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The Dynamics of Stress and Fatigue Across Menopause: Attractors, Coupling, and Resilience

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The Dynamics of Stress and Fatigue Across Menopause: Attractors, Coupling, and Resilience

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THE DYNAMICS OF STRESS AND FATIGUE ACROSS MENOPAUSE

1 **Title:** The Dynamics of Stress and Fatigue across Menopause: Attractors, Coupling and

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3 **Running Title:** Stress and Fatigue Dynamics across Menopause

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THE DYNAMICS OF STRESS AND FATIGUE ACROSS MENOPAUSE

Abstract

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Objective: The objective of this study was to evaluate the regulatory dynamics between stress and fatigue experienced by women during the menopausal transition (MT) and early post-menopause (EPM). Fatigue and perceived stress are commonly experienced by women during the MT and EPM. We sought to discover relationships between these symptoms and to employ these symptoms as possible markers for resilience.

Methods: Participants were drawn from the longitudinal XX Midlife Women's Health Study. Eligible women completed questionnaires on 60+ occasions (annual health reports and monthly health diaries) (n=56 women). The total number of observations across the sample was 4224. STRAW+10 criteria was used to stage women in either in late reproductive, early or late transition, or early post-menopausal stage. Change values were generated for fatigue and stress and analyzed with a multilevel structural equation model; slopes indicate how quickly a person returns to homeostasis after a perturbation. Coupling of stress and fatigue was modeled to evaluate resilience, the notion of maintaining stability during change.

Results: Eligible women were an average 35 years old (SD=4.71), well-educated, employed, married or partnered and white. Fit indices suggested the model depicts the relationships of stress and fatigue ($\chi^2(9 \text{ df}) = 7.638, p=.57$, correction factor=4.9244; RMSEA 90%CI = .000 <=.000 <=.032; CFI = 1.00). A loss in model fit across stages suggests that the four stages differed in their dynamics ($\chi^2\Delta(12 \text{ df}) = 21.181, p=.048$). All stages showed fixed point attractor dynamics for stress and fatigue. Fatigue became less stable over time; stress generally became more stable over time. Coupling relationships of stress on fatigue show evidence for shifts in regulatory relationships with one another across the MT.

Conclusions: Results are suggestive of general dysregulation via disruptions to coupling relationships of stress and fatigue across the MT. Findings support a holistic approach to understanding symptoms and supporting women during the MT.

51

52 **Key words:** Menopausal transition, stress, fatigue, dynamics, attractors

53

54

Introduction

55 Women undergo physiological, psychological, and behavioral changes during the
56 menopausal transition (MT) that impact quality of life and health outcomes.¹⁻³ Post-menopausal
57 women score lower on quality of life metrics than pre-menopausal women, a gap partially
58 explained by post-menopausal women's 10-fold higher risk of suffering vasomotor disorders, 3-
59 fold higher risk for psychosocial impairment, 5-fold higher risk for physical disorders, and 3-fold
60 higher risk for sexual disorders. Of symptoms experienced by women over the course of the
61 menopausal transition (MT), fatigue is clinically significant because it is disabling (Sharpe &
62 Wilks, 2002) and is one of the most common and distressing symptoms associated with
63 menopause. In a cross-sectional study of 300 women, 85.3% of post-menopausal women and
64 46.5% of peri-menopausal women reported symptoms of physical and mental exhaustion
65 compared to just 19.7% of the pre-menopausal women.¹⁴ There may be financial consequences
66 for midlife women experiencing fatigue. For example, a small qualitative study found that
67 women teaching kindergarten were more likely to retire due to fatigue as they aged, thus having
68 fiscal consequences for their retirement (Cau-Bareille, 2011) and for schools losing experienced
69 teachers.

70 Perceived stress is another frequently reported and bothersome symptom experienced
71 by women during the MT. The literature links perceived stress and MT-related symptoms.^{8,10-11}
72 For example, a cross-sectional study examining stressful life events and symptom severity
73 found that post-menopausal women seeking treatment had more severe symptoms than a
74 healthy comparison group.¹¹ Perceived stress may be higher during late transition stage than
75 late reproductive stage (Falconi, Gold & Janssen, 2016) with suggested links to a history of

THE DYNAMICS OF STRESS AND FATIGUE ACROSS MENOPAUSE

76 sexual abuse and depressed mood, while improvement in perceived stress was associated with
77 reduced role burden, improved perception of social support, and income adequacy (Woods,
78 Mitchell, Percival & Smith-DiJulio, 2009). For example, studies of cancer patients have shown
79 that fatigue, a common symptom of the MT and early post-menopause, is a major source of
80 frustration and psychological stress, and that ameliorating fatigue reduces psychological
81 stress.¹³

82 The co-occurrence of stress and fatigue experienced by women has been studied
83 with respect to the workplace (Ricci Chee Lorandegu Berger, 2007; Rose et al, 2017) with
84 work-related stress associated with fatigue, even when controlling for depression and
85 demographic variables (Rose 2017). However, stress and fatigue have not yet been
86 longitudinally examined with respect to midlife women and the menopausal transition.
87 Furthermore, the dynamics of stress and fatigue have not been studied, nor studied with
88 respect to women's health specifically. Given the incidence of midlife women experiencing
89 the potentially fatiguing and stressful phenomenon of "the sandwich generation"
90 (simultaneously caring for children and parents and often working outside the home, as
91 well), it is an important gap in our understanding of midlife women's health (Gillett & Crisp,
92 2017). While it is highly feasible that perceived stress could cause symptoms experienced
93 during the menopausal transition to worsen, it is equally plausible that worsening of these
94 symptoms could be a source of perceived stress.

95 The interactive dynamics of stress and fatigue within the context of the MT are
96 particularly interesting as their mutual co-regulatory functions may vary across different stages
97 of the transition. Just as stress is the body's way of mounting a response to meet the demands
98 of changes or challenges, fatigue is a natural by-product of prolonged exposure to stress.
99 Further, just as stress can drive fatigue, fatigue can down-regulate or up-regulate stress
100 depending on whether fatigue spurs restorative health behaviors (i.e. increased sleep) or

THE DYNAMICS OF STRESS AND FATIGUE ACROSS MENOPAUSE

101 interferes with healthy coping (i.e. insomnia) in an individual. Thus, we thought it important to
102 explore the dynamic and likely bidirectional coupling of stress and fatigue across the MT.

103

104 **Stress and Fatigue: A Nonlinear Dynamical Systems Approach**

105 The MT may be considered to be a key example of a developmental transition that
106 challenges biopsychosocial resilience over time. Nonlinear dynamical systems theory provides
107 the best approach to studying menopause from this perspective.¹⁶ A primary problem with
108 research regarding the MT to date is that symptoms, whether biological, psychological or social,
109 tend to be attributed to the MT rather than to other aspects, both past and present, of women's
110 lives.¹⁷ The present study aims to take into account the underlying biopsychosocial systemic
111 structures and processes prior to and across transition, rather than looking for the simpler
112 causal influences of isolated variables. More specifically, rather than looking at high or low
113 values on variable x or y for influence on "symptoms" experienced during the MT, the present
114 study will examine changes to biopsychosocial structural connections within and among two key
115 variables, aiming to understand systemic regulatory processes more directly and also more
116 holistically. It is our view that this broader, structural and systemic approach may be necessary
117 to more fully understand the complex and systemic mechanisms underlying biopsychosocial
118 resilience as individuals move through ubiquitous biopsychosocial life transitions such as
119 menopause. Specifically, if stress and fatigue shift in their mutual coupling strengths, then one
120 may lose one's ability to flexibly bounce back following higher loads of stress or fatigue.
121 Therefore, evidence of shifts in the coupling relationships among variables like stress and
122 fatigue across key life transitions such as the MT may improve one's understanding of the
123 underlying mechanisms of resilience in complex biopsychosocial systems.

