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Interpreting interactions of ordinal or continuous variables in moderated regression using the zero slope comparison: tutorial, new extensions, and cancer symptom applications

Richard B. Francoeur

Adelphi University School of Social Work, Social Work Building, 1 South Avenue, # 701, Garden City, NY 11530, USA, francoeur@adelphi.edu

Abstract

Moderated multiple regression (MMR) can model behaviours as multiple interdependencies within a system. When MMR reveals a statistically significant interaction term composed of ordinal or continuous variables, a follow-up procedure is required to interpret its nature and strength across the primary predictor (x) range. A follow-up procedure should probe when interactions reveal magnifier (or aggravating) effects and/or buffering (or relieving) effects that qualify the x - y relationship, especially when interpreting multiple interactions, or a complex interaction involving curvilinearity or multiple co-moderator variables. After a tutorial on the zero slope comparison (ZSC), a rarely used, quick approach for interpreting linear interactions between two ordinal or continuous variables, I derive novel extensions to interpret *curvilinear* interactions between two variables and linear interactions among *three* variables. I apply these extensions to interpret how co-occurring cancer symptoms at different levels influence one another – based on their interaction – to predict feelings of sickness malaise.

Keywords

cancer; curvilinear; depression; effect modifier; moderated regression; moderator; sickness behaviour; statistical interaction; symptom cluster; systems science; zero slope comparison; ZSC

1 Introduction

1.1 Zero slope comparison

The zero slope comparison (ZSC) is a procedure for interpreting *linear* interactions between *two* predictors that are scaled as ordinal or continuous variables (Nye and Witt, 1995). The ZSC is convenient and advantageous because it is based solely on regression output. Nye and Witt (1995) developed the ZSC to interpret quickly the nature and relative strength of regression relationships predicted by interactions of *two* ordinal or continuous x -variables. The ZSC determines whether the moderator variable within the interaction magnifies (aggravates) and/or buffers (relieves) the x - y regression relationship, at what values of the interacting variables, and to what degree. In Section 2 of this article, I will derive the original ZSC in greater detail than Nye and Witt (1995) reported. In Section 3, I will first extend the ZSC to assess interactions with curvilinear component(s). Following this, I will derive extensions of the ZSC to assess the nature and strength of linear interactions involving three interacting variables, which may occur alone as a single three-way interaction, or along with statistically significant two-way interaction derivatives. I will confirm the validity of these ZSC procedures by using them to replicate interpretations of co-occurring cancer symptom relationships that were published in Francoeur (2005).

1.2 Symptom cluster applications

As the components of the ZSC and its extensions are derived, they will be illustrated through applications to interpret previously published relationships from moderated regression analyses (Table 1) involving interactions of co-occurring physical symptoms that predict co-occurring depressive affect (within a one week period) in outpatients initiating palliative radiation.

In these moderated regression applications, a ‘symptom cluster’ occurs within the same individual when two or more co-occurring physical symptoms experienced over the past month interact to predict a mental health symptom (depressive affect) reported over the past week. (Note that in other specifications, the predicted y variable might reflect a *future* outcome, which could also be a symptom, although it would no longer be part of the same symptom cluster). The interaction between two physical symptoms implies that the size of the relationship between the more primal physical symptom and depression (y) is influenced (i.e., moderated) by the level of the other co-occurring physical symptom in the interaction, and the direction of this influence may be to magnify or buffer (i.e., reduce) the relationship between the primal physical symptom and depressive affect. Thus, the relationship may be magnified when the additional physical symptom occurs at certain levels and/or buffered when it occurs at other levels. In an interaction of three physical symptoms (or alternatively, of two physical symptoms and another variable), the relationship between the primal physical symptom and depression is magnified and/or buffered by each of two additional co-occurring physical symptoms (and in the alternative, by the remaining co-occurring physical symptom and other variable).

The co-occurring nature of symptoms is supported by the paradigm of ‘sickness behaviour,’ which posits malaise, or depressive affect from feeling sick, as a ubiquitous and systemic psychological symptom of cancer that coincides with the production of proinflammatory cytokines when clusters of physical symptoms are precipitated and perpetuated (Raison and Miller, 2003). The search for plausible symptom clusters in epidemiologic data, in which specific level(s) of a symptom magnifies (or *aggravates*) the relationship between a primary symptom and depression, may lead to efforts for identifying contexts in which:

1. *interventions to relieve one physical symptom* could have cross-over impacts by buffering (or *relieving*) the co-occurring physical symptom and/or the feelings of malaise (depressive affect from feeling sick)
2. *interventions to relieve depressive affect* could have cross-over impacts by buffering or relieving any or all of the co-occurring physical symptoms.

It is also important to identify when specific level(s) of a symptom may relieve or buffer the relationship between a primary symptom and depression, such that the joint presence of symptoms actually serves to protect the individual from developing more intense or severe symptom(s) or depressive affect. In these symptom clusters, symptom-specific interventions could magnify or *aggravate* (rather than relieve) the co-occurring physical symptom(s) or depression (i.e., iatrogenic effects of symptom management) (Barsevick et al., 2006; Kirkova and Walsh, 2007; Miaskowski et al., 2004). On the other hand, these symptom clusters could simply mark contexts that interfere with symptom reporting. Eventually, electronic medical record systems, integrated with online pharmacy data, could incorporate the ZSC procedure to monitor patients for symptom interactions that may reflect toxic side-effects or medication non-adherence.

2 The original ZSC for linear interactions of two predictors

This section closely follows, and further clarifies, the derivation of the original zero slope coefficient (ZSC) procedure by Nye and Witt (1995) to interpret interactions of two independent variables.

In moderated regression analysis, an equation involving an interaction term of two predictors may be specified as:

$$y' = a + b_1x + b_2w + b_3xw \quad (1)$$

Equivalently,

$$y' = (a + b_2w) + (b_1 + b_3w)x \quad (2)$$

The slope of y' with respect to the predictor (x) is the first partial derivative:

$$\partial y' / \partial x = b_1 + b_3w \quad (3)$$

If we set the slope ($\partial y' / \partial x$) equal to 0, the value of w that results in a zero slope for the relationship between the predictor (x) and the criterion (y) is:

$$w_0 = -b_1 / b_3 \quad (4)$$

where w_0 is the moderator value at which the slope of x is zero.

Terms for the separate quadratic variables x^2 and w^2 may also be specified in (1), however because these quadratic terms are *not* components of the interaction term (b_3xw), they do not influence the derivation of the original ZSC. Of course, statistically significant quadratic terms (along with their first-order derivative terms) should also be interpreted because they may intensify or counteract any interaction effect.

2.1 When w_0 falls within the range of moderator values

As an illustration, we analyse regression parameters in which Fatigue-weakness (w) moderates the relationship between Pain (x) and Depressive affect (y) (regression 3 in Table 1). The relationship ($b_1 = 0.463$) between a predictor (x) and a dependent variable (y) is moderated ($b_3 = -0.310$) by another variable (w). Applying equation (4), $w_0 = -0.463 / -0.310 = 1.49$. Thus, 1.49 is the value of the moderator variable at which the slope of x becomes zero.

Since the moderator variable is coded as the integers from 0 through 4, the direction of the slopes will differ for the integer values below 1.49 (i.e., 0, 1) compared to the integer values above 1.49 (i.e., 2, 3, 4). (If the moderator variable were continuous, the direction of the slopes would differ for all continuous values below 1.49 compared to those above 1.49). In equation (3), if w is set to 0 or 1, the slope ($\partial y' / \partial x$) is calculated to have a *positive* direction (representing magnifier or exacerbation effects), whereas if w is set to 2, 3, or 4, the slope is calculated to have a *negative* direction (representing buffering effects).

