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Depressed Mood but Not Fatigue Mediate the Relationship between Physical Activity and Perceived Stress in Middle-Aged Women

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Abstract

Objective—To determine whether depressed mood and fatigue mediate the relationships between physical activity, body mass index, menopausal hot flashes, and perceived stress.

Method—This study is a secondary analysis of data obtained from a sub-sample of peri- and postmenopausal women ($N = 212$) from the TREMIN Research Program on Women's Health.

Results—The hypothesized mediational model was tested using path analysis within a structural equation modeling framework in Mplus Version 5.1. In unadjusted analysis, the relationships between physical activity, menopausal hot flashes, and perceived stress were mediated by depressed mood; fatigue mediated the relationships between hot flashes, body mass index, and perceived stress. When adjusting for age, insomnia, menopausal and hormone use status, the mediational effects of depressed mood on stress remained significant only for physical activity, and fatigue mediated the relationship between hot flashes and stress. The adjusted model explained 70% of variance in perceived stress, 82% of variance in depressed mood, and 81% of variance in fatigue.

Conclusion—Depressed mood may partially explain the relationship between physical activity and perceived stress in middle-aged women, however further studies are needed to corroborate causality.

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AUTHOR CONTRIBUTIONS

Steriani Elavsky, Ph.D. - conceptualized study, conducted analysis, wrote the first manuscript draft and collaborated on revising the manuscript

I declare that I designed the study, conducted data analysis, and manuscript preparation. I have prepared and approved the final version. I have no conflicts of interest.

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Carol H. Gold, Ph.D. - collaborated on study design, analysis, manuscript preparation and writing

I declare that I participated in the planning of the study, data analysis, and manuscript preparation. I have seen and approved the final version. I have no conflicts of interest.

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COMPETING INTERESTS

There are no conflicts of interest associated with the journal, this submission, and the authors.

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1. Introduction

The menopausal transition is an individualized experience that is influenced by a woman's prior health and lifestyle. The most consistent psychosocial predictor of health and well-being during the menopausal transition (MT) is stress [1]. Both acute (e.g., interpersonal relationships or daily hassles) and chronic stressors (e.g., history of child abuse or victimization) have been linked to adverse health outcomes, more menopausal symptoms, and poorer well-being in middle-aged women. Moreover, there is a reciprocal relationship between stress and the menopausal transition as stress may exacerbate menopausal symptoms and menopausal experiences may, in turn, influence the perception, experience of, and coping with stressful life events [2]. Women who experience longer MT and increased symptoms have higher stress, and were found to be at increased risk for depression [3]. Menopause-related distress (i.e., experiencing symptoms) increases levels of inflammatory cytokines [4,5], and psychosocial stress in general has been associated with the development of hypertension, metabolic syndrome, and faster progression of CVD [6]. Recently also, stressors such as chronic or childhood stress, abuse, and victimization have been associated with increased reporting of vasomotor symptoms [2,7].

Physical activity has been recommended, as part of a healthy lifestyle, as the first line of defense against the negative consequences of menopause, including for the management of mild to moderate symptoms [8]. Maintaining or increasing participation in regular physical activity may also prevent or attenuate increases in total body fat and visceral adipose tissue [9] and CVD risk factors in midlife women [10-12]. Importantly, physical activity has been associated with lower levels of stress generally [13,14] and during ovarian aging [15], and both animal and human literature supports the role of physical activity in attenuating the adverse effects of stress on health [16]. In animal studies, for example, the physiological effects of exercise on reducing stress have been shown to occur through reductions in behavioral depression and immunosuppression brought about by different stressors [17,18]. The mechanisms of the effect of exercise on reducing perceived stress in humans remain unclear but likely involve multifactorial influences including physiological (e.g., neuroendocrine, cardiovascular, immune, etc.) and psychosocial pathways.