124 Two central biopsychosocial regulatory processes that drive menopausal symptoms are
125 stress and fatigue. Stress and fatigue each fluctuate over time (a) in their levels (i.e., high

THE DYNAMICS OF STRESS AND FATIGUE ACROSS MENOPAUSE

126 versus low), (b) in their flexibility (e.g. chronicity vs. lability), and (c) in their mutual influence on
127 one another (e.g., coupling strength). Changes in each of these dynamical features may have
128 functional significance. Apart from mean levels of stress, for example, the ability for stress to
129 rise in response to a challenge and then return to a lower stable set point may be used to define
130 one's stress resilience.^{16,18-19} Similarly, mean levels of fatigue say little about one's resilience
131 compared to one's ability to become revitalized after sufficient rest.

132 Certainly, understanding a key handful of factors that are associated with mean levels of
133 stress, fatigue, and other health parameters may provide some useful information about one's
134 health and functioning. However, to understand resilience during the MT, the most important
135 question is: How well do post-menopausal women maintain their ability to recover from stress
136 and fatigue? McEwen and Wingfield²⁰ defines the underlying mechanisms of resilience in
137 general terms as "maintaining stability through change" (p. 10), which begs the question: What
138 are the structural factors that underlie one's ability to remain flexible during the menopausal
139 transition? Therefore, it may prove especially useful to apply models and methods capable of
140 quantifying the relative stability of change dynamics to better understand resilience in complex
141 biopsychosocial systems as women move through key transitions such as the MT. In this
142 context resilience refers to the capacity to adapt to perturbations, including the ability to rebound
143 or bounce back to a higher level of functioning, recover to the same level of functioning or
144 experience some degree of improvement without returning to a prior level of functioning.²¹

145 A closely related question to how structure is maintained through change pertains to the
146 maintenance of self-regulatory relationships among key biopsychosocial parameters like stress
147 and fatigue over time. How are these key parameters connected to one another? And how
148 might changes in their dynamical coupling impact resilience during the MT and early post-
149 menopause? On a practical level, the potential for stress and fatigue to serve circular regulatory
150 functions is fairly clear. High levels of stress may adaptively drive up levels of fatigue, resulting

THE DYNAMICS OF STRESS AND FATIGUE ACROSS MENOPAUSE

151 in the corrective response of increased sleep and rest. In a complementary fashion, prolonged
152 fatigue may increase stress, ideally resulting in some adaptive correction through problem-
153 solving, social support, or shifts in one's mindset.

154 A recent line of investigations has tested the idea that a network approach (i.e.,
155 symptoms causing one another within a complex network structure) may be more valid than the
156 traditional "disease" approach (i.e., a latent condition exists which causes individual symptoms)
157 in psychopathology.²²⁻²⁴ The evidence gathered thus far has suggested that the structure of
158 symptom networks (i.e., generally looser symptom connectivity) is predictive of resilience from
159 psychopathology. For example, the density of network ties among symptoms predicts severity
160 and relapse in depressive disorders.²⁴

161 Just as the "symptoms" of conditions like depression may actually arise from a
162 dysregulated network structure (e.g., fatigue causing insomnia, which causes anhedonia and so
163 on), a similar network approach may explain the loss of resilience that can occur during the
164 menopausal transition. Shifts in coupling strength, or coordination among biopsychosocial
165 nodes across the transition, would be a key marker for such a shift in resiliency.^{16,25}

166 The present study aims to use an approach to science that is able to capture such
167 phenomena through the use of modeling approaches that are inherently nonlinear, dynamical
168 and systemic.

169

170 **The Present Study: Topological change and Coupling across Menopause**

171 Our method for capturing the dynamics of stress and fatigue involves studying the
172 changes in each over time. Dynamical systems models can be thought of as an expansion on
173 growth models whereby the observed trajectories are theorized to be a combination of patterns
174 through time, error, and the reactions to perturbations. We begin to capture these three
175 components by using models that focus on the relationships amongst derivatives. That is, a

THE DYNAMICS OF STRESS AND FATIGUE ACROSS MENOPAUSE

176 growth model is articulating change in terms of current value, change in the current value per
177 unit of time (velocity), and error. A systems model need merely examine how that current value
178 predicts the velocity combining the possibility for nonlinear trajectories over time and inherent
179 depictions of the stability of the pattern under an assumption that the system is constantly being
180 perturbed.²⁷

181 In this particular case, we generated discrete changes over time in stress and fatigue.
182 We then predicted these changes as a function of current stress and fatigue. Such a model
183 allows a linear dynamic in that stress and fatigue can combine to depict attractive behavior while
184 also allowing for the inclusion of coupling, which we believe to be particularly relevant to
185 resiliency. In this case, coupling comes out as the extent to which values in one variable are
186 able to uniquely predict changes in the other – changes in stress and fatigue predicting one
187 another over time.

188 We then further this logic into a nonlinear dynamic circumstance through two ways,
189 consistent with theory: (1) We allow the model parameters to be different at different stages of
190 the MT. (2) We test for interactions between levels of stress and fatigue to allow stress and
191 fatigue to have differential prediction as a function of one another. The first nonlinear method
192 will examine possible changes to stability and stress-fatigue coupling at each stage of the MT.
193 Do the dynamics change from late reproductive stage to early post-menopause? The second,
194 phase dependent, method allows for a finer look at coupling across different levels of stress and
195 fatigue. For example, it could be that coupling between fatigue and stress only occur when
196 stress is particularly high, allowing fatigue to serve a specific regulatory function selectively, only
197 on the highest levels of stress. The purposes of this study were to (1) investigate relationships
198 of stress and fatigue during the menopausal transition and (2) employ innovative analyses of
199 coupling dynamics to investigate system resilience or rigidity.

200

THE DYNAMICS OF STRESS AND FATIGUE ACROSS MENOPAUSE

201

Methods

202 *Participants*

203 Participants for this study were drawn from the XX Midlife Women's Health Study
204 (XMWHS) which is a longitudinal study of women experiencing the menopausal transition (the
205 parent study has been described in detail elsewhere).²⁸ Women entered the study between
206 1990 and 1992. Those eligible for the parent study included women ages 35-55 with at least
207 one ovary who had had a period within the previous 12 months, were not pregnant or lactating,
208 and were able to speak and read English. This age range was chosen because the
209 menopausal transition typically begins at an average age of 47 years, with the final menstrual
210 period occurring when a woman is around 51 years old. This age range allows researchers to
211 follow women over the transition from late reproductive stage to early post-menopause.²⁷ After
212 an initial in-person interview (n=508) with a registered nurse trained to interview, participants
213 began providing data in the form of an annual health report and monthly (or quarterly) health
214 diary and menstrual calendar (n=390).

215 Eligible participants for this study (n=56) were those who completed 60 or more annual
216 health reports and monthly health diaries. Women were staged using the STRAW+10 criteria²⁹
217 according to late reproductive (LR) stage, early menopausal transition (ET) stage, late
218 menopausal transition (LT) stage, or within 5 years of the final menstrual period, the early post-
219 menopausal (EPM) stage. An individual woman may have contributed data over more than one
220 stage as we followed them over several years. Women not eligible for this study included those
221 who had a prior hysterectomy, or received chemotherapy or radiation therapy. The total number
222 of observations across the sample was 4,224. Of this total, 356 observations lacked
223 menopausal stage information, so there was a subtotal of 3,868 observations with menopausal
224 stage information (i.e., LR, ET, LT, EPM). Participants completed on average 69.07 monthly
225 observations ($SD=22.61$). Table 1 presents the descriptive statistics of observations by

THE DYNAMICS OF STRESS AND FATIGUE ACROSS MENOPAUSE

226 menopausal stage. Women had observations on average for 3.44 menopausal stages

227 ($SD=.76$).

