Supplementary Material

Part A: *Post-Hoc* Analyses of Symptom Interactions to Derive Patient Profiles

The nature of the statistically significant symptom interaction effects in regressions 2 and 3 from Table 4 are assessed according to the Extended Zero Slope Comparison (EZSC) procedure for three-way, linear statistical interactions developed by Francoeur.[1] This procedure is an extension to the original two-way ZSC procedure developed by Nye and Witt.[2] The extended procedure is simpler and quicker, and yields fewer interpretations of moderator effects across predictor ranges, than post hoc approaches based on multiple, targeted regression re-estimates that are used to construct graphs at predetermined predictor values.

The three-way ZSC extension published by Francoeur[1] is applied to interpret regressions 2 and 3 from Table 4. (The equation numbers appearing at the far right correspond to equations for the general case that were derived in Francoeur).[1] Subsequently, an application of the original procedure by Nye and Witt[2] is used to interpret a statistically significant two-way interaction from a follow-up regression in the participant subgroup that did not experience fever.

Each reported post hoc analysis is based on SRC regression with mean centering; it should be noted that post hoc interpretations either do not shift, or shift in minor ways when these SRC regressions are re-estimated using mode centering or centering based on the ordinal value of the second-highest frequency category (when frequency > 30). Thus, all post hoc interpretations remain robust regardless how predictors are centered.

I. Application to Interpret the Symptom Interaction of Pain *x* Sleep Problems *x* Fever in Table 4

A. Interpreting Co-moderation by Fever:

Sequential Residual-Centered Regression 2 with *Mean Centering*

$$\partial y'/\partial x = (.474 - .228w) + (.445 - .361w)z \quad (2)$$

Setting $\partial y'/\partial x = 0$:

$$z_{0,w} = (-.474 + .228w) / (.445 - .361w) \quad (3)$$

$$\partial^2 y'/\partial x \partial z = (.445 - .361w) \quad (5)$$

Select w where $| .445 - .361w |$ are highest in absolute value: ($w_{high} = 4$, $w_{low} = 0$).

a. At $w_{high} = 4$: $z_{0,w=4} = -0.438$

The $z_{0,w=4}$ is *outside* the actual range of z values (0–4).

$$| 4 - (-0.438) | > | 0 - (-0.438) | \quad (7)$$

$$4.438 > 0.438$$

When there is no control over Sleep Problems (w = 4), Fever magnifies the Pain-Depressive Affect relationship over the full range of Fever, from complete control to no control (ie, z = 0 to 4),

(10 of the 57 participants reporting no control of Sleep Problems experienced incomplete control of Fever, z > 0).

b. At $w = 3$: $z_{0,w=3} = -0.329$

The $z_{0,w=4}$ is *outside* the actual range of z values (0–4).

$$| 4 - (-0.329) | > | 0 - (-0.329) | \quad (7)$$

$$4.329 > 0.329$$

When there is a little control over Sleep Problems (w = 3), Fever magnifies the Pain-Depressive Affect relationship over the full range of Fever, from complete control to no control (ie, z = 0 to 4),

(6 of the 17 participants reporting a little control of Sleep Problems experienced incomplete control of Fever, z > 0).

Combining (a) and (b):

When there is a little control or no control over Sleep Problems (w = 3 or 4), Fever magnifies the Pain-Depressive Affect relationship over the full range of Fever, from complete control to no control (ie, z = 0 to 4).

[16 of the 74 participants reporting a little or no control of Sleep Problems experienced incomplete control of Fever, z > 0]

Note: Conclusions for I.A.a and I.A.b are identical when statistical control variables are added for Gender, Age (< 65 versus 65+), an ordinal variable for Illness Comorbidity (none, one, more than one condition), and a series of dummy variables selecting out participants that did not experience any given symptom.