We can compare the respective slopes of any two values of moderator w :

$$[(w_{high} - w_0)b_3] \sim [(w_{low} - w_0)b_3] \quad (5)$$

where w_{high} represents a high moderator value, w_{low} represents a low moderator value, w_0 is the moderator value at which the slope between the y -outcome and x -predictor is zero, and $\sim$ is an operator that indicates a comparison of two quantities. Formally, b_3 is the second partial derivative [from equation (3)] of the change in the slope of y' with respect to the predictor x that can be attributed to the predictor w :

$$\partial^2 y' / \partial x \partial w = b_3 \quad (6)$$

The comparison in equation (5) can be reduced to one which reveals the relative magnitudes of the two slopes based on a comparison of their absolute values:

$$|w_{high} - w_0| \sim |w_{low} - w_0| \quad (7)$$

Of the two quantities, the one with the greater unit distance from w_0 indicates the moderator value with the greater relative slope and thus stronger moderation of the x - y relationship. In our illustration, a comparison of $w_{high} = 4$ with $w_{low} = 0$ is: $|4 - 1.49| \sim |0 - 1.49|$, or $2.51 \sim 1.49$. Thus, the buffering effects of the x - y relationship at $w_{high} = 4$ are stronger than the magnifier effects of the x - y relationship at $w_{low} = 0$. Table 2 applies the original ZSC to assess the nature and relative strength of the second-order simple interaction of Pain and Fatigue-weakness.

2.2 When w_0 falls outside the range of moderator values

The moderator value at which the slope of the predictor is zero (i.e., w_0) may fall below or above the range of actual moderator values, that is, $w_0 < w_{low}$ or $w_0 > w_{high}$. In our opening illustration at the beginning of Section 2.1, the value of w_0 would have to be less than 0 or greater than 4. Applying equation (3) to either scenario, all of the slopes ($y' \sim x$) across the actual range of moderator values would be in a *consistent direction*.

If the value of the moderator value where the slope is zero is *below* the range of moderator values (i.e., $w_0 < w_{low} < w_{high}$), then equation (7) reflects not only a comparison but the *consistent relationship*:

$$|w_{high} - w_0| > |w_{low} - w_0| \quad (8)$$

This consistent relationship is revealed in Figure 1, panel A, where b_1 is positive and b_3 is negative (as in our earlier illustration: $b_1 = 0.463$ and $b_3 = -0.310$), and in panel B, where both b_1 and b_3 are negative. In panel A, the slope becomes progressively *more positive* as moderator values increase; in panel B, the slope becomes progressively *more negative* as moderator values increase. In both panels, the slopes become progressively larger in absolute value. Thus, if $w_0 < w_{low}$, the absolute magnitude of the slopes will increase across the range of moderator values; these signify magnifier (or exacerbation) effects.

If the value of the moderator value where the slope is zero is *above* the range of moderator values (i.e., $w_0 > w_{high} > w_{low}$), then equation (7) reflects the *opposite consistent relationship*:

$$\left|w_{high} - w_0\right| < \left|w_{low} - w_0\right| \quad (9)$$

This consistent relationship is revealed in Figure 1, panels C and D: the slopes become progressively *smaller in absolute value* as moderator variables increase. Thus, *if $w_0 = w_{high}$, the absolute magnitude of the slopes will decrease across the range of moderator values; these signify buffering effects.*

3 Extensions to the ZSC and applications

Nye and Witt (1995) developed the ZSC to yield insights about the form of the relationships in the simplest case of moderated multiple regression (MMR) analysis (i.e., based on second-order interactions involving only two variables). Their exposition did not suggest how this procedure might be adapted to curvilinear interactions or to interactions involving three or more variables. I will first develop each of these extensions in Section 3.1; in Section 3.2, I will apply each extension to interpret the nature and strength of symptom clusters with these characteristics.

3.1 Extensions

3.1.1 Curvilinear interactions of two predictors—The extended ZSC can be applied to curvilinear moderators using the algebraic method of ‘completing the square’ to solve equation (3) for $y \sim x$ when a curvilinear moderator is added (w^2). In this section, I derive the most general case of interactions in which the primary variable is also curvilinear (i.e., both x^2 and w^2 are specified). Later, in Section 3.2.1, I provide an illustration when only the moderator is curvilinear (i.e., only w^2 is specified).

When the interaction between w and x involve curvilinearity in *both* variables, the regression equation may be specified as:

$$y' = a + b_1x + b_2w + b_3x^2 + b_4w^2 + b_5xw + b_6xw^2 + b_7w^2x^2 + b_8x^2w^2 \quad (10)$$

Rearranging the terms, we take the first derivative with respect to x :

$$\partial y' / \partial x = b_1 + b_5w + b_6w^2 + 2b_3x + 2b_7xw + 2b_8xw^2 \quad (11)$$

Setting $d = 2b_3$, $e = 2b_7$, and $f = 2b_8$:

$$\partial y' / \partial x = b_1 + b_5w + b_6w^2 + x(d + ew + fw^2) \quad (12)$$

$$\partial^2 y' / \partial x^2 = d + ew + fw^2 \quad (13)$$

The second derivative ($\partial^2 y' / \partial x^2$), the change in the slope ($\partial y' / \partial x$), is set equal to zero (in which the point of zero slope reflects either a concave minimum or a convex maximum); we solve for w_0 (the moderator value at which the slope of x is zero) using the algebraic method of completing the square.

3.1.2 Linear interactions among three predictors—As equation (4) revealed, the b_1 and b_3 parameters can be used to calculate the discrete (constant) value of w that results in a

zero slope for the relationship between the predictor (x) and the criterion (y). However, in interactions involving three or more variables, this value is no longer discrete but becomes a function of other variable(s), as in equation (16) below. Thus, the ZSC would appear to break down.

In this section, I will present extensions to the ZSC to overcome this limitation. These additional extensions of the ZSC assess the *nature of interactions involving three interacting ordinal or continuous variables*, which may occur alone as a single third-order interaction, or along with statistically significant second-order interaction derivatives. These extensions comply with the hierarchical principle of model fitting by addressing effects from derivative second-order interactions when assessing a third-order interaction, and they depend solely on regression output such as regression parameters and partial correlation coefficients.

In moderated regression analysis, an equation involving a three-way interaction term and all derivative terms, may be specified as:

$$y' = a + b_1x + b_2w + b_3z + b_4xw + b_5xz + b_6wz + b_7xwz \quad (14)$$

Again, the quadratic terms (x^2 , w^2 , z^2) are excluded here because they do not influence the derivation of the ZSC to interpret three-way interactions. It should be noted, however, that statistically significant quadratic terms should also be interpreted because they may intensify or counteract the interaction effect.

The slope of y' with respect to the predictor (x) is the first partial derivative:

$$\partial y' / \partial x = b_1 + b_4w + b_5z + b_7wz = (b_1 + b_5z) + (b_4 + b_7z)w \quad (15)$$

This slope can be assessed separately for each value of z , such that z , and consequently ($b_1 + b_5z$), are held constant. Only w , and $(b_4 + b_7z)w$, are free to vary when z is held constant. For instance, at $z = 1$:

$$\partial y' / \partial x|_{z=1} = (b_1 + b_5) + (b_4 + b_7)w \quad (15a)$$

The first term ($b_1 + b_5$) is a constant, while the second term $(b_4 + b_7)w$ remains free to vary at $z = 1$. If the absolute value of the second term coefficient ($b_4 + b_7$) is low, then $(b_4 + b_7)w$ will approach zero. In this situation, there will be *little or no change* in the slope of y' with respect to the predictor (x) across the range of values for moderator w when $z = 1$. However, if the absolute value of the second term coefficient ($b_4 + b_7$) is moderate to high, then $(b_4 + b_7)w$ will not approach zero: the slope of y' with respect to the predictor (x) *does change* across the range of values for moderator w when $z = 1$.