228

229 Table 1. Descriptive statistics of fatigue/stress raw score observations

	Menopausal stage			
	Late Reproductive	Early Transition	Late Transition	Early Post-Menopause
Number of women with data from each stage ¹	46	52	49	42
Mean observations (SD) within women	32.11 (23.93)	19.98 (16.59)	12.73 (10.54)	17.33 (10.63)
Total observations per stage	1,477	1,039	624	728

230 *Note.* Number is only of fatigue observations. Descriptive statistics for stress observations are
 231 identical to fatigue. ¹Numbers of women with data from each stage are not mutually exclusive.

232

233 Change scores were made from the “raw score” stress and fatigue variables. Because
 234 change scores are the difference scores between consecutive months of observations, this lead
 235 to there being fewer change score observations than raw score observations, since not all
 236 observations were made consecutively. That is, sometimes the timing between observations
 237 exceeded 1 monthly unit, and so prevented the creation of a corresponding change score for
 238 that raw score observation. Thus, of the 3868 raw score observations with menopausal stage
 239 information, a smaller total of 2316 change score observations were derived from raw scores
 240 with consecutive monthly responding. The average number of change scores per participant
 241 was 41.36 ($SD=15.06$). Table 2 presents the descriptive statistics of the stress and fatigue
 242 change scores.

243

244 Table 2. Descriptive statistics of fatigue/stress change score observations in model

	Menopausal stage
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THE DYNAMICS OF STRESS AND FATIGUE ACROSS MENOPAUSE

	Late Reproductive	Early Transition	Late Transition	Early Post- Menopause
Number of women with data from each stage ¹	45	42	27	14
Mean observations (SD) within women	25.69 (20.21)	17.12 (14.84)	11.00 (11.35)	10.29 (16.01)
Total observations per stage	1,156	719	297	144

245 *Note.* Number is only of fatigue change score observations. Descriptive statistics for stress
 246 change score observations are identical to fatigue change score. ¹Numbers of women with data
 247 from each stage are not mutually exclusive.
 248

249 *Stages of reproductive aging using the STRAW+10 Criteria* were used to classify
 250 women’s menstrual cycle patterns for those not taking any type of estrogen or progesterone.
 251 Menstrual calendar data were used to determine whether women were in the LR, ET, LT, or
 252 EPM stage. Classification is based on staging criteria originally developed by Mitchell, Woods,
 253 and Mariella³⁰, and validated by the ReSTAGE collaboration.³¹ Stages include LR (typified by
 254 subtle changes in menstrual cycle length), ET (increased variability in menstrual cycle length
 255 with persistent difference of 7+ days in length of consecutive cycles), LT (occurrence of
 256 amenorrhea of 60 days or longer and menstrual cycles are characterized by increased
 257 variability in cycle length, extreme fluctuations in hormonal levels, and increased prevalence of
 258 anovulation) and EPM (first 6 years since the final menstrual period). Symptoms are often the
 259 most frequent, severe and/or bothersome in the LT and EPM stages.³²⁻³⁵

260
 261 *Measures*

THE DYNAMICS OF STRESS AND FATIGUE ACROSS MENOPAUSE

262 The health diary included a symptom checklist that included questions about perceived
263 stress and fatigue. Diary data were obtained on days 5, 6, and 7 of the menstrual cycle in pre-
264 menopausal women (post-menopausal women provided diaries on a monthly schedule).

265 *Fatigue* was assessed with a single question from the annual health report and monthly
266 diaries (“Think back over the last 24 hours and rate overall how severe was each symptom
267 listed below – fatigue”) and was rated on a scale of 0 to 4 (0 not present, 1 minimal, 2 mild, 3
268 moderate, 4 extreme). Test retest reliability was .39.

269 *Perceived stress* was assessed with one question from the annual health report and
270 monthly diaries: “How stressful was today?” Participants answered using a scale ranging from 1
271 to 6 where 1 indicated none, and 6 indicated extremely. Test retest reliability was .37.

272

273 *Overview of Data Analytic Strategy*

274 Fatigue and stress were converted into discrete differences between the reported value
275 one step into the future minus the current value. These differences were positive when
276 stress/fatigue is increasing over time and negative when decreasing. Consecutive time-points
277 that were greater than 30 days apart were treated as missing data to maintain some degree of
278 temporal consistency in the changes. We then treated the changes in fatigue and changes in
279 stress as simultaneous outcomes through a multivariate multilevel model in Mplus.³⁶

280 We utilized a multilevel structural equation model, an analytic technique designed to
281 account for data dependency. In this case, we accounted for two different dependencies. The
282 first involved multiple measures of fatigue and stress from each individual (captured through the
283 two level model). The second involved having two different dependent variables, changes in
284 stress and fatigue respectively (captured by modeling stress and fatigue simultaneously with the
285 inclusion of error covariances between them). This method is analogous to conducting
286 regressions within the dependencies, saving out coefficients and then summarizing and

THE DYNAMICS OF STRESS AND FATIGUE ACROSS MENOPAUSE

287 predicting these coefficients. However, structural equation modeling is a maximum likelihood
288 estimation procedure and therefore instead generates results as if these steps were carried out,
289 rather than actually taking each step. As a set, we can depict the basic model as a pair of
290 nested equations, one for change in fatigue as the dependent variable and one for the change
291 in stress. For a given individual (i) at a given point in time(t) the basic equations were:

$$292 \quad (Fatigue_{t+1} - Fatigue_t)_i = \beta_{0i} + \beta_{1i}Fatigue_{ti} + \beta_{2i}Stress_{ti} + e_{ti} \quad (1)$$

$$293 \quad (Stress_{t+1} - Stress_t)_i = \beta_{3i} + \beta_{4i}Fatigue_{ti} + \beta_{5i}Stress_{ti} + e_{ti} \quad (2)$$

294 The betas (β) represent average effects across individuals. The errors terms (e) were captured
295 as separate error variances for each of the dependent variables with a covariance between
296 them to account for any remaining dependency.

297 This linear dynamic equation is capable of capturing three different kinds of effects: (1)
298 do individuals' stress and fatigue function homeostatically, returning to some combined level of
299 stress and fatigue? (2) How stable is homeostasis for stress and fatigue: if a person moves
300 away from their homeostatic level, how quickly do they return? And (3), do stress and fatigue
301 relate to one another in terms of if one is moved away from their homeostatic level, do we see
302 patterns consistent with the other being further stabilized or disrupted? The homeostatic nature
303 of stress and fatigue (1) can be assessed through beta 1 and beta 5 (the effects of how a
304 variable predicts its own change). When both are negative, it indicates that when diverging from
305 the homeostatic value for stress and fatigue people invariably return to that value. The stability
306 or resiliency of stress and fatigue (2) are captured by the steepness of the negative slopes. A
307 steeper slope indicates that a person returns to the homeostatic level following a perturbation
308 more quickly.

309 The third question about the relationship between stress and fatigue (3) are captured by
310 beta 2 and beta 4 (the crossover or coupling effects). For example, if a person alters their diet
311 (a perturbation), this might temporarily induce an increase in stress, Beta 2 implies that this

THE DYNAMICS OF STRESS AND FATIGUE ACROSS MENOPAUSE

312 would carry over into changes in fatigue which could then carry back through to stress via beta

313 4.