B. Interpreting Co-moderation by Sleep Problems:

Sequential Residual-Centered Regression 2 with *Mean Centering*

$$\partial y'/\partial x = (.474 - .445z) + (-.228 - .361z)w \quad (2)$$

Setting $\partial y'/\partial x = 0$:

$$w_{0,z} = (-.474 + .445z) / (-.228 - .361z) \quad (3)$$

$$\partial^2 y'/\partial x \partial w = (-.228 - .361z) \quad (5)$$

Select *w* where | –.228 – .361*z* | are highest in absolute value: ($z_{high} = 4$, $z_{low} = 0$).

a. At $z_{high=4}$: $w_{0,z=4} = -.841$

The $w_{0,z=4}$ is *outside* the actual range of *w* values (0–4).

$$| 4 - (-.841) | > | 0 - (-.841) | \quad (7)$$

$$4.841 > 0.841$$

When there is no control of Fever (z = 4), Sleep Problems magnify the Pain-Depressive Affect relationship over the full range of Sleep Problems, from complete control to no control (ie, w = 0 to 4). (8 of the 11 participants reporting no control of Fever experienced incomplete control of Sleep Problems, w > 0).

b. At z_3: $w_{0,z=3} = -.657$

The $w_{0,z=3}$ is *outside* the actual range of *w* values (0–4).

$$| 4 - (-.657) | > | 0 - (-.657) | \quad (7)$$

$$4.657 > 0.657$$

When there is a little control of Fever (z = 3), Sleep Problems magnify the Pain-Depressive Affect relationship over the full range of Sleep Problems, from complete control to no control (ie, w = 0 to 4). (3 of the 3 participants reporting a little control of Fever experienced incomplete control of Sleep Problems, w > 0).

c. At z_2: $w_{0,z=2} = -.438$

The $w_{0,z=2}$ is *outside* the actual range of *w* values (0–4).

$$| 4 - (-.438) | > | 0 - (-.438) | \quad (7)$$

$$4.438 > 0.438$$

When there is some control of Fever (z = 2), Sleep Problems magnify the Pain-Depressive Affect relationship over the full range of Sleep Problems, from complete control to no control (ie, w = 0 to 4). (The 1 participant reporting some control of Fever experienced complete control of Sleep Problems, w = 0).

Combining (a), (b), and (c):

When there is some control to no control of Fever (z = 2, 3, or 4), Sleep Problems magnify the Pain-Depressive Affect relationship over the full range of Sleep Problems, from complete control to no control (ie, w = 0 to 4).

(14 of the 15 participants reporting some control to no control of Fever experienced incomplete control of Sleep Problems, w > 0).

d. At z_1 : $w_{0,z=1} = .049$

The $w_{0,z=1}$ is *inside* the actual range of *w* values (0–4).

$$| 4 - .049 | \sim | 0 - .049 | \qquad (6)$$

$$3.951 > 0.049$$

$$0 < 0.049 < 1, 2, 3, 4$$

When there is a lot of control of Fever (z = 1), Sleep Problems magnify the Pain-Depressive Affect relationship when Sleep Problems are completely controlled (ie, w = 0) and buffer the Pain-Depressive Affect relationship over the range of Sleep Problems from a lot of control to no control (ie, w = 1 to 4). (9 of the 12 participants reporting a lot of control of Fever experienced incomplete control of Sleep Problems, w > 0).

e. At z_0 : $w_{0,z=0} = 2.079$

The $w_{0,z=0}$ is *inside* the actual range of *w* values (0–4).

$$| 4 - 2.079 | \sim | 0 - 2.079 | \qquad (6)$$

$$1.921 < 2.079$$

$$0, 1, 2 < 2.079 < 3, 4$$

When there is complete control of Fever (z = 0), Sleep Problems magnify the Pain-Depressive Affect relationship over the range of Sleep Problems from complete to some control (ie, w = 0 to 2) and buffer

the Pain-Depressive Affect relationship over the range of Sleep Problems from a little control to no control (ie, w = 3 and 4).

(8 of 240 participants reporting complete control of Fever experienced incomplete control of Sleep Problems, w > 0).

II. Application to Interpret the Symptom Interaction of Pain *x* Fever *x* Fatigue/weakness in Table 4

A. Interpreting Co-moderation by Fever:

Sequential Residual-Centered Regression 3 with *Mean Centering*

$$\partial y'/\partial x = (.125 - .220w) + (-1.190 + .660w)z \quad (2)$$

Setting $\partial y'/\partial x = 0$:

$$z_{0,w} = (-.125 + .220w) / (-1.190 + .660w) \quad (3)$$

$$\partial^2 y'/\partial x \partial z = (-1.190 + .660w) \quad (5)$$

Select *w* where | –1.190 + .660*w* | are highest in absolute value: ($w_{low} = 0$, $w_{high} = 4$).

a. At $w_{high} = 4$: $z_{0,w=4} = 0.521$

The $z_{0,w=4}$ is *inside* the actual range of *z* values (0–4).

$$| 4 - 0.521 | \sim | 0 - 0.521 | \quad (6)$$

$$3.479 > 0.521$$

$$0 < 0.521 < 1, 2, 3, 4$$

Effects will not be assessed at $z = 0$ where there are only 2 participants.