This process is repeated for each of the remaining ordinal values of z (or across a set of discrete values from a continuous z) and the results across the range of z are compared. Again, if the absolute value of the second term coefficient is moderate to high (comparatively speaking) at any of these remaining z values, the slope of y' with respect to the predictor (x) *does change* across the range of values for moderator w at that z value(s).

A specific value, $w_{0,z}$, is then calculated separately for each z value in which the absolute value of the second term coefficient is moderate to high. Returning to equation (15), if we set slope (y' / x) equal to 0, the value of w that results in a zero slope for the relationship between the predictor (x) and the criterion (y) is:

$$w_{0,z} = (b_1 - b_5z) / (b_4 + b_7z) \quad (16)$$

where $w_{0,z}$ is the moderator value at which the slope of x is zero. Because z remains free to vary, $w_{0,z}$ will be different for each value of z .

3.1.2.1 When $w_{0,z}$ falls within the range of moderator values: We can compare the respective slopes of any two values of moderator w for the three-way model:

$$[(w_{high} - w_{0,z})(b_4 + b_7z)] \sim [(w_{low} - w_{0,z})(b_4 + b_7z)] \quad (17)$$

where w_{high} represents a high moderator value, w_{low} represents a low moderator value, $w_{0,z}$ is the moderator value at which the slope of the predictor (x) is zero at a given value of z , and $\sim$ is an operator that indicates a comparison of two quantities. Formally, $(b_4 + b_7z)$ is the second partial derivative [from equation (15)] of the change in the slope of y' with respect to the predictor (x) that can be attributed to the predictor (w):

$$\partial^2 y' / \partial x \partial w = b_4 + b_7z \quad (18)$$

If we conduct the comparison in equation (17) separately at each value of z (i.e., z is held constant), it can be reduced to one which reveals the relative magnitudes of the two slopes based on a comparison of their absolute values:

$$|w_{high,z} - w_{0,z}| \sim |w_{low,z} - w_{0,z}| \quad (19)$$

where $w_{high,z}$ represents the highest moderator value of w at a given value of z , $w_{low,z}$ represents the lowest moderator value of w at a given value of z , and $w_{0,z}$ represents the moderator value of w at which the slope of the predictor (x) is zero at a given value of z .

First, considering only the set of z values that result in *positive* values for equation (18) [which is also the second term coefficient in equation (15)], we select only those z value(s) in which the absolute value of equation (18) are moderate to high (comparatively speaking). We repeat this process considering only the set of z values that result in *negative* values for equation (18), and again select only those z value(s) in which the absolute value of equation (18) are comparatively moderate to high. Then, for each selected value of z , when $w_{0,z}$ falls between $w_{high,z}$ and $w_{low,z}$ the direction of the slopes will be positive at some values of w (i.e., magnifier effects) and negative at others (i.e., buffering effects). *In comparing the magnifier and buffering effects at $w_{high,z}$ and $w_{low,z}$ the extreme w value (i.e., $w_{high,z}$ or $w_{low,z}$) with the greater unit distance from $w_{0,z}$ is the moderator value with the greater relative slope and thus stronger moderation of the x - y relationship at that particular value of z .* Thus, this procedure is repeated for all of the selected z values that are considered moderate to high in absolute value. The process is very similar to that for the two-way model delineated earlier. An illustration to assess a third-order interaction when $w_{0,z}$ falls within the range of moderator values is provided in Section 3.2.2.

3.1.2.2 When $w_{0,z}$ falls outside the range of moderator values: Of the selected z values that are moderate to high in absolute value, those in which $w_{0,z}$ fall outside the range between $w_{high,z}$ and $w_{low,z}$ reflect slopes for the x - y relationship that are in a consistent direction due to the same form of moderation (i.e., either a magnifier or buffering effect). Recall in the second-order model (Section 2.2.2) that when w_0 , w_{low} or w_0 , w_{high} all of

the slopes for the x - y relationship are in a consistent direction due to the same form of moderation (i.e., either a magnifier or buffering effect).

In the third-order model, the counterpart to equation (8) is:

$$\left| w_{high,z} - w_{0,z} \right| > \left| w_{low,z} - w_{0,z} \right| \quad (20)$$

Figure 1, panels A and B, illustrated previously for the second-order model, are now assessed separately at each z value. The implication of equation (20) is that *due to* $w_{0,z}$ $w_{low,z}$ the absolute magnitude of the slopes will increase across the range of moderator values; these *signify magnifier effects*.

Similarly, in the third-order model, the counterpart to equation (9) is:

$$\left| w_{high,z} - w_{0,z} \right| < \left| w_{low,z} - w_{0,z} \right| \quad (21)$$

Figure 1, panels C and D, illustrated previously for the second-order model, are now assessed separately at each z value. The import of equation (21) is that *due to* $w_{0,z}$ $w_{high,z}$ the absolute magnitude of the slopes will decrease across the range of moderator values; these *signify buffering effects*.

Note that w_{high} , w_{low} and w_0 in equations (8) and (9) from Section 2.2 are replaced, respectively, by $w_{high,z}$, $w_{low,z}$ and $w_{0,z}$ in equations (20) and (21). In contrast to the second-order model in which there is only one value of w at which the slope of the predictor (x) is zero (i.e., w_0), the moderator value of w at which the slope of the predictor (x) is zero will differ for each particular value of z considered; thus, $w_{0,z}$, $w_{low,z}$ or $w_{high,z}$. It follows that consistent directional form across the range of moderator values for w may occur within certain (but not necessarily all) values of z . Moreover, consistent direction at one value of z (e.g., magnifier effects) may differ from the consistent direction at another value of z (e.g., buffering effects).

Therefore, a measure of moderation is needed for cross-comparisons, both among particular z values with moderator effects in the same consistent direction (e.g., z values with consistent magnifier effects), and between pairs of particular z values in which moderator effects are internally consistent, yet in different directions from each other (e.g., a pair of z values in which one is a magnifier effect, the other a buffering effect). A measure appropriate for these cross-comparisons was illustrated earlier in the discussion about the absolute value of the second term coefficient from equation (15a) evaluated at $z = 1$. Formally, this measure is the absolute value of equation (18) *calculated separately for each z value* [i.e., the absolute value of $(\partial^2 y / \partial x \partial w)_{z=1 \dots 5}$]. After these separate calculations, *the magnifier and buffering effects of w across these values of z can be compared to determine which values of z correspond to the stronger co-moderator effects*. An illustration of the extended ZSC to assess a third-order interaction in the context of one statistically significant two-way derivative interaction, when $w_{0,z}$ falls outside the range of moderator values, is provided in Section 3.2.3.

3.1.2.3 Assessing the strength of buffering and magnifier effects: In this section, I will simply introduce an extension to the original ZSC to allow for a measure of the *strength* of the buffering and magnifier relationships in a three-way interaction. In order to simplify the

presentation, the extension will not be derived here but within the context of a symptom cluster illustration in Section 3.2.4.

Let us return to equations (17) and (18), the initial equations in Section 3.1.2.1 (when $w_{0,z}$ falls *within* the range of moderator values):

$$\left[(w_{high} - w_{0,z})(b_4 + b_7z) \right] \sim \left[(w_{low} - w_{0,z})(b_4 + b_7z) \right] \quad (17)$$

$$\partial^2 y' / \partial x \partial w = b_4 + b_7z \quad (18)$$

As in equation (17), our initial focus will be on the co-moderator w . As in our earlier assessment of the *nature* of the moderator relationship, we will assess the *strength* of the relationship that can be attributed to *buffering* effects by w separate from the strength of the relationship that can be attributed to *magnifier* effects by w .