314 In this paper, we also utilize prediction plots of where we would expect a person's fatigue
315 and stress to go next as a visual way to interpret these effects. This involves creating a vector
316 plot where combinations of values in stress and fatigue are factored forward to ask where the
317 equations would predict the values to be after some period of time. The homeostatic point (or
318 set point) is the point in which all the arrows converge. The length of arrows captures the
319 stability as longer arrows bring one back to the homeostatic point faster. Swirling depictions
320 capture coupling. For example, if only the coupling effects existed, and momentum effects
321 (beta1 and beta 5) were zero, the model would then depict a cycle (i.e., an orbit around a fixed
322 point) where upon the emergent pattern is a repeating cycle for both fatigue and stress over
323 time. Graphically, this would create a circle on these prediction plots.

324 Adding in main effects of other variables essentially depict the change in location of the
325 set point. However, building nonlinear models (in this case through the inclusion of interactions)
326 alters the form of the relationships and can depict changes in the properties of dynamic patterns
327 (i.e. the stability and coupling relationships can also change).²⁷ For example, a variable that
328 interacts with their own effects (beta 1 and beta 5) can strengthen, weaken and even extinguish
329 the homeostatic nature of stress and fatigue. Variables that interact with the coupling effects
330 (beta 2 and beta 4) can alter the coupling relationships. As resilience may be a case of multiple
331 forms of altering the underlying topology simultaneously (e.g. changing the coupling, the
332 strength, and location of the dynamic properties) we included all plausible linear interactions.
333 Specifically, we included interactions within both equations between stress and fatigue. The
334 utilized models were therefore:

335

THE DYNAMICS OF STRESS AND FATIGUE ACROSS MENOPAUSE

$$336 \quad (Fatigue_{t+1} - Fatigue_t)_i = \beta_{0i} + \beta_{1i}Fatigue_{ti} + \beta_{2i}Stress_{ti} + \beta_{3i}StressXFatigue_{ti} + e_{ti}$$

337 (3)

$$338 \quad (Stress_{t+1} - Stress_t)_i = \beta_{4i} + \beta_{7i}Fatigue_{ti} + \beta_{5i}Stress_{ti} + \beta_{6i}StressXFatigue_{ti} + e_{ti}$$

339 (4)

340 To account for different attractor dynamics during each stage, we then treated the model as a
341 stacked or multiple group analysis in Mplus. This essentially allows for different estimates of
342 every coefficient for each stage and also allows the possibility to compare stages through
343 equality constraints of sets of parameters. We also chose to person-center fatigue and stress
344 bringing the focus onto intrinsic dynamics where the models characterize deviations from one's
345 own average. We excluded random effects with the exception of the residual variances by
346 using the 'complex' estimation method to avoid oversaturation of the model. The resultant
347 model utilized FIML with the Yuan and Bentler adjustment for non-normality.³⁹ Significance is
348 reported at alpha=.05, two-tailed.

349

350

Results

351

352 Sample

353 *Descriptive Statistics for this subsample*

354 The women who were eligible for inclusion had a mean age of 35 years (SD=4.71) years
355 at the beginning of the study, a mean of 16 years of education (SD=2.57), and a median family
356 income of \$22,660 (SD \$6,900). Most of the eligible participants were currently employed
357 (93%), 73% were married or partnered, 19% were divorced or widowed, and 7% had never
358 been partnered or married. Eligible women described their ethnicity at the start of the study as
359 2% African American, 7% Asian American, 91% White and no one self-described as Hispanic or
360 other. Refer to Table 3 for a comparison of women eligible for this study and those determined

THE DYNAMICS OF STRESS AND FATIGUE ACROSS MENOPAUSE

361 ineligible. As demonstrated in Table 3, all women considered for this study are of similar age,
 362 education and income to those excluded. Women included in analyses were more likely to be
 363 white than those who were not eligible for these analyses. The groups were similar with respect
 364 to employment and marital status.
 365
 366

TABLE 3.

Sample Characteristics of Eligible and Ineligible Women for Inclusion

	Eligible women (n=56)	Ineligible women (n= 451)	
Characteristics	Mean (SD)	Mean (SD)	P ^a
Age, y	35(4.71)	42(4.68)	.45
Years of education	16(2.57)	16(2.82)	.80
Family income, \$	22,660(6,900)	17,950(7,650)	.82
Characteristics	n(%)	n(%)	P ^b
Currently employed			.03
Yes	52(92.9)	388(86)	
No	4(7.1)	63(14)	
Race/ethnicity			.05
African American	1(1.8)	57(12.6)	
Asian/Pacific Islander	4(7.1)	39(8.6)	
White	51(91.1)	339(75.2)	
Other (Hispanic, mixed)	0	16(3.5)	
Marital status			.86

THE DYNAMICS OF STRESS AND FATIGUE ACROSS MENOPAUSE

Married/partnered	41(73)	306(67.8)	
Divorced/widowed/ not partnered	11(19.17)	114(23.5)	
Never married/partnered	4(7.1)	31(6.9)	
^a Independent t test.			
^b χ^2 test.			

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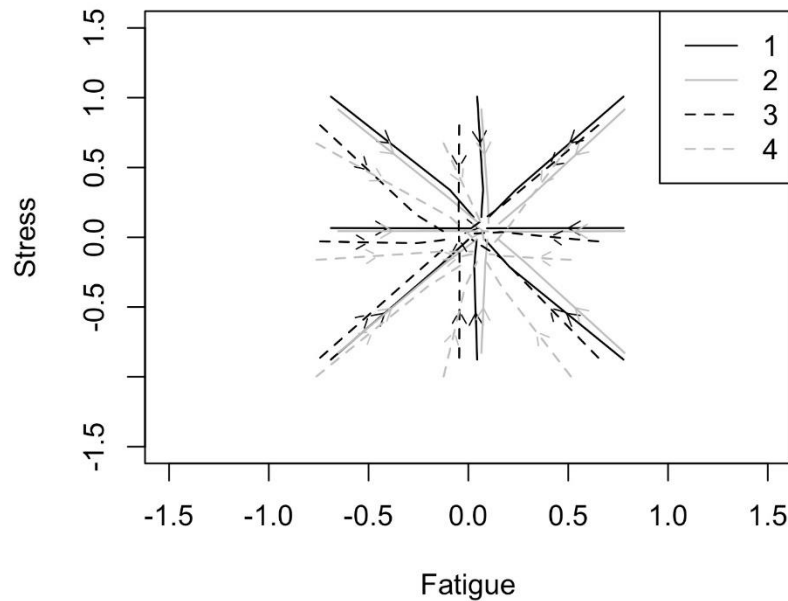
384

All fit indices suggested that the model adequately depicts the relationships ($\chi^2(9 \text{ df}) = 7.638, p=.57$, correction factor=4.9244; RMSEA 90%CI = .000 <=.000 <=.032; CFI = 1.00). The level-1 and level-2 sample sizes for LR were $n_1=46$ and $n_2=1477$, for ET were $n_1=52$ and $n_2=1039$, for LT $n_1=49$ and $n_2=624$, and for EPM were $n_1=42$ and $n_2=728$. These sample sizes correspond to the raw scores because Mplus uses full information maximum likelihood to estimate the model using all the sample data, including the raw scores with missing change scores. The R^2 values for each outcome in each group accounted for between 37-48% of changes in fatigue and 40-45% of changes in stress in the data. To test for the equivalency of the four reproductive aging stages (LR, ET, LT, and EPM), we equated all own and coupling parameters across groups. This induced a significant loss in model fit ($\chi^2\Delta(12 \text{ df}) = 21.181, p=.048$) suggesting that the four stages, in fact, differed in their dynamics. To illustrate the higher order emergent dynamics for each stage, we estimated trajectories from the equations using the Runge-Kutta 4th order algorithm and overlaid them onto a Fatigue by Stress space akin to a velocity flow field.⁴⁰ Trajectory starting points were one standard deviation above, at the mean, and below the mean for fatigue and stress respectively for each group. All four stage-specific patterns were homeostatic (i.e., attractors; stress and fatigue returning to set-points), but they differed in the location of their set-points, the strength of the attraction, and the coupling

THE DYNAMICS OF STRESS AND FATIGUE ACROSS MENOPAUSE

385 relationships between stress and fatigue (see Figure 1). Note that the labels in Figure 1 are:

386 Late Reproductive (1), Early Transition (2), Late Transition (3) and Early Post-Menopause (4).



387

388 Fig. 1. Velocity flow field diagram depicting trajectories of stress and fatigue at each of

389 the four stages of menopause (1 = LR, 2 = ET; 3 = LT; 4 = EPM).