Since $\partial y'/\partial x |_{w = 4,\ z = 1, 2, 3, 4} > 0$, *magnifier* effects at $z = 1, 2, 3, 4$

When there is no control of Fatigue/weakness (w = 4), Fever magnifies the Pain-Depressive Affect relationship over the range of Fever from a lot of control to no control (ie, z = 1, 2, 3, 4).

(9 of the 54 participants reporting no control of Fatigue/weakness experienced incomplete control of Fever, z > 0).

b. At $w = 3$: $z_{0,w=3} = 0.677$

The $z_{0,w=3}$ is *inside* the actual range of *z* values (0–4).

$$| 4 - 0.677 | \sim | 0 - 0.677 | \quad (6)$$

$$3.323 > 0.677$$

$$0 < 0.677 < 1, 2, 3, 4$$

Since $\partial y'/\partial x \,|_{w = 3,\, z = 0} < 0$, *buffering* effects at $z = 0$; however, there are only 2 participants

Since $\partial y'/\partial x \,|_{w = 3,\, z = 1, 2, 3, 4} > 0$, *magnifier* effects at $z = 1, 2, 3, 4$

Effects will not be assessed at $z = 0$ where there are only 2 participants.

When there is a little control of Fatigue/weakness (w = 3), Fever magnifies the Pain-Depressive Affect relationship over the range of Fever from a lot of control to no control (ie, z = 1, 2, 3, 4).

(5 of 23 participants reporting a little control of Fatigue/weakness experienced incomplete Fever control, z > 0).

Combining (a) and (b):

When there is a little control or no control of Fatigue/weakness (w = 3 or 4), Fever magnifies the Pain-Depressive Affect relationship over the range of Fever from a lot of control to no control (ie, z = 1, 2, 3, 4). [14 of the 77 participants reporting a little or no control of Fatigue/weakness experienced incomplete control of Fever, z > 0]

c. At $w = 1$: $z_{0,w=1} = -0.179$

The $z_{0,w=1}$ is *outside* the actual range of z values (0–4).

$$| 4 - (-0.179)| \sim | 0 - (-0.179)| \qquad (7)$$

$$4.179 > 0.179$$

When there is a lot of control of Fatigue/weakness (w = 1), Fever magnifies the Pain-Depressive Affect relationship over the full range of Fever, from complete control to no control (ie, z = 0 to 4).

(7 of 79 participants reporting a lot of control of Fatigue/weakness experienced incomplete control of Fever, z > 0).

(Considering (a), (b), and (c) together, 21 of 156 participants reporting a lot, a little, or no control of Fatigue/weakness experienced incomplete control of Fever)

Note: The conclusions for II.A.a and II.A.b are similar when statistical control variables are added for Gender, Age (< 65 versus 65+), Illness Comorbidity (none, one, two or more conditions), and a series of dummy variables selecting out participants who did not experience any given symptom. Magnifier effects of Fever occur within a somewhat more restricted Fever range, starting from some control ($z = 2$ when

w_{high} = 4) or a little control (z = 3 when w = 3), yet still occurring up to no control (z = 4) in both cases. The conclusion for II.A.c is identical.

B. Interpreting Co-moderation by Fatigue/weakness:

Sequential Residual-Centered Regression 2 with *Mean Centering*

$$\partial y'/\partial x = (.125 - 1.190z) + (-.220 + .660z)w \quad (2)$$

Setting $\partial y'/\partial x = 0$:

$$w_{0,z} = (-.125 + 1.190z) / (-.220 + .660z) \quad (3)$$

$$\partial^2 y'/\partial x \partial w = (-.220 + .660z) \quad (5)$$

Select w where $| -.220 + .660z |$ are highest in absolute value: (z_{low} = 0, z_{high} = 4).

a. At $z_{high=4}$: $w_{0,z=4}$ = 1.915

The $w_{0,z=4}$ is *inside* the actual range of z values (0–4).

$$| 4 - 1.915 | \sim | 0 - 1.915 | \quad (6)$$

$$2.085 > 1.915$$

$$0, 1 < 1.915 < 2, 3, 4$$

Since $\partial y'/\partial x |_{w = 0, 1, z = 4} < 0$, *buffering* effects at w = 0 and 1

Since $\partial y'/\partial x |_{w = 2, 3, 4, z = 4} > 0$, *magnifier* effects at w = 2, 3, 4

When there is no control of Fever (z = 4), Fatigue/weakness buffers the Pain-Depressive Affect relationship when there is complete control to a lot of control of Fatigue/weakness (w_{low} = 0 and 1) and magnifies the Pain-Depressive Affect relationship when there is some control to no control of Fatigue/weakness (w = 2, 3, 4).