Equation (18) reveals that $(b_4 + b_7z)$ is the second partial derivative of the change in the slope of y' with respect to the predictor (x) that can be attributed to the predictor (w). We can replace $(b_4 + b_7z)$ in equation (17) with the partial correlation coefficient of the symptom interaction (xwz) and y' (i.e., with $pr_{y,xwz}$) that can be apportioned at each w ordinal category from w_{low} to w_{high} (or across a set of continuous w values), *across* the range of z values that reflect buffering versus magnifier effects. Thus, our new version of equation (17) can be changed from a comparison of quantity *portions* to a comparison of quantity *proportions* that reveal the strength of the buffering and/or magnifier influences by each co-moderator (w, z).

3.2 Symptom cluster applications

3.2.1 Curvilinear interaction of two predictors—In Section 3.1, both components of the interaction term were curvilinear (w^2 and x^2). A similar, yet simpler, derivation results when only one of the components of the interaction term (w^2) is curvilinear. We illustrate the method of completing the square when pronounced fever (Fever² represented by w^2) moderates the relationship between Pain (x) and Depressive affect (y). Applying the respective regression parameters from Table 1, regression 1 into the first three parameter terms in equation (11):

$$\begin{aligned} \partial y' / \partial x &= -0.484 - 3.616w + 1.009w^2 \\ w_{high} &= 4, w_{low} = 0 \end{aligned} \quad (11)$$

Setting equal to zero and solving for w_0 by completing the square:

$$\begin{aligned} 0.484 &= 1.009w_0^2 - 3.616w_0 \\ 3.6906 &= (w_0 - 1.7919)^2 \\ w_0 &= -0.129; w_0 = 3.713 \end{aligned}$$

Choose $w_0 = 3.713$ since it falls inside the range of ordinal values (0 to 4):

$$\begin{array}{l} \left| 4 - 3.713 \right| \sim \left| 0 - 3.713 \right| \\ 0.287 \sim 3.713 \\ 0, 1, 2, 3 < 3.713 < 4 \end{array} \quad (7)$$

$$\begin{array}{l} \text{Since } \partial y' / \partial x |_{w=0,1,2,3} < 0, \text{ buffering at } w=0, 1, 2, 3 \\ \text{Since } \partial y' / \partial x |_{w \text{ high}=4} > 0, \text{ magnifier effects at } w=4 \\ \text{At } \partial y' / \partial x |_{w \text{ low}=0} = -0.484; \text{ At } \partial y' / \partial x |_{w \text{ high}=4} = 1.196 \\ \left| 1.196 \right| > \left| -0.484 \right| \end{array} \quad (3)$$

Thus, *magnifier* effects at $w_{\text{high}} = 4$ are *much stronger* than *buffering* effects at $w = 0, 1, 2, 3$. ‘Uncontrolled’ Fever (at $w_{\text{high}} = 4$) *magnifies* the Pain-Depressive affect relationship, while ‘complete’ (at $w = 0$) to ‘a little’ (at $w = 3$) Fever *buffers* the relationship (controlling for Sleep^x Fever² and its derivative term).

Similar applications are illustrated in Table 3, which applies the method of completing the square to interpret how pronounced fever (Fever²) moderates the relationships of Sleep and Nausea-vomiting to Depressive affect. (The parameters are from Table 1, regressions 1 and 2).

3.2.2 Interaction among three predictors: magnifier effects of Sleep problems when Appetite problems are uncontrolled—The third-order interaction (Breathing difficulty^x Sleep problems^x Appetite problems) from Table 1, regression 4 is first assessed *within* the context of uncontrolled (high) Appetite problems ($z_{\text{high}} = 4$), in which the Sleep problems value, $w_{0,z}$, falls within the range of moderator values. Applying the respective regression parameters into (15):

$$\begin{array}{l} \partial y' / \partial x = (-0.894 - 0.023z) + (-0.568 + 0.230z)w \\ w_{\text{high}}=4, w_{\text{low}}=0 \end{array} \quad (15)$$

$$\partial^2 y' / \partial x \partial w = -0.568 + 0.230z \quad (18)$$

Select z where $|-0.568 + 0.230z|$ are highest in absolute value ($z_{\text{high}} = 4, z_{\text{low}} = 0$):

$$\begin{array}{l} w_{0,z} = (0.894 + 0.023z) / (-0.568 + 0.230z) \\ z_{\text{high}}=4: w_{0,z}=4 = 0.986 / 0.352 = 2.80 \end{array} \quad (16)$$

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

$$\begin{array}{l} \left| 4 - 2.80 \right| \sim \left| 0 - 2.80 \right| \\ 1.20 \sim 2.80 \\ 0, 1, 2 < 2.80 < 3, 4 \end{array} \quad (19)$$

$$\partial y' / \partial x |_{w \text{ low}=0, z \text{ high}=4} = [-0.894 - 0.023(4)] + [-0.568 + 0.230(4)]0 = -0.986 < 0. \quad (15)$$

Thus, buffering effects at $w_{low} = 0, 1, 2$.

Since $\gamma^1 x |_{w=3,4} > 0$, magnifier effects at $w = 3, 4$.

$$\text{At } \gamma^1 x |_{w_{high}=4, z_{high}=4} = [-0.894 - 0.023(4)] + [-0.568 + 0.230(4)]4 = 0.422$$

$$|0.422| < |-0.986|$$

Thus, when there is *no control* of Appetite problems ($z_{high} = 4$), *complete control* of Sleep problems ($w_{low} = 0$) *buffers* the Breathing difficulty-Depressive affect relationship and *no control* of Sleep problems ($w_{high} = 4$) *magnifies* the relationship. The *buffering* effect is *marginally stronger* than the *magnifier* effect. Table 4 provides a more detailed analysis.

3.2.3 Interaction among three predictors: magnifier effects of Sleep problems when Appetite problems are completely controlled—We return to the three-way interaction (Breathing difficulty^x Sleep problems^x Appetite problems) from Table 1, regression 4 that is assessed within Table 4. In the last illustration, we examined the context of high Appetite problems ($z_{low} = 4$). I now illustrate the context of completely controlled (low) Appetite problems ($z_{low} = 0$). Applying the respective regression parameters into (16):

$$w_{0,z} = (0.894 + 0.023z) / (-0.568 + 0.230z)$$

$$z_{low}=0: w_{0,z=0} = 0.894 / -0.568 = -1.57 \quad (16)$$

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

$$\left| \begin{array}{l} 4 - (-1.57) \\ 5.57 \end{array} \right| > \left| \begin{array}{l} 0 - (-1.57) \\ 1.57 \end{array} \right| \quad (20)$$

Thus, when there is *complete control* of Appetite problems ($z_{low} = 0$), the Breathing difficulty-Depressive affect relationship is *magnified* across the full range of Sleep problems (w_{low} to w_{high}).

In this context, the Sleep problems value $w_{0,z=0}$ falls *outside and below* the range of w moderator values. This finding leads to the interpretation that when there is *complete control* over Appetite problems ($z_{low} = 0$), *the full range of Sleep problems* (w_{low} to w_{high}) *magnifies* the Breathing difficulty-Depressive affect relationship. Note that this context of complete control of Appetite problems ($z_{low} = 0$) occurs when the third-order interaction equals zero, cancels out, and therefore *defaults to the situation of evaluating the only derivative second-order interaction from this regression that is also statistically significant* (i.e., Breathing difficulty^x Sleep problems). That is, $w_{0,z=0}$ from the third-order regression is equivalent to w_0 that would result if a second-order regression was estimated instead. As in the prior illustration of completely uncontrolled (high) Appetite problems, a more detailed analysis is provided in Table 4.

On the other hand, unlike regression 4 from Table 1 (probed in Table 4), the presence of a third-order interaction in the context of *multiple* significant two-way interactions in regression 5 from Table 1 does not default to a situation of evaluating a *single* derivative interaction. This situation can benefit from the approach introduced in Section 3.1.2.3 to assess the strength of buffering and magnifier effects, which will be developed next.