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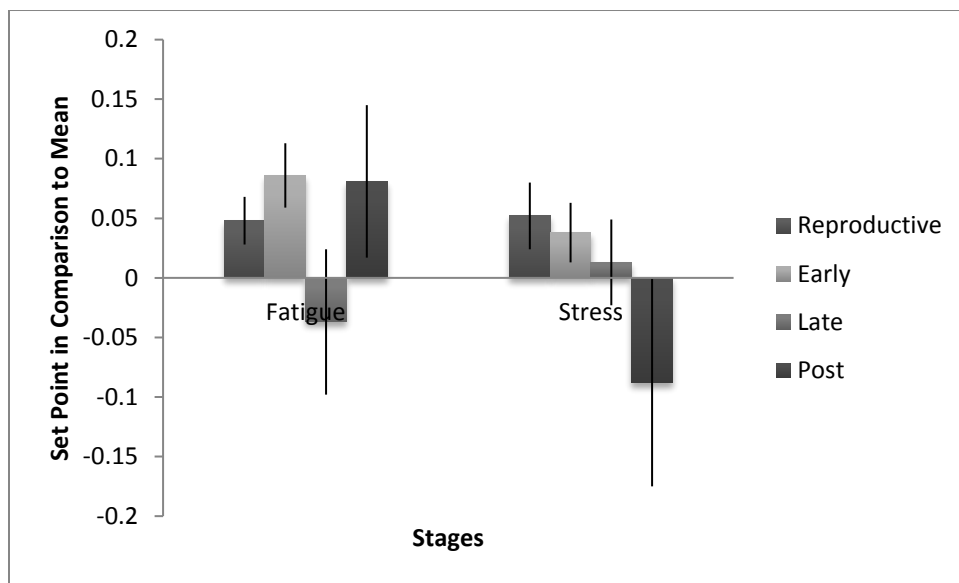
391 Given that the data were person-centered (change is depicted in standard-deviation
392 units), the overall location of attraction is expected to closely approximate zero. As such, slight
393 shifts from zero at each stage may indeed represent meaningful shifts within the intrinsic
394 stability of each parameter (i.e., stress and fatigue) across the menopausal stages. Within the
395 model under this centering logic, changes in the intercepts from the equations directly represent
396 the set points. Figure 2 illustrates these intercepts in relation to one another and in relation to
397 means. Overall, the intercepts did not differ from one another (determined by comparing the
398 model to one where the intercepts were equated, $\chi^2\Delta(6 \text{ df}) = 9.385, p=.153$). However, some

THE DYNAMICS OF STRESS AND FATIGUE ACROSS MENOPAUSE

399 individual intercepts were different from zero while others were not. For both the LR and ET
400 stages, the set point for fatigue is significantly higher than individual's mean fatigue ($p=.017$ and
401 $p=.001$, respectively). This was not true for the later stages ($p=.537$ for LT and $p=.208$ for EPM),
402 nor were any of the stress set points significantly different from the individual's means.

403 Note that the labels in Figures 2-5 are: Late Reproductive (Reproductive), Early
404 Transition (Early), Late Transition (Late) and Early Post-Menopause (Post).

405



406

407 Fig. 2 Set point differences and standard error bars. Reproductive stage $N_1 = 1477$, $N_2 =$
408 46; Early stage $N_1 = 1039$, $N_2 = 52$; Late stage $N_1 = 624$, $N_2 = 49$; Post stage $N_1 = 728$,
409 $N_2 = 42$.

410

411 Effects of how each variable predicts its own changes represents a form of Lyapunov
412 exponent characterizing the strength of attraction towards the set point, but also the influence of
413 perturbations within the system.²⁷ The inclusion of the interactions to account for phase
414 dependent coupling allow these effects to differ at levels of one variable in regards to the other
415 (e.g. the attraction of fatigue can differ at levels of stress and vice versa). However, our

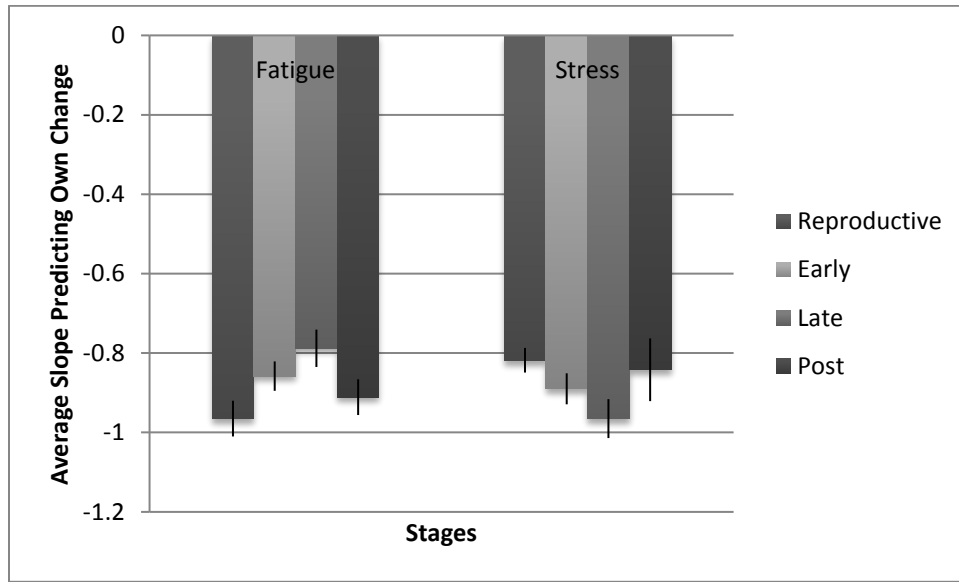
THE DYNAMICS OF STRESS AND FATIGUE ACROSS MENOPAUSE

416 centering procedure modifies the interpretation of the main effects to the average within person
417 effects. The more negative the coefficient, inherently the more stable the attractor in that
418 dimension. That is, when perturbed, the more negative slope indicates less effect as a function
419 of the same size of perturbation and faster return to the set point. In all cases, the coefficient
420 was significantly different from zero (all p values less than .001).

421 To test the equivalency of these effects across reproductive aging stages, we conducted
422 a chi-square difference test equating the like coefficients across stages. The constraints
423 significantly worsened model fit ($\chi^2\Delta(6 \text{ df}) = 21.491, p=.001$) suggesting that the stabilities of the
424 stress and fatigue dimensions of the attractors vary by stage. Chi-square difference tests
425 revealed the fatigue dimension of attractor significantly weakens from LR ($\beta=-.965$) to ET ($\beta=-$
426 $.858$) ($\chi^2\Delta(1 \text{ df}) = 4.389, p=.036$), and weakens again from ET to LT ($\beta=-.788$) ($\chi^2\Delta(1 \text{ df}) =$
427 $5.012, p=.025$). The fatigue attractor strength did not significantly change from LT to EPM
428 ($\chi^2\Delta(1 \text{ df}) = 2.235, p=.135$). As for the stress dimension of the attractor, it strengthened from ET
429 ($\beta=-.818$) to LT ($\beta=-.965$) ($\chi^2\Delta(1 \text{ df}) = 6.834, p=.009$, and nearly significantly weakened, but did
430 not meet criteria, from LT to EPM ($\beta=-.842$) ($\chi^2\Delta(1 \text{ df}) = 3.640, p=.056$). In sum, fatigue showed
431 a pattern of decreasing stability from LR to EPM and stress showed a pattern of increasing
432 stability.