(11 of the 11 participants reporting no control of Fever experienced incomplete control of Fatigue/weakness, w > 0).

b. At z_3: $w_{0,z=3}$ = 2.009

The $w_{0,z=3}$ is *inside* the actual range of z values (0–4).

$$| 4 - 2.009 | \sim | 0 - 2.009 | \quad (6)$$

$$1.991 > 2.009$$

$$0, 1, 2 < 2.009 < 3, 4$$

Since $\partial y'/\partial x |_{w = 0, 1, 2, z = 3} < 0$, *buffering* effects at $w = 0, 1, 2$

Since $\partial y'/\partial x |_{w = 3, 4, z = 3} > 0$, *magnifier* effects at $w = 3, 4$

When there is a little control of Fever (z = 3), Fatigue/weakness buffers the Pain-Depressive Affect relationship when there is complete control to some control of Fatigue/weakness (w_{low} = 0, 1, and 2) and magnifies the Pain-Depressive Affect relationship when there is a little control to no control of Fatigue/weakness (w = 3, 4).

(2 of the 3 participants reporting a little control of Fever experienced incomplete control of Fatigue/weakness, w > 0).

c. At z_2 : $w_{0,z=2} = 2.050$

The $w_{0,z=2}$ is *inside* the actual range of *z* values (0–4).

$$| 4 – 2.050 | \sim | 0 – 2.050 | \quad (6)$$

$$1.950 < 2.050$$

$$0, 1, 2 < 2.050 < 3, 4$$

Since $\partial y'/\partial x |_{w = 0, 1, 2, z = 2} < 0$, *buffering* effects at $w = 0, 1, 2$

Since $\partial y'/\partial x |_{w = 3, 4, z = 2} > 0$, *magnifier* effects at $w = 3, 4$

When there is some control of Fever (z = 2), Fatigue/weakness buffers the Pain-Depressive Affect relationship when there is complete control to some control of Fatigue/weakness (w_{low} = 0, 1, and 2) and magnifies the Pain-Depressive Affect relationship when there is a little control to no control of Fatigue/weakness (w = 3, 4).

(1 participant reporting some control of Fever experienced incomplete control of Fatigue/weakness, w > 0).

d. At z_2 : $w_{0,z=2} = 2.420$

The $w_{0,z=1}$ is *inside* the actual range of *z* values (0–4).

$$| 4 – 2.420 | \sim | 0 – 2.420 | \quad (6)$$

$$1.580 < 2.420$$

$$0, 1, 2 < 2.420 < 3, 4$$

Since $\partial y'/\partial x |_{w = 0, 1, 2, z = 1} < 0$, *buffering* effects at $w = 0, 1, 2$

Since $\partial y'/\partial x |_{w = 3, 4, z = 1} > 0$, *magnifier* effects at $w = 3, 4$

When there is a little control of Fever (z = 1), Fatigue/weakness buffers the Pain-Depressive Affect relationship when there is complete control to some control of Fatigue/weakness (w_{low} = 0, 1, and 2) and magnifies the Pain-Depressive Affect relationship when there is a little control to no control of Fatigue/weakness (w = 3, 4).

(10 of the 12 participants reporting no control of Fever experienced incomplete control of Fatigue/weakness, w > 0).