3.2.4 Interaction among three predictors: strength of buffering and magnifier effects from Fatigue-weakness (option 1) and Sleep problems (option 2)—

The first panel of Table 5 (i.e., option 1) evaluates *ranges* of the co-moderator Fatigue-weakness at *distinct values* of the other co-moderator (Sleep problems). $w_{0,z}$ is calculated for each value of z (in the far-left column) and is used to estimate the proportionate partial correlations (*ppr* values) that can be apportioned to buffering and magnifier effects by Fatigue-weakness (w ; in the far-right column). In the second column, the inflection point at which $w_{0,z} = 0$ distinguishes the range of buffering (where w_0 is negative) from the range of magnifier effects (where w_0 is positive). Buffering occurs at certain distinct values ($z = 2$ to $z_{high} = 4$) and magnifier effects at others ($z_{low} = 0$ to $z = 1$). Thus, we can express the *ppr* of the interaction (xwz) to y that can be attributed to buffering versus magnifier effects from w , in order to identify ranges of co-moderator values at which buffering and magnifier effects are strongest.

At $w_{high} = 4$, for instance, the *ppr* values calculated in the far-right column of the first panel in Table 5 correspond to the following comparison:

$$\left[\frac{w_{high=4} - [(a_2 w_{0,z=2} + a_3 w_{0,z=3} + a_4 w_{0,z=4}) / (a_2 + a_3 + a_4)]}{(\# z \text{ values})} \right] pr_{y,xwz} \sim \left[\frac{w_{high=4} - [(a_0 w_{0,z=0} + a_1 w_{0,z=1}) / (a_0 + a_1)]}{(\# z \text{ values})} \right] pr_{y,xwz}, \quad (22)$$

where $pr_{y,xwz}$ is the partial correlation of the interaction (xwz) and y , and a_z represents the number of observations in the respective z category in which $w_{high} = 4$. [The different ranges of discrete a_z on the left versus right sides of the comparison ($\sim$) are used to create a weighted average of values for w_0 for each of these ranges.]

In the far right column of Table 5, the *ppr* for each z range is calculated by replacing these variables with the actual values estimated in the table. Thus, the buffering effect by $w_{high} = 4$ from $z = 2$ to $z_{high} = 4$ is:

$$\left[\frac{4 - [(1 * (12.70) + 4 * (6.40) + 25 * 4.81) / 30] / 3}{0.178} = 0.076 \right]$$

(Note here that 25 observations occur at $z_{high} = 4$, while only four observations occur at $z = 3$ and one observation occurs at $z = 2$, such that the buffering effect of 0.076 is strongly weighted, and therefore valid, at the extreme of $z_{high} = 4$, in the same way that two-way models were shown earlier to be valid at the extreme).

The magnifier effect by $w_{high} = 4$ from $z_{low} = 0$ to $z = 1$ is:

$$\left[\frac{4 - [(23 * (-3.29) + 1 * (-20.19)) / 24] / 2}{0.178} = 0.711 \right]$$

(Similarly, note that 23 observations occur at $z_{low} = 0$ and only one observation occurs at $z = 1$, such that the magnifier effect of 0.711 is strongly weighted at the extreme of $z_{low} = 0$).

Comparing both quantities, $0.076 \sim 0.711$, the magnifier effect by $w_{high} = 4$ from $z_{low} = 0$ to $z = 1$ is *stronger* than the buffering effect by $w_{high} = 4$ from $z = 2$ to $z_{high} = 4$.

A similar comparison corresponds to the *ppr* values at $w_{low} = 0$ in the far-right column of the first panel in Table 5. Thus, the buffering effect by $w_{low} = 0$ from $z = 2$ to $z_{high} = 4$ is:

$$\left[\frac{0 - [(2 * (12.70) + 4 * (6.40) + 8 * 4.81) / 14] / 3}{0.178} = 0.379 \right]$$

The magnifier effect by $w_{low} = 0$ from $z_{low} = 0$ to $z = 1$ is:

$$[|0 - [57 * (-3.29) + 6 * (-20.19)]| / 63] / 2 * 0.178 = 0.436$$

(The magnifier effect here is strongly weighted at $z_{low} = 0$).

Comparing both quantities, $0.379 \sim 0.437$, the buffering effect by $w_{high} = 4$ from $z = 2$ to $z_{high} = 4$ and the magnifier effect by $w_{high} = 4$ from $z_{low} = 0$ to $z = 1$ are *similar* in strength.

Finally, we cross-compare these four *ppr* findings to distinguish buffering from magnifier ranges:

1. When $z = 2$, $z = 3$, or $z_{high} = 4$ (*no control over Sleep problems*), Fatigue-weakness (w) *buffers* the Breathing difficulty-Depressive affect relationship, with *ppr falling* from 0.379 at $w_{low} = 0$ to 0.076 at $w_{high} = 4$.
2. When $z_{low} = 0$ (*complete control over Sleep problems*), or when $z = 1$, Fatigue-weakness (w) *magnifies* the Breathing difficulty-Depressive affect relationship, with *ppr increasing* from 0.436 at $w_{low} = 0$ to 0.711 at $w_{high} = 4$.

The similar changes in both sets of ppr reveal that the buffering and magnifier effects are comparable in strength [i.e., $(0.379 - 0.076) \sim (0.711 - 0.436)$; $0.303 \sim 0.275$].

This entire process is also repeated in the second panel (i.e., option 2) of Table 5 to assess buffering and magnifier effects *by Sleep problems (z) across the relevant ranges of discrete w values (i.e., Fatigue-weakness is held constant)*. Compared to the first panel, the inflection point in the second panel distinguishes different ranges for buffering versus magnifier effects, which requires a modified version of equation (22).

Comparing the changes in *ppr* for all four interpretations across *both* panels of Table 5 reveals *comparable* buffering effects by both co-moderators, while magnifier effects are *stronger* by Sleep Problems than Fatigue-weakness. It is important to recognise that this type of comparison regarding the relative influence of each co-moderator within an interaction is not readily facilitated by viewing ‘snapshot’ two-dimensional *post-hoc* plots in which w moderates the x - y relationship *at specific levels of z*.

4 Conclusions

The use and interpretation of moderated regression is an important approach to model behaviours as multiple interdependencies that take place within a system. *There is considerable scope for applying moderated regression and the extended ZSC beyond biopsychological systems such as symptom clusters to other social systems in which ordinal or continuous variables are likely to interact.* For instance, in the inaugural issue of this journal, Tang and Shum (2008) reassessed international risk-return relationships during up and down markets; their multiple regression models of panel data could be expanded for more finely grained analyses by specifying linear and curvilinear interactions among interrelated predictors (such as across each market’s systematic, unsystematic, and total risks, or between each market’s standardised skewness and kurtosis coefficients). The extended ZSC provides analysts, evaluators, and clinicians with a new approach for predictive cluster analysis and a new method to identify at-risk subgroups that may need targeted intervention or tailored treatment.

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Biography

Richard B. Francoeur, PhD, is an Associate Professor at the Adelphi University School of Social Work and a Research Affiliate at the Center for the Psychosocial Study of Health and Illness, Columbia University. A Medical Social Worker at the VA Pittsburgh Healthcare System for over seven years, he worked with older adults who were experiencing co-occurring medical conditions, multiple physical symptoms, and at times, depression. His innovative research and grantsmanship involve studying interactions of socioeconomic and biopsychosocial factors, such as physical symptoms and depression, to identify patient subgroups that may be at risk of forgoing needed healthcare, including palliative care to relieve symptoms.