Among the psychosocial mediators implicated in the exercise-stress relationship are mood and fatigue. Exercise can reduce fatigue and fatigue-related symptoms [19,20], reduce depression [21] and enhance mood [16]. Although not specific to menopause [22], depressed mood and fatigue-related symptoms are among the most commonly reported problems by menopausal women [23,24], and women with chronic fatigue conditions report more menopausal symptoms [25]. Other influences on stress during the menopausal transition include vasomotor symptoms such as hot flashes and a woman's weight status. Vasomotor symptoms, for example, may increase levels of fatigue as a result of impairing sleep. They are also more common in overweight and obese women who are more likely to experience symptoms of depression [26]. Although the evidence remains mixed, physical activity has been linked to vasomotor symptoms and influences weight status [27]. Thus, it is conceivable that in addition to its effects on depressed mood and fatigue, physical activity can influence stress levels by modulating vasomotor symptoms and weight status. The objective of this study was to examine cross-sectionally the relationship between physical activity and perceived stress in middle-aged women. Specifically, we hypothesized that depressed mood and fatigue would mediate the relationship between physical activity and perceived stress. Additionally, we hypothesized that hot flashes and body mass index would be related to physical activity, and both would also indirectly relate to stress through depressed mood and fatigue.

2. Material and methods

2.1. Participants

The study drew data from a sub-sample of women participating in the Tremin Research Program on Women's Health (Tremin), a longitudinal and intergenerational study of menstrual characteristics and health outcomes in women over the life course (for detailed Tremin description see Mansfield & Bracken, 2003) [28]. The Tremin population initially included 2,350 women; a second group of 1,600 women were enrolled between 1961-1963, ranging in age from teenage years to mid-nineties. In 1990, a subgroup of 505 premenopausal women (aged 35–55) from the TREMIN program and Douglass College (Rutgers University) were recruited into an ongoing longitudinal study of the menopausal transition (The Midlife Women's Health Survey) [29]. In this secondary analysis, a sample of 212 participants was drawn from women who responded to the annual Tremin survey in 2000. This survey timepoint was selected because physical activity data were available, allowing us to compute minutes of exercise per week. Although two other time points included exercise related questions (1987 and the 1997 Midlife Women's Health Survey), the format of exercise questions was inconsistent and not all variables under consideration in this study were available at each of the time points. Only women who were peri- or postmenopausal by the time of the 2000 Tremin survey were included but no restrictions were placed on the sample relative to type of menopause (i.e., surgical versus natural) or exogenous hormone use.

2.2. Measures

Demographics and background information—The basic demographic information in the Tremin survey included age, race and ethnicity, marital status, employment, household income, education, and self-reported weight and height from which body mass index (BMI) was computed.

Menopausal status and HRT use—Menopausal status of the women was determined by self-report through a series of questions about menstrual bleeding patterns and characteristics. Women reporting changing periods or those who had not menstruated for three months or longer were further asked to indicate a reason. Based on the responses we categorized women into peri- and postmenopausal categories. Perimenopausal women were those who reported changing periods due to menopause with irregular bleeding patterns or no bleeding in the last three months, but no longer than 12 months. Postmenopausal women were those who reported having no menstrual bleeding in the past 12 months either due to natural or surgical menopause. Women were also asked about their hormone therapy (HT) and other medication use in the previous year, including type, dosage, and brand. The sample was subsequently categorized into HT users and HT non-users.

Symptoms—Women were asked to rate their experience with 41 different symptoms in the previous year on a scale ranging from 0 (did not experience) to 4 (debilitating). The symptoms considered for this study were “Tiredness/fatigue”, “Feeling depressed/having ‘the blues’”, and “Hot flashes”; “Insomnia” was used as a covariate in the analysis.

Physical activity level—Women were asked to report their exercise pattern in the previous year by season, including frequency and duration of exercise. We averaged these responses for the entire year and computed average minutes of exercise per week.

Stress—Perceived stress was assessed using the 4-item version of the Perceived Stress Scale [30]. The scale assesses a global appraisal of stress and includes questions such as “In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?”. Respondents rated their responses on a scale ranging from 0 (never) to 4 (very often).

Positively worded items were reverse coded and responses were summed across all four items arriving at a possible range of scores from 0 to 16. The internal consistency of the scale in this study was acceptable (Cronbach's $\alpha = .75$).