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THE DYNAMICS OF STRESS AND FATIGUE ACROSS MENOPAUSE



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435 Fig. 3. Attractor strength across menopausal stages with standard error bars. More negative
 436 slopes indicate greater attractive strength.

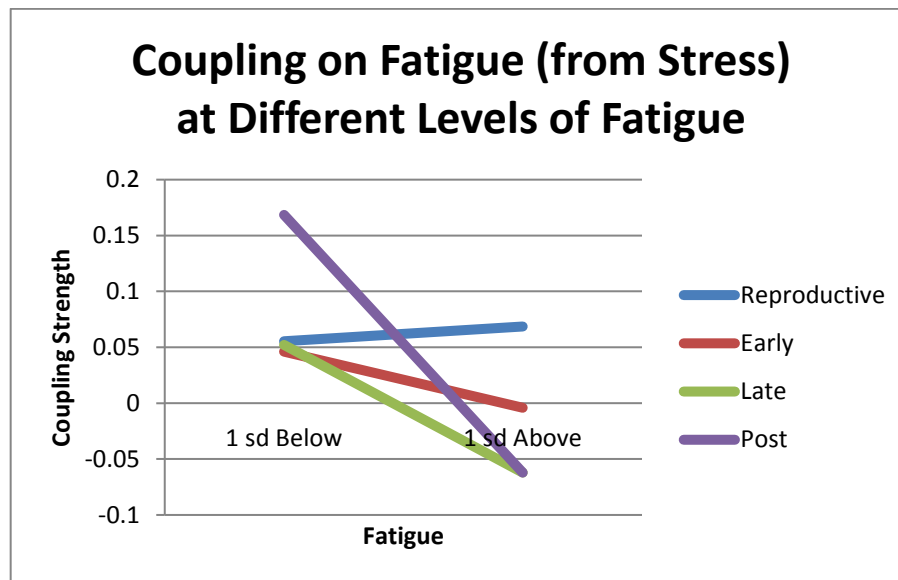
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438 Coupling is represented by the crossover prediction of stress predicting changes in
 439 fatigue and fatigue predicting changes in stress (the curvature observed in the trajectories of
 440 Figure 1). Since we envisioned the possibility that coupling could vary across different levels of
 441 stress and fatigue, we specifically interpret the interactions as if the variable predicting its own
 442 changes moderated the coupling relationships. Coupling is best interpreted both in terms of its
 443 deviation from zero and in the interpretation of the sign. The deviation from zero indicates the
 444 occurrence of coupling, that the current level of stress or fatigue perturbs the level of the other
 445 variable carrying over the influence of one outcome to the other. The sign indicates the form of
 446 this perturbation - positive values indicate that when one is higher, it pushes the other variable
 447 to be higher. Negative values indicate that when one is higher it pushes the other to be lower.

448 Figure 4 illustrates the relationships of stress on changes in fatigue. For the LR stage,
 449 there was significant coupling under all circumstances ($\beta_{\text{main effect}}=.062$, $p=.029$; $\beta_{\text{interaction}}=.009$,
 450 $p=.792$) indicating that higher stress corresponded to a higher level of fatigue no matter the level

THE DYNAMICS OF STRESS AND FATIGUE ACROSS MENOPAUSE

451 of fatigue. During ET there was no evidence of coupling ($\beta_{\text{main effect}}=.021$, $p=.494$; $\beta_{\text{interaction}}=-$
452 $.035$, $p=.314$). This was also true for LT ($\beta_{\text{main effect}}=-.005$, $p=.948$; $\beta_{\text{interaction}}=-.082$, $p=.182$) For
453 EPM, coupling on fatigue from stress was phase-dependent upon the level of fatigue (β_{main}
454 $\text{effect}=.106$, $p=.172$; $\beta_{\text{interaction}}=-.098$, $p=.030$). Specifically, stress was coupled when fatigue was
455 low.
456



457

458

459 Fig. 4. Coupling effects of stress on fatigue at high and low levels of fatigue.

460

461 The coupling of fatigue on changes in stress had quite a different pattern, illustrated in

462 Figure 5. Fatigue showed no coupling during ET ($\beta_{\text{main effect}}=.001$, $p=.978$; $\beta_{\text{interaction}}=-.042$,

463 $p=.166$). During LT, coupling was constantly positive ($\beta_{\text{main effect}}=.14$, $p=.035$; $\beta_{\text{interaction}}=.016$,

464 $p=.822$). And as before, we observed phase dependent coupling only in the EPM stage (β_{main}

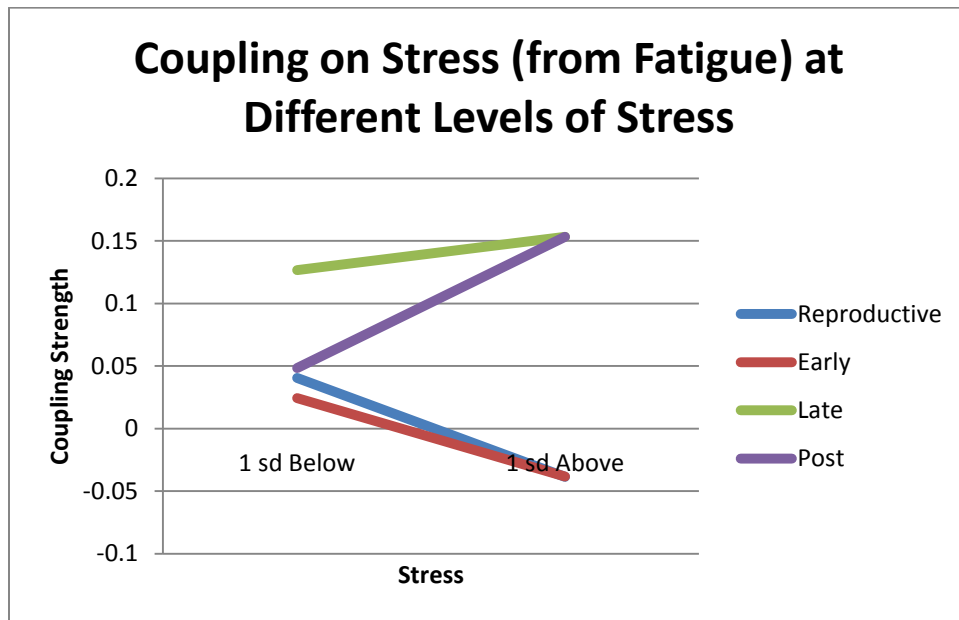
465 $\text{effect}=-.076$, $p=.284$; $\beta_{\text{interaction}}=-.149$, $p=.036$). Here positive coupling between fatigue and

466 changes in stress occurred under higher stress, allowing changes in fatigue to correspond to

467 more changes in stress. In sum, coupling only occurred during LR, LT and EPM. During LR

THE DYNAMICS OF STRESS AND FATIGUE ACROSS MENOPAUSE

468 changes in stress predicted changes in fatigue. During LT, changes in fatigue predicted
469 changes in stress. During EPM, both coupling directions appeared, but phase dependently such
470 that only one of the coupling directions appeared at a given point in time.
471



472
473 Fig. 5. Coupling of fatigue on stress at different levels

474

475 Discussion

476 The present study aimed to directly measure the regulatory dynamics of stress and
477 fatigue across the stages of the MT and early post-menopause. Because there is no prior
478 research directly analyzing stability and coupling of women's experiences across the full
479 menopausal transition, our hypotheses were somewhat open-ended and exploratory: (a) a
480 decrease in attractor strength in key parameters during the transition in response to
481 biopsychosocial stress – signaling a loss of coherence in the dynamics of stress and of fatigue;
482 and (b) shifts in the regulatory coupling relationships between stress and fatigue from late

THE DYNAMICS OF STRESS AND FATIGUE ACROSS MENOPAUSE

483 reproductive stage to early post-menopause. In general, the evidence did support each of these
484 hypotheses.

