ (small), $R^2 = .06$ (moderate), $R^2 = .14$ (large).
Sleep disturbances = sleep quality (PSQI) and insomnia severity (ISI).

Table 3. Moderation analysis of the relationships between sleep reactivity, menopausal groups, transition stage and sleep disturbances.

		F	*p*	η^2
ISI	FIRST	57.90	.001*	.11
	FIRST*Stage	0.69	.632	.00
	FIRST*Groups	0.31	.732	.00
	FIRST*Stage*Groups	0.95	.489	.01
PSQI	FIRST	45.60	.001*	.08
	FIRST*Stage	0.18	.971	.00
	FIRST*Groups	2.09	.125	.01
	FIRST*Stage*Groups	0.36	.962	.00

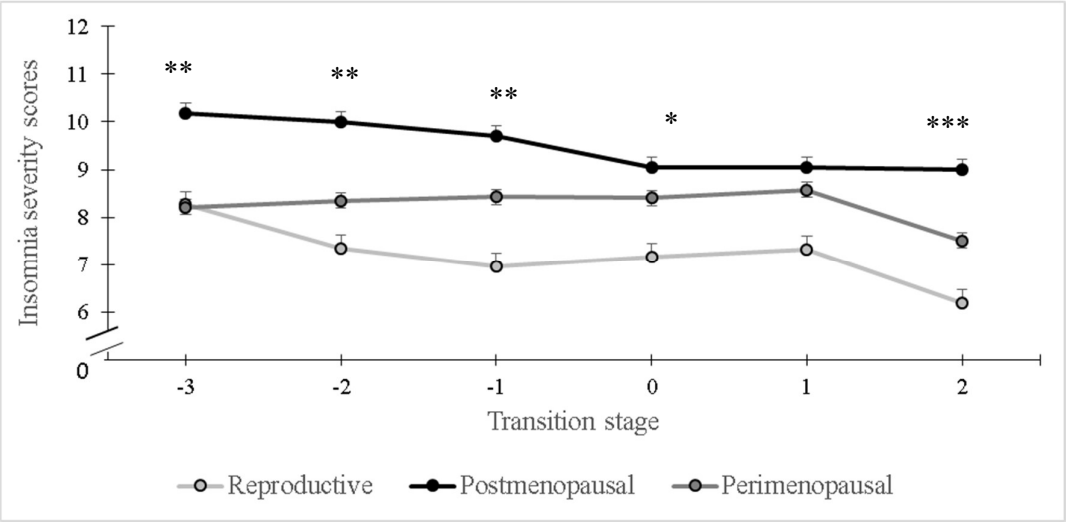
Note. Significant ($p < .05$).
Effect size: $\eta^2 = .01$ (small), $\eta^2 = .06$ (moderate), $\eta^2 = .14$ (large).
Stage = timing of menopausal transition (-3 to 2); groups = reproductive, peri- and postmenopausal women; sleep disturbances = sleep quality (PSQI) and insomnia severity (ISI); FIRST = sleep reactivity.

Table 4. Moderation analysis of the relationships between arousal predisposition, menopausal groups, transition stage and sleep disturbances.

		F	*p*	η^2
ISI	APS	65.71	.001*	.12
	APS*Stage	1.11	.355	.00
	APS*Groups	0.83	.439	.00
	APS*Stage*Groups	0.64	.781	.00
PSQI	APS	51.14	.001*	.09
	APS*Stage	0.92	.469	.00
	APS*Groups	1.19	.305	.01
	APS*Stage*Groups	1.16	.313	.01

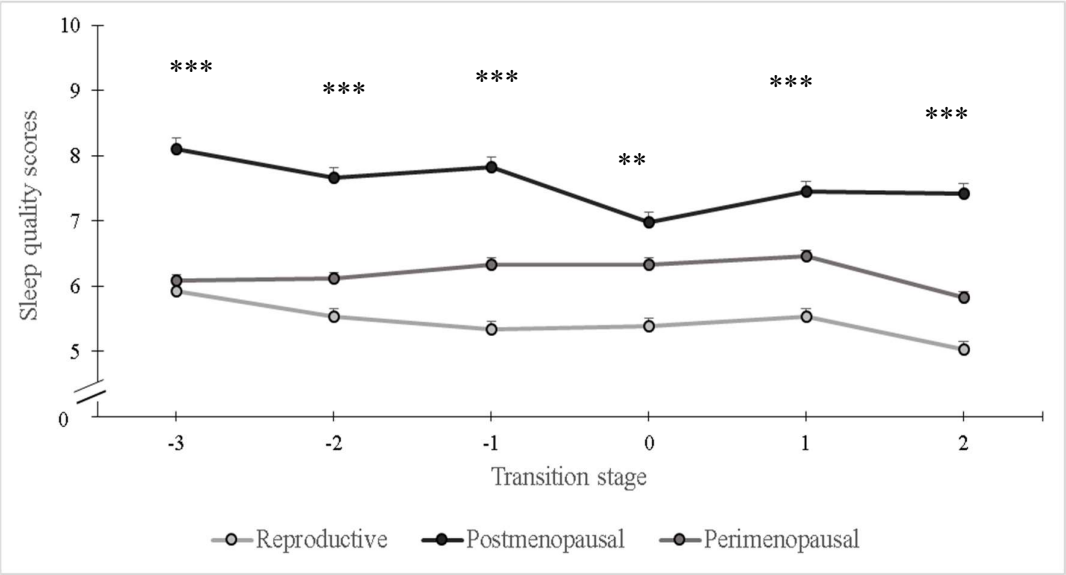
Note. Significant ($p < .05$).
Effect size: $\eta^2 = .01$ (small), $\eta^2 = .06$ (moderate), $\eta^2 = .14$ (large).
Stage = timing of menopausal transition (-3 to 2); groups = reproductive, peri- and postmenopausal women; sleep disturbances = sleep quality (PSQI) and insomnia severity (ISI); APS = arousal predisposition.

Figure 1. Severity of insomnia according to menopausal groups.



Note. On x-axis, transition stage is centered relative to the assessement when perimenopausal women reported a transition from reproductive to perimenopausal status (transition time = 0). Assessments before the transition are represented by negative value (-1 = one assessment before transition) while assessments after the transition is represented by positive values. To compare the change, the perimenopausal women were matched (where possible) with reproductive and postmenopausal women during the five years.
Asterisks correspond to the significant difference between groups for a specific time (transition stage) (*$p < .05$; **$p < .01$; *** $p < .001$). Error bars represent the standard error.

Figure 2. Sleep quality according to menopausal groups.



Note. On x-axis, transition stage is centered relative to the assessement when perimenopausal women reported a transition from reproductive to perimenopausal status (transition time = 0). Assessments before the transition are represented by negative value (-1 = one assessment before transition) while assessments after the transition is represented by positive values. To compare the change, the perimenopausal women were matched (where possible) with reproductive and postmenopausal women during the five years.
Asterisks correspond to the significant difference between groups for a specific time (transition stage) (*$p < .05$; **$p < .01$; ***$p < .001$). Error bars represent the standard error.

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