2.3. Data Analysis

Descriptive statistics were used to examine the background characteristics of the sample and means and standard deviations for the outcome variables of interest. Subsequently, correlational analysis was conducted to evaluate bivariate associations among the outcomes. The proposed mediational model was tested using the Mplus 5.1 statistical software program [31] with the full-information maximum likelihood estimator. The full-information estimator was used because there were missing data for hot flashes (1.4%), fatigue (1.9%), depressed mood (1.4%), stress (1.4%), and physical activity (7%).

The model tested examined (a) direct associations between physical activity, hot flashes, BMI and depressed mood and fatigue, and (b) indirect associations of physical activity, hot flashes, and BMI with perceived stress through depressed mood and fatigue. The data are reported for both an unadjusted model and model adjusted for covariates including age, menopausal and hormone use status, and insomnia. Model-data fit was assessed using standard indices: the chi-square statistic [32]; the standardized root mean square residual (SRMR) [33] (the SRMR should approximate or be less than .08 for a good fitting model [34]); the root mean square error of approximation (RMSEA) (values approximating .06 or less are indicative of a close fit [35]); and comparative fit index (CFI) [35] (the CFI should approximate 0.95 or greater for a good fitting model [34]). All path coefficients and correlations are reported as standardized estimates. Significance was evaluated based on a two-tailed test with a critical value set at .05.

3. Results

3.1. Sample Description

The mean age for the sample was 56.7 ($SD = 3.9$) and it was composed of primarily White non-Latina women (97%). About a quarter of the sample was perimenopausal (52 women) and the remainder was postmenopausal (160 women). Hormone therapy use was reported by 135 women (nearly 64%). The majority of the women were either married or in a committed relationship (82%) and most of them were working (46.7% full-time and 26.3 % part-time), with some indicating being home-makers (12.7%) or retired (10%). Although the sample was highly educated overall, with nearly 92% of women having earned a college or postgraduate degree, there was variation in household income which was reported by 90% of the sample. Nearly 20% of women reported annual income under \$45,000, 42% reported annual income between \$45,000-\$100,000, and 28% above \$100,000. Means and standard deviations for all main study variables are presented in Table 1. Bivariate correlations among all variables are also presented in Table 1. The majority of the hypothesized relationships were supported. As can be seen, perceived stress was significantly associated with both depressed mood and fatigue. Physical activity, hot flashes, and BMI were associated with depressed mood but only hot flashes and BMI were significantly associated with fatigue. Although the traditional approach to testing mediation suggest that the independent variable (here physical activity, hot flashes and BMI) should be associated with the outcome (here perceived stress) prior to proceeding with tests for mediation [36], more recent studies have suggested that this approach substantially reduces power to detect mediation and is not recommended [37]. Contrary to our expectations, physical activity was not associated with hot flashes, although it was associated with BMI. Although not all predicted associations were supported at the bivariate level, the pattern of the correlations indicated that testing the proposed mediational model was still feasible.

3.2. Analyses of the Proposed Mediation Model

The proposed mediational model fit the data well ($\chi^2 = 3.291$, $df = 3$, $p = 0.3489$; SRMR = 0.021, RMSEA = 0.021; CFI = 0.998). The value of the chi-square was nonsignificant and the SRMR, RMSEA and CFI values indicated good model-data fit. As can be seen in the top panel of Figure 1, there were statistically significant path coefficients ($p < .05$) for direct effects of physical activity ($\beta = -.16$) and hot flashes on depressed mood ($\beta = .18$), and the effects of BMI on depressed mood approached statistical significance ($\beta = .13$, $p = .061$). Hot flashes ($\beta = .21$) and BMI ($\beta = .14$) were significantly associated with fatigue. In turn, depressed mood ($\beta = .31$) and fatigue ($\beta = .32$) were both associated with perceived stress. There was also a moderate association between depressed mood and fatigue ($\beta = .42$). Women reporting higher levels of physical activity and lower levels of hot flashes, and with lower BMI, had lower levels of depressed mood and fatigue (for hot flashes and BMI only) and, in turn, also lower perceived stress. Women reporting lower levels of hot flashes and having lower BMI had lower levels of fatigue, and, in turn, also lower perceived stress.