Combining (b), (c), and (d):

When there is a lot of control to a little control of Fever (z = 1, 2, or 3), Fatigue/weakness buffers the Pain-Depressive Affect relationship when there is complete control to some control of Fatigue/weakness (w_{low} = 0, 1, and 2; n = 9) and magnifies the Pain-Depressive Affect relationship when there is a little control to no control of Fatigue/weakness (w = 3, 4; n = 7).

e. At $z_{low=0}$: $w_{0,z=0}$ = .568

The $w_{0,z=0}$ is *inside* the actual range of *z* values (0–4).

$$| 4 - .568 | \sim | 0 - .568 | \quad (6)$$

$$3.432 > .568$$

$$0 < .568 < 1, 2, 3, 4$$

Since $\partial y'/\partial x |_{w = 0,\ z = 0} > 0$, *magnifier* effects at *w* = 0

Since $\partial y'/\partial x |_{w = 1, 2, 3, 4,\ z = 0} < 0$, *buffering* effects at *w* = 1, 2, 3, 4

When there is complete control of Fever (z = 0), Fatigue/weakness buffers the Pain-Depressive Affect relationship when there is complete control of Fatigue/weakness (w_{low} = 0, 1, and 2) and magnifies the Pain-Depressive Affect relationship when there is a lot of control to no control of Fatigue/weakness (w = 1, 2, 3, 4).

(166 of 240 participants reporting no control of Fever experienced incomplete control of Fatigue/weakness, w > 0).

Combining (a) and (e):

At both extremes, when there is either complete control or no control of Fever (z = 0 or 4),

Fatigue/weakness buffers the Pain-Depressive Affect relationship when there is complete control to a lot of control of Fatigue/weakness (w_{low} = 0 and 1; n = 149) and magnifies the Pain-Depressive Affect relationship when there is some control to no control of Fatigue/weakness (w = 2, 3, 4; n = 102).

III. Application of the *Original* ZSC to Interpret Pain *x* Fatigue/weakness in Table 4 *when Fever Control is Not a Concern* (ie, subgroup of 238 participants)

A. Interpreting Co-moderation by Fever:

Sequential Residual-Centered Regression 1B with *Mean Centering*

$$\partial y'/\partial x = .554 + (-.327)w$$

Setting $\partial y'/\partial x = 0$:

$$w_0 = -.554 / -.327 = 1.694$$

The w_0 is *inside* the actual range of *z* values (0–4).

$$| 4 - 1.694 | \sim | 0 - 1.694 |$$

$$2.306 > 1.694$$

$$0, 1 < 1.694 < 2, 3, 4$$

Since $\partial y'/\partial x |_{w = 0,1} > 0$, *magnifier* effects at $w = 0, 1$

Since $\partial y'/\partial x |_{w = 2,3,4} < 0$, *buffering* effects at $w = 2, 3, 4$

When Fever control is not a concern, Fatigue/weakness magnifies the Pain-Depressive Affect relationship when there is complete control to a lot of control of Fatigue/weakness (ie, w = 0, 1) and buffers the Pain-Depressive Affect relationship when there is some control to no control of Fatigue/weakness (ie, w = 2, 3, 4).

[240 participants do not report Fever; 90 of these participants report concurrent Pain and Fatigue/weakness].

Part B: Advantages of Classical Moderated Regression Analysis Over Other Statistical Procedures for Detecting Symptom Clusters

The follow-up patient profiles are derived from the original regression findings of pairs or clusters of responses across physical symptom items (ie, clustering by *variables*)—and not by clustering the *individuals per se* that all share a patient profile. In contrast to moderated regression, the method of regression mixture analysis accounts for population heterogeneity by classifying individuals into latent classes characterized by different sets of regression parameter estimates. While this option would appear attractive for revealing separate patient profiles by avoiding the need for a separate *post-hoc* procedure (Extended ZSC), several limitations of the regression mixture analysis procedure are aggravated when non-normal regression predictors, including quadratic terms and statistical interaction terms, are specified. In particular, skewness or non-normality in latent classes and/or predictor variables results in latent class artifacts that do not reflect population heterogeneity.[3]

Moderated Bayesian regression is not appropriate as well for this small-sample study. Although multicollinearity does not occur in Bayesian regression, avoiding the need for multicollinearity adjustments, the procedure requires large samples. Demands for mastering and executing Bayesian regression make it inaccessible to many researchers. In addition, researchers exposed to the same previous evidence supporting a particular hypothesis may differ in their confidence in that evidence, resulting in different choices of subjective prior distributions as inputs for the procedure. These deviations are inconsequential in large samples but distort findings and inferences in smaller samples.[4]