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Appendix

1. Unlike the *overall* partial correlation for the third-order interaction term (*pr*), the *ppr* at each discrete *z* is not constrained to be 1. To constrain the *ppr* at each discrete *z* to be 1, the weighted average must be based on *all* participants across all *z* who fall within each $z_{0,w}$ category, and not only those participants at that particular discrete *z* who fall within the $z_{0,w}$ category, for instance, in Table 5 option 2:

Buffering effect by $z_{high} = 4$ from $w = 3$ to $w_{high} = 4$:

$$[4 - [(23 * (9.59) + 54 * (5.16)) / 77] / 2] * 0.178 = 0.221$$

Buffering effect by $z_{low} = 0$ from $w = 3$ to $w_{high} = 4$:

$$[0 - [(23 * (9.59) + 54 * (5.16)) / 77] / 2] * 0.178 = 0.577$$

Magnifier effect by $z_{high} = 4$ from $w_{low} = 0$ to $w = 2$:

$$[4 - [(77 * (-2.04) + 79 * (-5.01) + 35 * (-52.79)) / 191] / 3] * 0.178 = 0.983$$

Magnifier effect by $z_{low} = 0$ from $w_{low} = 0$ to $w = 2$:

$$[0 - [(77 * (-2.04) + 79 * (-5.01) + 35 * (-52.79)) / 191] / 3] * 0.178 = 0.076$$

Figure 1.

Changes in slope between outcome (y) and predictor (x) across the range of a moderator (w)

Notes: w_{high} is the highest moderator value; w_{low} is the lowest value; and w_0 is the value at which the slope between the y -outcome and x -predictor is 0.

Table 1

Depressive affect predicted by physical symptoms and symptom interactions: moderator regressions ^{a, b}

Independent Variables ^{c, d}	1 ^e	2	3	4	5
Pain	-.484 (.464)	.612 (.229) **	.463 (.324)	.350 (.345)	.370 (.340)
Breath	-.133 (.243)	-.236 (.248)	-.085 (.232)	-.894 (.619)	-1.084 (.599)
Sleep	.814 (.460)	.246 (.410)	.504 (.188) **	.061 (.386)	.078 (.356)
Nausea	.787 (.229) ***	-.592 (.580)	.489 (.217) *		.000 (.543)
Fever	-1.368 (1.641)	1.196 (1.748)	-.139 (.339)	.765 (2.277)	.491 (1.395)
Appetite				1.425 (.718) *	
Weight loss				-1.189 (.812)	
Fatigue	.224 (.232)	.367 (.229)	.241 (.253)	.038 (.284)	.107 (.261)
Pain ²	.153 (.187)		.187 (.182)	.082 (.190)	.046 (.189)
Breath ²				.501 (.247) *	.518 (.247) *
Sleep ²	.294 (.223)	.317 (.220)		.301 (.229)	.376 (.224)
Nausea ²		.401 (.231)			.282 (.232)
Fever ²	.437 (.518)	-.292 (.532)		-.213 (.435)	-.239 (.423)
Appetite ²				-.306 (.213)	
Weight loss ²				.397 (.234)	
Fatigue ²			.226 (.173)	.126 (.189)	.259 (.183)
Pain ^x Sleep					
Pain ^x Fever	-3.616 (1.301) **				
Pain ^x Fatigue			-.310 (.126) *		
Fever ^x Sleep	2.663 (1.092) *	.652 (.873)			
Nausea ^x Fever		-2.161 (.860) *			
Breath ^x Sleep				-.568 (.222) *	-.531 (.166) ***
Breath ^x Appetite				-.023 (.212)	
Breath ^x Weight loss				-.188 (.197)	
Breath ^x Fatigue					-.329 (.163) *

Independent Variables <i>c, d</i>	<i>1^e</i>	<i>2</i>	<i>3</i>	<i>4</i>	<i>5</i>
Sleep ^x Appetite				.169 (.134)	
Sleep ^x Weight loss				-.106 (.123)	
Sleep ^x Fatigue					-.209 (.122)
Nausea ^x Fatigue					
Pain ^x Fever ²	1.009 (.378) **				
Sleep ^x Fever ²	-.846 (.323) **	-.278 (.262)			
Nausea ^x Fever ²		.579 (.251) *			
Breath ^x Sleep ^x Appetite				.230 (.106) *	
Breath ^x Sleep ^x Weight loss				-.131 (.097)	
Breath ^x Sleep ^x Fatigue					.249 (.087) ***

Notes: n = 268,
* p < 0.05,
** p < 0.01,
*** p < 0.005 and
**** p < 0.001 (z-tests are two-tailed).

Although italicised in Table 1 and throughout the body of the article, the *b* coefficients represent unstandardised coefficients and should not be mistaken for standardised or beta coefficients.

^aThe secondary data are from a comprehensive 1992–1993 National Cancer Institute study of factors influencing home care and involve a sample of 268 with recurrent cancer who were initiating outpatient palliative radiation to reduce bone pain. Five hospitals from a northeastern US city referred patients, and about half participated. Eligible participants were at least age 30, neither receiving curative care nor deemed terminally ill, and had a prognosis of a year or more. Each outpatient was interviewed at home, and the healthcare team and medical record were consulted for additional medical information.

^bDepressive affect is an index of eight self-reported items of negative affect and three items of positive affect from the Center for Epidemiologic Studies-Depression (CES-D) scale. The items reflect frequency over the past week on a four-category scale. The degree of difficulty in controlling each physical symptom over the past month is self-reported on a Likert scale (none a little, some, a lot, complete). All first-order components are centred. Note: *Breath* refers to the variable ‘Breathing difficulty-shortness of breath.’ *Nausea* refers to ‘Nausea-vomiting.’ *Fatigue* refers to ‘Fatigue-weakness.’ *Sleep* refers to ‘Sleep problems.’ *Appetite* refers to ‘Appetite problems.’ Variance inflation factors were examined to assess whether multicollinearity across predictors was problematic; influential multivariate outliers were screened using Cook’s D statistic.

^cInitially, all possible three-way interactions were created; each three-way interaction was specified and tested in a *separate descriptive* regression, along with all derivative two-way interactions and quadratic and first-order terms. In regressions with statistically significant second- or third-order interactions, additional symptoms and their quadratic effects were then specified that might overlap these interactions, either confounding or suppressing them; the original interactions remained statistically significant. Thus, the interactions are robust and do not reflect an over-fitted model. Further, optimal internal validity for estimates of interaction effects result from simultaneous specification of potentially overlapping quadratic terms, as well as other common symptoms and symptom interactions that overlap with symptoms contributing to the interaction.

^d All first-order predictors are centred about their respective means (i.e., the mean is subtracted from the predictor value). Each interaction is interpreted along the point of the regression surface when all remaining variables that are not components of the interaction (i.e., control and secondary variables) are considered at their mean values. When considered at their respective means, all terms involving the remaining (centred) variables equal zero, leaving only the interaction and its derivatives (i.e., any lower-order terms and first-order variables) for *post-hoc* assessment (Aiken and West, 1991) using the ZSC. All of the symptom variables are positively skewed.

^e In regression 1, although the three-way interaction Pain^x Fever^x Sleep was not statistically significant, two derivative interactions (Pain^x Fever and Fever^x Sleep) remain statistically significant *only* when both are specified. This finding suggest that these interactions are 'suppressor effects' involving many of the same participants.

¹ Tests interaction effects between Pain and Fever²; $R^2 = 0.200$, $F = 4.872$ ($p < 0.001$).

² Tests interaction effects between Nausea and Fever², controlling for interaction effects between Sleep and Fever²; $R^2 = 0.202$, $F = 4.935$ ($p < 0.001$).

³ Tests interaction effects between Pain and Fatigue; $R^2 = 0.188$, $F = 6.584$ ($p < 0.001$).

⁴ Tests interaction effects between Breath, Sleep, and Appetite, and between Breath, Sleep, and Weight Loss; $R^2 = 0.239$, $F = 3.661$ ($p < 0.001$).