Because some of the associations may have been impacted by other factors such as age, menopausal and hormonal status, or experiencing insomnia, we proceeded to test the same model controlling for these factors. The results of the adjusted model are presented in the lower panel of Figure 1. The fit of the model did not change substantially ($\chi^2 = 2.800$, $df = 3$, $p = 0.4236$; SRMR = 0.012, RMSEA = 0.000; CFI = 1.000), however, some of the paths were no longer statistically significant. Namely, the association between hot flashes and depressed mood was reduced and no longer significant, and BMI was no longer significantly associated with fatigue. The effects of physical activity on perceived stress remained mediated by depressed mood ($\beta = -.15$) and the effects of hot flashes on perceived stress were mediated by fatigue ($\beta = .14$). The associations between depressed mood, fatigue and perceived stress were only slightly reduced. The analysis indicated that only age and insomnia were significant covariates of these effects, primarily due to the associations of age with BMI ($-.15$) and insomnia with hot flashes ($.18$). Menopausal and hormone use status were significantly associated with hot flashes but these associations appeared to have little effect on the modeled paths. Overall the model accounted for 70% of the variation in perceived stress, 82% of variation in depressed mood, and 81% of the variation in fatigue.

4. Discussion

The level of perceived stress is an important indicator of a trouble-free menopausal transition. There appears to be increased vulnerability to stress during the menopausal transition as women in early perimenopause report the highest rate of psychological distress as compared to premenopausal and postmenopausal women, and postmenopausal women respond more intensely to stress than premenopausal women [2]. Stress has been associated with increased reporting of menopausal symptoms such as hot flashes [2,7], and, over time, high levels of perceived stress may lead to adverse physical and mental health outcomes, including cardiovascular disease [38] or clinically defined depression [39]. Thus, it is important to identify modifiable risk factors for stress. Our study aimed to examine how one such modifiable factor, physical activity, influences the level of perceived stress in middle-aged women.

Both physiological and psychosocial mechanisms are implicated in determining stress levels, although the exact causal mechanisms remain unclear. We hypothesized that the effect of physical activity may occur indirectly through depressed mood and fatigue and that factors such as menopausal hot flashes and weight status also play a role. The results of our analysis provided only partial support for this hypothesis. Although in the unadjusted model the effects of physical activity and hot flashes on stress were mediated by depressed mood, and the effects of hot flashes and BMI on stress were mediated by fatigue, after controlling for covariates the mediated paths remained significant only for physical activity through depressed mood and

for hot flashes through fatigue. Both depressed mood and fatigue had significant associations with perceived stress and of similar magnitude. Both fatigue and depressed mood have been consistently linked to stress [40]. For example, a recent observational study described longitudinal changes in the level of perceived stress across the menopausal transition and although stress levels tended to decline in postmenopause, factors such as employment, history of sexual abuse, depressed mood, and poor self-perceived health were associated with higher levels of stress [41].

The mediated effect of physical activity on perceived stress through depressed mood is consistent with previous literature. Regular exercise enhances mood during the menopausal transition [42]; it has proven antidepressive and anxiolytic effects, and reduces sensitivity to stress [16]. The results of our study suggest that, regardless of weight status and level of hot flashes, women who spend more time on exercise per week experience less depressed mood and as a result perceive less stress. On the contrary, although other literature suggests that chronic exercise reduces fatigue [20], this study did not demonstrate a significant association between average minutes of exercise per week and fatigue. Although this lack of association may be a function of the rather crude measures of both physical activity and fatigue used in this study, the pattern of the remaining significant associations observed in our model may indicate an alternative causal pathway. That is, it is possible that physical activity may reduce fatigue but indirectly through its effects on depressed mood. Physical activity was associated with depressed mood in our study and depressed mood was associated with fatigue. A meta-analytic study of exercise effects on fatigue demonstrated that depression status moderates the effect of exercise on fatigue and indicated that depressive symptoms may also mediate the exercise-fatigue relationship [20]. Future studies should further examine the plausibility of the causal pathways between physical activity, depressed mood, fatigue, and stress.