In factor, principal components, and cluster analyses, which constitute much of the published literature on symptom clusters,[5] the choice of an *a priori* and typically arbitrary threshold for determining when each symptom should be considered may determine in unknown ways which symptoms end up forming a symptom pair/cluster, while the failure to make such *a priori* choices may influence the composition of a symptom pair/cluster in other unknown ways. Thus, it is not surprising that symptom clusters in cancer patients with bone metastases have consistently been found to vary depending upon which of these three statistical methods were used.[6-8] In contrast, moderated regression incorporates the full range of symptom values for unbiased detection of a highest-order symptom interaction term along with all derivative lower-order symptom interaction terms, even when the symptom cluster is active only

within a limited range(s) of one or more component symptom(s). Another advantage over factor and cluster analyses is that the influence(s) of each co-moderating symptom on the relationship between the primary or sentinel symptom within the cluster and an outcome can be interpreted as patient profiles, using a follow-up procedure.

Moreover, while factor, principal components, cluster, and moderated regression analyses all detect symptom clusters when different symptoms occur within the same individuals either simultaneously or during the same time period, only moderated regression further refines and delimits the selection of symptom clusters when they predict an important outcome (*y* variable), such as depressive affect (sickness malaise). In this way, moderated regression may perform better (if still imperfectly) in avoiding the selection of symptoms that just happen to occur together but stem from unrelated biological mechanisms. The predicted outcome provides a non-arbitrary, context-specific, outcome-based threshold for defining when symptoms will contribute to the symptom interactions. In addition, not only can control and other explanatory variables be specified, but quadratic terms can also be specified as predictors that prevent nonlinear (ie, curvilinear) effects of each symptom from confounding effects by symptom interactions. (The potential for such confounding increases when one or more quadratic terms missing from the model are correlated with any specified interaction terms).

Along with these strengths, however, moderated regression can usually accommodate far fewer symptoms than the all-possible symptom approach using factor, cluster, or principal components analysis.[5] The analyst must determine which set of symptoms will be components of the highest-order statistical interaction and its derivative lower-order interactions (in practice, no more than four symptoms in a four-way interaction) and of all derivative lower-order interactions. But even this apparent tradeoff does not constitute a true comparative weakness since the other statistical procedures create symptom clusters from a broad range of symptoms, *which are not necessarily mutually influential*. Consequently, few respondents are likely to endorse all of the symptoms that contribute to a given symptom cluster when identified by these other statistical procedures. Because interpretation of findings from these procedures is intended to occur at the level of the overall sample, the findings do not reflect population heterogeneity and may be subject to ecological fallacies and clinical irrelevance when interpreted for subgroups or at the level of individual patients. Unlike these procedures, moderated regression analysis identifies fewer symptoms as components of symptom clusters, and these symptoms are necessarily

mutually influential, increasing the potential that more than a few respondents endorse all of the symptoms. Furthermore, moderated regression analysis includes statistics such as Cook's d to identify individual outlier observations that demonstrate disproportionate influence on the magnitude and statistical significance of regression slope parameters for interaction terms. When highly influential outlier observations are limited in number and excluded, parameters from statistically significant interaction terms yield more accurate estimates by remaining participants experiencing the cluster.

In sum, these strong comparative advantages make moderated regression analysis most suitable for the current study and, it is hoped, will rekindle interest in symptom clusters from research teams.

Part C: Sequential Residual Centering (SRC) in the Contexts of Mean- and Other-Centered Variables

Until recently, mean-centered moderated regression was the recommended approach for conditioning away inessential multicollinearity.[9-11] However, when predictors are mean centered, only SRC regression—and not raw regression—conditions away inessential multicollinearity. In Table 4, the decision to retain mean-centered predictors in both the raw and SRC regressions fosters comparisons between parallel estimates for the standard errors (SE and ESE) and the variance inflation factor (VIF and EVIF). As such, these parallel estimates appear to be truly commensurate. Otherwise, differences in these parallel estimates may be questioned as to whether they necessarily or entirely result from conditioning away inessential multicollinearity—they might also be due to differences in how predictors are scaled (an issue resolved later in this section).

Although the symptom predictors are ordinal variables, the use of mean centering is also justified by the realization that many ordinal variables (such as symptom control items) are not true ordinal variables consisting of discretely bounded, rank-ordered categories—the existence of an underlying continuous dimension across the ordinal categories implies that these hybrid variables occupy an intermediate dimension between true ordinal and true continuous measures. In support of this perspective, an experimental study[12] revealed that the extension of Likert (five-category) scales into seven and ten ordinal categories, which more closely approximate a true continuous measure, resulted in minor alterations in regression parameters and distribution statistics (mean, standard error). While some researchers do not consider the mean and standard deviation to be meaningful statistics for ordinal variables, these results support contentions by other researchers that means and standard deviations can be meaningful statistics for ordinal measures with underlying continuous dimensions. Moreover, regression itself is an interval-level statistical procedure that analyzes the data for each predictor as if it were a continuously distributed variable.