485 Overall, the dynamical menses-by-menses time-series model provided an adequate fit to
486 changes in each parameter over time, with R^2 values across MT stages ranging 37-48% for
487 fatigue, and 40-45% for stress. Furthermore, there was a significant loss in model fit ($\chi^2\Delta(12 \text{ df})$
488 = 21.181, $p=.048$) when including menopausal stages, suggesting that the four stages, in fact,
489 differed in their dynamics.

490 All stages showed fixed point attractor dynamics for stress and fatigue, and there was
491 some mixed evidence for changes to attractor location for fatigue between ET and LT (see
492 Figure 1). Overall, the intercepts did not differ from one another (determined by comparing the
493 model to one where the intercepts were equated, $\chi^2\Delta(6 \text{ df}) = 9.385$, $p=.153$). However, some
494 individual intercepts were different from zero (the individual's mean) while others were not. For
495 both the LR and ET stages, the set point for fatigue is significantly higher than individual's mean
496 fatigue ($p=.017$ and $p=.001$, respectively). This was not true for the later stages ($p=.537$ for LT
497 and $p=.208$ for EPM). One logical interpretation of this result is that when a woman becomes
498 more fatigued than usual, there is a tendency for fatigue to hang around longer – what goes up,
499 doesn't tend to come down as quickly. None of the stress set points differed significantly from
500 the individual's means (see Figure 2).

501 In terms of attractor strength, the homeostatic pull of stress and fatigue, the results
502 suggest that fatigue became less stable (less pull) from LR to LT and continuing into EPM;
503 however, stress generally became *more* stable (stronger pull from LR to LT; see Figure 3). We
504 had predicted decreased stability for both variables, and so this hypothesis was only partially
505 supported (for fatigue only). The opposite shift was observed for stress as was predicted –
506 increasing stability across the menopausal transition. Of course, there is no clear way to
507 interpret whether increasing or decreasing stability is healthy or not without considering levels.

THE DYNAMICS OF STRESS AND FATIGUE ACROSS MENOPAUSE

508 For example, if stress is more stable and also higher, this would be bad, whereas if stress is
509 generally low, stability is good. At this point, all we can say is that stability appears to change
510 across the MT, with fatigue becoming less stable and stress becoming more stable.

511 The results for coupling have more clear-cut implications for health and resilience
512 (though clearly this study is only a first step), with both stress and fatigue showing evidence for
513 shifting their regulatory relationships with one another across the MT. For the impact of stress
514 on fatigue: In LR, increasing stress was associated with increasing fatigue (across all levels of
515 stress). This is likely a smooth healthy regulatory function early on, whereby up-ticks in one's
516 stress during a first menses pull for a proportional uptick in fatigue during the next menses, no
517 matter the degree of stress. Interestingly, during the middle stages of transition (i.e., from ET to
518 LT) the coupling relationship disappears – which suggests a disconnection or breaking down of
519 this adaptive regulatory function. After the MT, fatigue is once again driven by stress; however,
520 the smooth proportionality now appears warped. No longer smoothly connected across all
521 levels of stress, fatigue is driven by stress only at the lower fatigue levels (see Figure 4). This
522 may indicate some loss of resilience since the regulatory function of fatigue is no longer
523 operating when one is at higher levels of fatigue.

524 Regarding the opposite relationship, fatigue driving stress, it appears that at the early
525 years (LR and ET) there is no coupling relationship: being tired doesn't make one stressed.
526 This seems to make sense in terms of healthy functioning because there is no obvious reason
527 why fatigue should be stressful. However, during LT, fatigue at any level of stress tends to
528 make one even more stressed. Various explanations may be offered for this phenomenon, for
529 example that fatigue becomes more threatening once one has reached LT because of negative
530 experiences with being fatigued during the transition. Whatever the explanation, it would
531 appear ideal for one's resilience from fatigue or for stress regulation. Further, the warping effect
532 appears again at EPM but with the opposite pattern as stress driving fatigue. Fatigue is

THE DYNAMICS OF STRESS AND FATIGUE ACROSS MENOPAUSE

533 apparently only stressful for post-menopausal women when they are at higher levels of stress
534 (see Figure 5). Again, this result may indicate that the MT is a time when women learn to react
535 negatively to their own fatigue levels during the menopausal transition, with a lingering
536 sensitivity during EPM when their stress levels are high.

537 Putting these two sets of coupling results together, it appears that these women tended
538 to go into the MT with a smooth healthy regulatory function of increasing stress leading to
539 increasing fatigue, and fatigue not leading to stress at all. During the MT, stress loses its driving
540 relationship to fatigue, while fatigue forms a driving relationship with stress. Finally, at EPM the
541 connections in both directions are left significantly warped, with stress driving up fatigue only
542 when stress is low, and fatigue driving up stress only when stress is high.

543 Altogether, these results are suggestive of some general dysregulation via disruptions to
544 coupling relationships across the MT, and likely serving to decrease one's ability to bounce back
545 from either stress or fatigue (i.e., resilience). Nevertheless, these interpretations are also
546 somewhat speculative and have been derived post-hoc. Numerous other interpretations may
547 be offered, and so replication with a more specific set of hypotheses will be necessary before
548 any firm conclusions may be drawn.

549 Despite their preliminary nature, the present results are cutting edge in providing support
550 for a more holistic approach to understanding and supporting women's transition through
551 menopause. First, health care providers may wish to sensitively consider their assumptions
552 about the MT in order to provide a more accurate and helpful story about what the MT actually
553 is.

554 There is evidence that positive health behaviors are related to fewer symptoms in this
555 population,⁴¹ but how should such messages be tailored? Rather than viewing the MT as a time
556 of symptoms (based perhaps on a faulty disease metaphor), the MT may more accurately be
557 described as one of several critical biopsychosocial life transitions. Nevertheless, most women

THE DYNAMICS OF STRESS AND FATIGUE ACROSS MENOPAUSE

558 should be taught to expect some degree of self-regulatory shifts to the dynamics of key
559 hormonally-driven experiences, such as stress, fatigue, and changes in mood. Patients may
560 benefit from being taught to understand self-regulation in terms of network dynamics; beyond
561 temporary increases or decreases in stress or fatigue, they may also find that it is more difficult
562 to manage their stress as they did before because it no longer triggers fatigue. Or, they may
563 find that when they get tired, it is accompanied by stress for no good purpose. The present
564 study only examined these two parameters and found signs of dysregulation across the MT.
565 Numerous other processes may shift similarly, and different patients may have unique sets of
566 increase or decrease in coupling processes across the biopsychosocial spectrum. Through
567 increased awareness of these particular shifts, as well as the use of intentional strategies to
568 compensate for loss of automatic regulatory functions (e.g., purposefully resting when stressed)
569 women may be empowered to understand how the transition process works, and how to take
570 better holistic care of themselves as they move through the transition.