Contrary to our expectations physical activity was associated only with BMI but not hot flashes, adding to the controversy over whether or not physical activity ameliorates menopausal hot flashes. The support for this association has been inconsistent and few randomized controlled trials have been conducted to test this association experimentally [27,43]. The most recent studies indicate that the effects of physical activity on hot flashes may depend on weight status [44] or body fatness [45] and the intensity of exercise or fitness [27,46]. In our study, physical activity was associated with BMI but neither was associated with hot flashes. It is possible that the lack of association may once again be a function of the rather crude and retrospective measures employed in this study. Our measure of physical activity reflected average minutes of exercise per week and weight status was self-reported and based on BMI. Unfortunately, the Tremin survey did not assess the intensity of exercise and BMI is not an accurate indicator of body fatness. Although the cross-sectional design of this study does not allow us to draw definite conclusions about the relationship between physical activity and menopausal hot flashes, it must be noted that the health benefits of regular exercise for menopausal women are far reaching regardless of whether physical activity reduces hot flashes or not. The effect of physical activity on lowering the likelihood of depressed mood is itself of great value. A more important point from the public health perspective may be that although these benefits are well-known, only a small percentage of middle-aged women engage in regular physical activity [47].

This study found that physical activity and menopausal hot flashes impact levels of perceived stress in middle-aged women regardless of menopausal or hormone use status. These effects are however indirect, occurring through the mediation of depressed mood and fatigue. This is the first study to examine these psychosocial pathways in peri- and postmenopausal women and we seek further corroboration. The findings must also be interpreted in light of the study's limitations. First, it should be noted that establishing true mediation requires experimental manipulation of both the independent and mediating variable(s). That is, in order to establish

causal inferences, subjects must be randomly assigned to levels of the independent variable(s) as well as to levels of the mediating variable [37]. Given the cross-sectional nature of our data, the sequencing and/or direction of the hypothesized relationships cannot be certain. For example, it is possible that women with higher levels of stress experience more depressed mood and fatigue and as a result more hot flashes which, in turn, leads them to avoid physical activity and over time to gain weight. It is also possible that there may be additive effects among some of these factors or complex interactions which we did not consider (and could not evaluate due to small sample size). For example, a recent study demonstrated an additive effect of depressed mood and vasomotor symptoms on postmenopausal insomnia.[48]. In our study, age covaried with BMI and insomnia with hot flashes, which were associated with fatigue. Although the analysis controlled for both factors, this approach may have been inappropriate if either of these factors are in the causal pathway. More research is needed to systematically investigate these possibilities.

The sample in this study was homogeneous and the findings must be replicated in more diverse samples. The number of women using hormone therapy was relatively high but this is consistent with the nature of the sample (primarily White, highly educated women) and the fact that these data were collected prior to the early termination of the WHI studies in the U.S. The reported levels of hot flashes, depressed mood, fatigue, and stress were relatively low in this study. It is possible that the effects of physical activity may be more pronounced in a more “impaired” sample. Our outcome measures were relatively crude, retrospective and self-reported, including weight and height on which the BMI was calculated. It should be noted, however, that although self-reported BMI is considered an imprecise measure of weight status, the correlations between measured and self-reported BMI are relatively high in diverse samples ($r > .90$) and self-reported BMI correlates equally with disease biomarkers, making it an acceptable measure [49]. Future studies should incorporate more comprehensive measures of these psychosocial outcomes and when possible, incorporate objective measures of physical activity and other physical/fitness indicators. Finally, we focused on depressed mood and fatigue as potential mediators of the physical activity – stress relationship; however, there may be other important mediating factors such as role conflicts or social support [41].

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Figure 1. Proposed Mediational Model

Note. Solid lines represent relationships statistically significant at $p < .05$.

Table 1

Descriptive Statistics and Bivariate Correlations among All Variables

Variable	Mean	SD	1.	2.	3.	4.	5.	6.
1. Physical activity	161.61	139.80	1.00					
2. Hot flashes	0.85	1.15	0.05	1.00				
3. Body mass index	24.75	4.35	-0.21**	0.03	1.00			
4. Depressed mood	1.00	1.14	-0.18*	0.17*	0.17*	1.00		
5. Tiredness/fatigue	1.49	1.15	-0.09	0.21**	0.16*	0.46**	1.00	
6. Perceived stress	4.09	2.90	-0.15*	0.04	0.10	0.46**	0.46**	1.00

Note.
* $p < .05$,
** $p < .01$.