⁵ Tests interaction effects between Breath, Fatigue, and Sleep; $R^2 = 0.243$, $F = 5.003$ ($p < 0.001$).

Table 2

Linear moderator effects when two physical symptoms interact

Moderator variable and symptom interaction term from Table 1, regression 3	Nature and relative strength of moderator effects	
	Application of text equations	Interpretation
Fatigue-weakness (w) as moderator of Pain (x) and Depressive affect (y) relationship	(3) $y' = 0.463 - 0.310w$ $w_{\text{high}} = 4, w_{\text{low}} = 0$ (4) $w_0 = -0.463 / -0.310 = 1.49$ (7) $4 - 1.49 \sim 0 - 1.49$ $2.51 \sim 1.49$	
Pain ^x Fatigue-weakness	0, 1 < 1.49 < 2, 3, 4 (3) Since $y' = 0.463 - 0.310w$, $w = 0, 1 > 0$, <i>magnifier</i> effects at $w_{\text{low}} = 0$ and $w = 1$. Since $y' = 0.463 - 0.310w$, $w = 2, 3, 4 < 0$, <i>buffering</i> at $w = 2, 3, 4$. At $y' = 0.463$ at $w_{\text{low}} = 0$ At $y' = -0.777$ at $w_{\text{high}} = 4$ $-0.777 > 0.463$	<i>Buffering</i> effects across the range of $w = 2, 3, 4$ are stronger than <i>magnifier</i> effects at $w = 0, 1$.

Table 3

Curvilinear moderator effects when two physical symptoms interact

Moderator variables and symptom interaction terms from Table 1, regression 1	Nature and relative strength of moderator effects		Moderator variables and symptom interaction terms from Table 1, regression 2	Nature and relative strength of moderator effects	
	Application of test equations	Interpretation		Application of test equations	Interpretation
Fever (w) and Fever ² (w ²) as linear and curvilinear moderators of the Sleep problems (s) and Depressive affect (y) relationship	(1) $\partial y / \partial x = 0.814 + 2.663w - 0.846w^2$ $w_{high} = 4, w_{low} = 0$ Solving for w_0 by completing the square: $-0.814 = -0.846w_0^2 + 2.663w_0$ $3.4394 = (w_0 - 1.5739)^2$ $w_0 = -0.281; w_0 = 3.429$ Choose $w_0 = 3.429$ since it falls inside the range of values.	'Uncontrolled' Fever buffers the Sleep problems-Depressive Affect relationship, while 'Complete' to 'A little' control of fever magnify the relationship (controlling for Pain ² Fever ² and its derivative term).	Fever (w) and Fever ² (w ²) as linear and curvilinear moderators of Nausea-vomiting (x) and Depressive Affect (y) Relationship	(1) $\partial y / \partial x = -0.592 - 2.161w + 0.579w^2$ $w_{high} = 4, w_{low} = 0$ Solving for w_0 by completing the square: $0.592 = 0.579w_0^2 - 2.161w_0$ $4.5049 = (w_0 - 1.8661)^2$ $w_0 = -0.256; w_0 = 3.989$ Choose $w_0 = 3.989$ since it falls inside the range of values.	'Complete' to 'A little' control of Fever buffers the Nausea-vomiting-Depressive Affect relationship, but 'Uncontrolled' Fever does not moderate it
Sleep problems ² Fever and	(7) $ 4 - 3.429 \sim 0 - 3.429 $ $0.571 < 3.429$	Pain ² Fever ² and its derivative term).	Nausea-vomiting ² Fever	(7) $ 4 - 3.989 \sim 0 - 3.989 $ $0.011 < 3.989$	(controlling for Sleep problems ² Fever ²
Sleep problems ² Fever ²	$0, 1, 2, 3 < 3.429 < 4$ (3) Since $\partial y / \partial x _{w=0,1,2,3} > 0$, magnifier effects at $w = 0, 1, 2, 3$ Since $\partial y / \partial x _{w=high=4} < 0$, buffering at $w = 4$ At $\partial y / \partial x _{w=low=0} = 0.814$ At $\partial y / \partial x _{w=high=4} = -2.070$ $ -2.070 > 0.814 $	Buffering effects at $w_{high} = 4$ are much stronger than magnifier effects at $w = 0, 1, 2, 3$.	Nausea-vomiting ² Fever ²	(3) Since $\partial y / \partial x _{w=0,1,2,3} < 0$, buffering at $w = 0, 1, 2, 3$ Since $\partial y / \partial x _{w=high=4} \approx 0$, no moderator effect at $w = 4$ At $\partial y / \partial x _{w=low=0} = -0.592$ At $\partial y / \partial x _{w=high=4} = 0.028$ $ -0.592 > 0.028 $	and its derivative). Buffering across $w = 0, 1, 2, 3$ are much stronger than no moderator effect at $w_{high}=4$

Co-moderator effects when a third-order interaction and a *single* second-order derivative interaction are statistically significant

Table 4

Sleep problems co-moderator	Nature of co-moderator effects (two columns)	Interpretation
Third-order co-moderators and interaction term from regression 3:	(15) $y' \mid x = (-0.894 - 0.023z) + (-0.568 + 0.230z)w$ $w_{high} = 4, w_{low} = 0$ (18) $^2y' \mid x \mid w = -0.568 + 0.230z$ Select z where $[-0.568 + 0.230z]$ are highest in absolute value: $z_{high} = 4, z_{low} = 0$	<u>No control of Appetite problems ($z_{high} = 4$):</u> (19) $ 4 - 2.80 \sim 0 - 2.80 $ $1.20 \sim 2.80$ $0, 1, 2 < 2.80 < 3, 4$ $y' \mid x \mid w_{low} = 0, z_{high} = 4 = [-0.894 - 0.023(4)] + [-0.568 + 0.230(4)]0 = -0.986 < 0$ Thus, buffering effects at $w_{low} = 0$, and $w = 1, 2$. $y' \mid x \mid w_{high} = 4, z_{high} = 4 = [-0.894 - 0.023(4)] + [-0.568 + 0.230(4)]4 = 0.422 > 0$ Thus, magnifier effects at $w = 3$ and $w_{high} = 4$. $ 0.422 < -0.986 $ <u>A little control of Appetite problems ($z = 3$):</u> Again, $w_{0,z=3}$ value is outside the actual range of w values (0–4) (21) $ 4 - (7.89) < 0 - (7.89) $ $ -3.89 < -7.89 $ <u>Complete – some control of Appetite problems</u> $(z_{low} = 0, z = 1, z = 2)$: Again, $w_{0,z=0}$ through $w_{0,z=2}$ values are outside the actual range of w values (0–4) (20) $ 4 - (-1.57) > 0 - (-1.57) $ $ 5.57 > 1.57 $ $ 4 - (-2.71) > 0 - (-2.71) $ $ 6.71 > 2.71 $ $ 4 - (-8.70) > 0 - (-8.70) $ $ 12.70 > 8.70 $
Sleep problems (w) and Appetite problems (z) as co-moderators of the Breathing difficulty (x) and Depressive affect (y) relationship	$z_{high} = 4; w_{0,z=4} = 0.986 / 0.352 = 2.80$ $z = 3; w_{0,z=3} = 0.963 / 0.122 = 7.89$ Zero inflection point: $w_{0,z<z<3} = 0$ $z = 2; w_{0,z=2} = 0.940 / -0.108 = -8.70$ $z = 1; w_{0,z=1} = 0.917 / -0.338 = -2.71$ $z_{low} = 0; w_{0,z=0} = 0.894 / -0.568 = -1.57$	When there is <i>a little control</i> of Appetite problems ($z = 3$), the Breathing difficulty-Depressive affect relationship is <i>buffered</i> across the full range of Sleep problems (w_{low} to w_{high}).
Breathing difficulty ^x Sleep problems ^x Appetite problems	Thus, $w_{0,z=0}$ through $w_{0,z=3}$ values are outside the actual range of w values (0–4)	When there is <i>complete to some control</i> of Appetite problems ($z_{low} = 0, z = 1, z = 2$), the Breathing difficulty-Depressive affect relationship is <i>magnified</i> across the full range of Sleep problems (w_{low} to w_{high}).