Except for the highest-order interaction term, regression slopes and standard errors for remaining predictors may shift, sometimes dramatically, when comparing findings from mean centering and other centering options (eg, mode-centering[9]). Nevertheless, even with these shifts, *post-hoc* analyses reveal the same types and patterns of moderation in the patient profiles, as other analysts have demonstrated.[9] The *post-hoc* procedure results in very similar interpretations of the SRC mean-centered findings when

mean-centering is replaced with 1) mode-centering; and 2) a second alternative centering where the mode is replaced with the value of the second highest frequency category, assuming over 30 participants fall in that category. *The interpretations from mean centering that are replicated with both ordinal-centering options are evidence that the moderator effects are robust and stable when symptoms of the interaction and remaining predictors are assessed across a range of values.* With respect to interpretation of the current study data, these findings reveal the choice to be moot about whether to center predictors based on the mean, mode, or another ordinal value.

The SRC innovation is critical for valid interpretations of the data. Regression 4, in particular, in Table 4 shows that *compared to mean centering alone, SRC can be effective in overcoming problematic multicollinearity,* as evidenced by dramatic reductions in VIF values (compare VIF and EVIF). The inflated VIF values for three of the four three-way interactions, and for three of the six two-way interactions, all fall in the SRC regression to EVIF values less than 10 that no longer reveal problematic multicollinearity.[13] The *mean* EVIF in regression 4 is approximately 2.6; it is ambiguous whether this finding meets the stricter, if rather vague, criterion that the mean EVIF across predictors is not considerably larger than one,[14] although any biasing influence from remaining essential multicollinearity would appear to be limited. Regardless whether this stricter criterion is met, the exhaustive and simultaneous specification in regression 4 provides a strict test about whether to confirm the three-way interactions that were tested separately within the more traditional explanatory models (ie, regressions 1B, 2, and 3).

Thus, it would appear that in contrast to mean centering alone, SRC is reliable for specifying, in the same regression, more than one interaction term of the highest order while considerably reducing problematic multicollinearity (but not necessarily conditioning the full range of multicollinearity on account of remaining impacts from essential ill-conditioning).

Part D: Suppressor and Spurious Influences from Common Drugs on Study Findings

It is important to consider the influence of other common drugs, including those that *reduce* fever, on patient profiles. Nonsteroidal antiinflammatory drugs (NSAIDs) are perhaps the most common medication used by cancer survivors. Pain and fever may lead to NSAID use, which would be expected to reduce fatigue, weakness, and depressive affect (sickness malaise). Although I was unable to control for NSAID use in these analyses due to data limitations, the lack of control of NSAIDs should not introduce a spurious influence that *undermines the nature* of the interaction effects, but in contrast, may make it more difficult to detect them. That is, assuming the effect of NSAID use is statistically significant, it is likely to constitute a *suppressor effect*, which would reveal that the magnitudes of the interaction regression slopes are reduced when NSAID use is not specified in the regression equation. In this respect, it appears that study findings are conservative, robust, and valid when NSAID use is not controlled.

Other medications not controlled in the analyses of participants with or without fever could have suppressor or even spurious influences. Compared to their influences in a main effects (i.e., one-way) regression model, however, spurious effects may be less serious in a moderator regression model based on SRC, which is well honed to detect targeted interaction effects. For any given participant, a spurious influence would need to undermine not simply symptoms tested individually (as in a main effects regression) but rather all multiple symptom components within the targeted interaction term. Although possible, it appears much less likely that spurious influences from a medication would consist of the very same co-occurring set of symptoms that comprise the interaction term. Thus, bias due to any spurious influence may be more pronounced in separate one-way terms than in derivative interaction terms. Since the interaction *effect* is determined by the interaction *term* and all lower-order component terms, this influence could shift the predictor ranges determined from the EZSC procedure (see part A), in which interaction terms demonstrate magnifier effects that reveal symptom clusters. This weakness suggests we should be more confident in the *presence* of detected symptom clusters compared to the *precision* of their estimated ranges.

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