571 The present study had a number of limitations that should be considered prior to any
572 applications and any subsequent follow up investigations. First, the sampling interval was
573 menses-by-menses. As such, it started at around a one-month lag, and became more irregular
574 across the phases of the MT. For those concerned with regular sampling intervals in time-
575 series analysis, this could be viewed as problematic because regularity in sampling is usually
576 ideal for time-series designs. Similarly, one could argue that the data were under-sampled,
577 inasmuch as stress and fatigue shift more quickly than a month-to-month pace.

578 On the other hand, biological time is arguably different than chronological time, and it
579 would be a hard stretch to try to form inferences about the impact of menopause on stress and
580 fatigue if the sampling had been done outside of the menstrual period. In an ideal scenario, the
581 data would have been collected on a daily rate, and then within and between menstrual periods
582 could have been investigated. With more than a minimum of 60 months of data collection,

THE DYNAMICS OF STRESS AND FATIGUE ACROSS MENOPAUSE

583 however, it would have been quite difficult to obtain daily samples, especially given the lack of
584 cell phone and other mobile data collection devices at the time this study was launched.

585 A second, related, limitation of the present study is the regulatory interpretations made
586 between stress and fatigue when the lag interval is one menstrual period (several weeks to a
587 month long). One could argue that it would be more appropriate to consider the regulatory
588 functions between stress and fatigue as occurring *within a single cycle*. Indeed, hourly
589 measurements could hypothetically be collected across 3-4 days within a cycle to test similar
590 hypotheses at a more micro-temporal level. However, the shifts to the monthly dynamics, in
591 both stability and regulatory influence may also be seen as rather impressive precisely because
592 the lag is so long. If the stability of both stress and fatigue, as well as their driver-driven
593 dynamics, are showing permanent shifts at a monthly lag, it is highly unlikely that they are not
594 shifting at a more micro (hourly or daily) scale as well.

595 A third problem with the present study is that there was a substantial degree of missing
596 data, with an average of 75 instances per individual representing 58% of measurements
597 missing, and also the fact that this sample was generally very healthy throughout their
598 transitions (average fatigue of 1.11 on a scale of 0 to 4 and stress of 2.37 on a scale of 1 to 6
599 across the sample). Further, growth models (which have some connections to systems models
600 generally) have been argued to sometimes account for missingness in data that would
601 otherwise be thought due to nonrandom missingness (Lisa add reference: Graham JW. Missing
602 data analysis: Making it work in the real world. Annual review of psychology. 2009 Jan 10;60:549-76.).
603 Again, however, these are not the sort of limitations that would increase the likelihood of a type-I
604 error, but would instead place a damper on statistical power. Finding dynamical results with
605 only 56 individuals with high levels of missing data may be seen as good support for the
606 application of SEM and HLM approaches to nonlinear time-series investigations. Traditional

THE DYNAMICS OF STRESS AND FATIGUE ACROSS MENOPAUSE

607 time-series methods that depend on very long, complete, and clean data are not feasible in
608 situations such as this.

609 A fourth problem with the present study is that there may have been other cofounders
610 involved in the dynamics of stress and fatigue during the MT. Specifically, it is possible that
611 women may have had varying levels of coping, as well as varying stressors. Stressors may
612 have included stress with family members, children, co-workers, financial stressors or health
613 stresses. We could not account for any of these in our analyses.

614 Finally, as has already been emphasized, the current hypotheses were rather broad –
615 essentially predicting shifts in both the stability of, and the driver-driven linkages between stress
616 and fatigue across menopause. Following this first important step towards a more direct
617 approach to understanding biopsychosocial dynamics and structural resilience processes,
618 subsequent investigations should make more specific hypotheses about which shifts are likely
619 to occur, and in which directions.

620 There is a wide and potentially groundbreaking set of follow-up investigations that may
621 now be carried out using the methods developed for the present study, including follow-up
622 studies using the present data set. For example, it may be interesting to derive individual
623 parameters for change in stability and coupling strength (from the HLM analysis) to predict
624 functional outcomes across this sample of women. One would predict that the greater the shifts
625 in stability and coupling strengths, the greater would be the degree of post-menopausal
626 problems experienced, such as anxiety, depression, fatigue, cortisol dysregulation and relational
627 conflict. Other predictors could be fruitfully investigated apart from menopausal stage, such as
628 attitudes toward menopause, key hormonal levels, or pre-menopausal transition functioning,
629 each of which might hypothetically moderate changes to dynamical processes over time (e.g.,
630 attractor stability and coupling strength). Finally, other key variables are likely to form nodes
631 within a broader network that includes stress and fatigue. A likely third variable, for example,

THE DYNAMICS OF STRESS AND FATIGUE ACROSS MENOPAUSE

632 would be hot flashes, which emerge specifically during the MT and which may help to explain to
633 some extent the stability shifts and warped coupling between stress and fatigue that have been
634 observed here. Specifically, higher levels of hot flashes in the nighttime may help to explain
635 why fatigue becomes more stressful across the menopausal transition, as may the shift in one's
636 social roles that also tends to occur at around this time of life.

637 From the broader perspective, the present study may be viewed as supportive of the use
638 of a nonlinear dynamical systems approach to understanding biopsychosocial resilience. Both
639 science and practice should reconsider the very idea that something like menopause could have
640 "symptoms," which imply some latent "illness" that causes fatigue, stress, insomnia, hot-flashes,
641 and interpersonal functioning and such in a linear and one-directional manner. Instead,
642 practitioners and researchers alike should consider that these biological, psychological and
643 social parameters are each potentially linked together within a self-regulatory network, where
644 each may influence the other over time. Through this lens, features such as stuckness and
645 linkage have more to do with health and resilience than solitary levels at any particular point in
646 time. Indeed, such an approach is being fruitfully applied to reconsidering how psychiatric
647 symptoms operate within a network model rather than the traditional latent disease process
648 model.^{22,24}

649 Such an approach may indeed be a more accurate and fruitful quantitative approach to
650 both science, and also for patient care across each of the most common chronic conditions
651 (e.g., overweight, diabetes, and heart disease). Distinct from acute care, where simple causes
652 lead to clear illnesses, with simple treatments, the quantitative science of chronic conditions
653 may benefit from a focus that is more holistic and consistent with the views of the most
654 experienced and talented practitioners. Rather than focusing on ups and downs in simple signs
655 and symptoms, quantitative research may move toward viewing the dynamics of person as a
656 holistic network, viewing the movement within the net, and not just a snapshot of its nodes.

THE DYNAMICS OF STRESS AND FATIGUE ACROSS MENOPAUSE

657 In sum, this study shows that the dynamic relationship between the body's regulatory
658 relationship between stress and fatigue changes dramatically over the course of the MT. We
659 believe this insight will be important in helping to inform interventions for women. For example,
660 if women are assisted in tracking important changes in the self-regulatory functions of stress
661 and fatigue, they may then develop healthy compensatory habits, such as increasing the
662 regularity of sleep schedules to assist in fatigue-related stress, or learning to better self-assess
663 their stress levels and to take planned breaks even if they don't feel immediately fatigued. A
664 better understanding of the menopausal transition will also help lead to a better understanding
665 of the differences among menopausal symptoms, mid-life stressors within a modern Western
666 cultural context, and experiences that unfold through natural aging. On the broadest scope,
667 understanding the dynamics of the menopausal transition may help us to better grasp the
668 mechanisms that underlie human resilience in general.

669

670

Conclusion

671 We observed that fatigue became less stable and stress became more stable over time
672 and that the two variables were less coupled during ET to LT, suggesting a breakdown of this
673 adaptive function. The regulatory relationship between stress and fatigue changes over the
674 course of the MT with distinctly different patterns by stage. These findings suggest changes in
675 system-wide resilience during the MT. Suggestions are made to evaluate midlife women in a more
676 holistic manner, to better understand this complex developmental transition.

677

Lisa will fix all refs when we have a final draft for resubmission: References

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