Options for assessing co-moderator effects when a third-order interaction and two second-order derivative interactions are statistically significant

Table 5

<i>Fatigue-weakness co-moderator: option 1</i>	<i>Nature of Fatigue-weakness co-moderator effects (two columns)</i>	<i>Strength of Fatigue-weakness co-moderator and interpretation</i>
<i>Third-order co-moderators and interaction term from regression 2:</i>	(15) $\partial^3 y / \partial x = (-1.084 - 0.531z) + (-0.329 + 0.249z)w$ $w_{high} = 4, w_{low} = 0$	<i>High Sleep problems ($z_{high} = 4, z = 3, 2$)</i> $ w_{high} - w_{low} \sim w_{low} - w_{low} $ (21) $z_{high} = 4: 4 - 4.81 < 0 - 4.81 $ $0.81 < 4.81$ $z = 3: 4 - 6.40 < 0 - 6.40 $ $2.40 < 6.40$ $z = 2: 4 - 12.70 < 0 - 12.70 $ $8.70 < 12.70$ (w) buffering effect at $z = 2, z = 3$, and $z_{high} = 4$
Fatigue-weakness (w) and Sleep problems (z) as co-moderators of the Breathing difficulty (x) and Depressive affect (y) relationship	(18) $\partial^2 y / \partial x \partial w = -0.329 + 0.249z$ Select z where $ -0.329 + 0.249z $ are highest in absolute value: $z_{high} = 4, z_{low} = 0$	<i>Fatigue-weakness (w) co-moderator proportionate partial correlations (ppr)</i> Buffering effect by $w_{high} = 4$ from $z = 2$ to $z_{high} = 4$: (22) $[4 - [1 * (12.70) + 4 * (6.40) + 25 * 4.81]] / 30 / 3 = 0.178 = 0.076$ Buffering effect by $w_{low} = 0$ from $z = 2$ to $z_{high} = 4$: $[0 - [2 * (12.70) + 4 * (6.40) + 8 * 4.81]] / 14 / 3 = 0.178 = 0.379$ Magnifier effect by $w_{high} = 4$ from $z_{low} = 0$ to $z = 1$: (22) $[4 - [23 * (-3.29) + 1 * (-20.19)]] / 24 / 2 = 0.178 = 0.711$ Magnifier effect by $w_{low} = 0$ from $z_{low} = 0$ to $z = 1$: (22) $[0 - [57 * (-3.29) + 6 * (-20.19)]] / 63 / 2 = 0.178 = 0.436$
(Breathing difficulty ^x Fatigue-weakness ^x Sleep problems)	(16) $w_{0,z} = (1.084 + 0.531z) / (-0.329 + 0.249z)$ $z_{high} = 4: w_{0,z=4} = 3.208 / 0.667 = 4.81$ $z = 3: w_{0,z=3} = 2.677 / 0.418 = 6.40$ $z = 2: w_{0,z=2} = 2.146 / 0.169 = 12.70$ Zero inflection point: $w_{0,z>w>1} = 0$ $z = 1: w_{0,z=1} = 1.615 / -0.080 = -20.19$ $z_{low} = 0: w_{0,z=0} = 1.084 / -0.329 = -3.29$ Thus, $w_{0,z=4}$ and $w_{0,z=0}$ values are <i>outside</i> the actual range w values (0–4)	<i>Interpretation</i> 1 When $z = 2, z = 3$, or $z_{high} = 4$ (no control over Sleep problems), Fatigue-weakness (w) buffers the Breathing difficulty-Depressive affect relationship, with <i>ppr falling</i> from 0.379 at $w_{low} = 0$ to 0.076 at $w_{high} = 4$. 2 When $z_{low} = 0$ (complete control over Sleep problems), or when $z = 1$, Fatigue-weakness (w) magnifies the Breathing difficulty-Depressive affect relationship, with <i>ppr increasing</i> from 0.436 at $w_{low} = 0$ to 0.711 at $w_{high} = 4$.

Note: ¹For the second panel only of Table 5, see (1) in the Appendix.

Sleep problems (z)		Strength of Sleep problems co-moderator and interpretation	
co-moderator: option 2		Nature of Sleep problems co-moderator effects (two columns)	
Third-order co-moderators and interaction term from regression 2:		High Fatigue-weakness ($w_{high} = 4, w = 3$)	
(15) $\partial^2 y / \partial x^2 = (-1.084 - 0.329w) + (-0.531 + 0.249w)z$ $z_{high} = 4, z_{low} = 0$		Sleep problems (z) proportionate partial correlations (ppr) Buffering effect by $z_{high} = 4$ from $w = 3$ to $w_{high} = 4$: [$4 - [[9 * (9.59) + 25 * (5.16)] / 34]$] / 2] * 0.178 = 0.208 Buffering effect by $z_{low} = 0$ from $w = 3$ to $w_{high} = 4$: [$0 - [[6 * (9.59) + 23 * (5.16)] / 29]$] / 2] * 0.178 = 0.541 Magnifier effect by $z_{high} = 4$ from $w_{low} = 0$ to $w = 2$: [$4 - [[8 * (-2.04) + 9 * (-5.01) + 6 * (-52.79)] / 23]$] / 3] * 0.178 = 1.213 ¹ Magnifier effect by $z_{low} = 0$ from $w_{low} = 0$ to $w = 2$: [$0 - [[57 * (-2.04) + 51 * (-5.01) + 17 * (-52.79)] / 125]$] / 3] * 0.178 = 0.602 Interpretation 1 When $w = 3$, or $w_{high} = 4$ (no control over Fatigue-weakness) Sleep problems (z) buffers the Breathing difficulty-Depressive affect relationship, with ppr falling from 0.541 at $z_{low} = 0$ to 0.208 at $z_{high} = 4$.	
Fatigue-weakness (w) and Sleep problems (z) as co-moderators of the Breathing difficulty (x) and Depressive affect (y) relationship (Breathing difficulty ^x , Fatigue-weakness ^z , Sleep problems)		2 When $w_{low} = 0$ (complete control over Fatigue-weakness), or $w = 1$ or $w = 2$, Sleep problems (z) magnifies the Breathing difficulty-Depressive affect relationship, with ppr increasing from 0.602 at $z_{low} = 0$ to 1.213 at $z_{high} = 4$.	
(18) $\partial^2 y / \partial x \partial z = -0.531 + 0.249w$ Select z where $-0.531 + 0.249w$ are highest in absolute value: $w_{high} = 4, w_{low} = 0$		Low Fatigue-weakness ($w_{low} = 0, w = 1, 2$) $z_{high} = 4, z_{low} = 0$ $w_{high} = 4: z_{0,w=4} = 2.400 / 0.465 = 5.16$ $w = 3: z_{0,w=3} = 2.071 / 0.216 = 9.59$ Zero inflection point: $z_0, z < w < 3 = 0$ $w = 2: z_{0,w=2} = 1.742 / -0.033 = -52.79$ $w = 1: z_{0,w=1} = 1.413 / -0.282 = -5.01$ $w_{low} = 0: z_{0,w=0} = 1.084 / -0.531 = -2.04$ Thus, $z_{0,w=4}$ and $z_{0,w=0}$ values are outside the actual range z values (0–4)	

Note: For the second panel only of Table S₃, see (1) in the Appendix.