*Development and Psychopathology* (2023), **35**, 12–23
doi:10.1017/S0954579421000493

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**Regular Article**

# Three-variable systems: An integrative moderation and mediation framework for developmental psychopathology

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## Abstract

In this article, we consider an often overlooked model that combines mediation and moderation to explain how a third variable can relate to a risk factor–psychopathology relationship. We refer to it as moderation and mediation in a three-variable system. We describe how this model is relevant to studying vulnerability factors and how it may advance developmental psychopathology research. To illustrate the value of this approach, we provide several examples where this model may be applicable, such as the relationships among parental externalizing pathology, harsh parenting, and offspring psychopathology as well as between neuroticism, stressful life events, and depression. We discuss possible reasons why this model has not gained traction and attempt to clarify and dispel those concerns. We provide guidance and recommendations for when to consider this model for a given data set and point toward existing resources for testing this model that have been developed by statisticians and other methodologists. Lastly, we describe important caveats, limitations, and considerations for making this approach most useful for developmental research. Overall, our goal in presenting this information to developmental psychopathology researchers is to encourage testing moderation and mediation in a three-variable system with the aim of advancing analytic strategies for studying vulnerability factors.

**Keywords:** developmental psychopathology, longitudinal research, mediation, moderation, risk factors

(Received 15 December 2020; revised 2 May 2021; accepted 2 May 2021; First Published online 22 June 2021)

## Introduction

Developmental psychopathology is a maturing discipline, and this is exemplified by advances in how vulnerability factors are studied (Cicchetti & Toth, 2009). Rather than simply demonstrating that a given vulnerability factor predicts an outcome, a primary aim of modern vulnerability factors research is to establish which *variables or conditions influence* the relationship between a vulnerability factor and an outcome as well as whether there are *intermediate processes between* the vulnerability factor and the disorder. These topics are respectively explored using moderation and mediation analyses (Baron & Kenny, 1986); these two models highlight the need to consider additional variables in order to understand fully the relationship between a vulnerability factor and outcome. The questions addressed by moderation and mediation appear distinct (Baron & Kenny, 1986; Kraemer, Kiernan, Essex, & Kupfer, 2008; Kraemer, Wilson, Fairburn, & Agras, 2002), but the information gained from these models can be complementary and provide a richer theoretical picture. This has led to the growth of models that integrate moderation and mediation within the same analysis (Fairchild & MacKinnon, 2009; Hayes, 2015; Muller, Descartes, Judd, & Yzerbyt, 2005; Preacher, Rucker, & Hayes, 2007).

Curiously, there is one particular scenario that is consistently overlooked in developmental psychopathology – namely, when moderation and mediation occur with just three variables. In this model, a single variable assumes the role of both moderator and mediator at the same time. At first glance, researchers may assume that a variable cannot simultaneously be both a mediator and moderator, perhaps on theoretical grounds, and that if this scenario occurs, it must be exceptionally rare. However, we argue that such cases are not only plausible in developmental psychopathology research, but might be much more common than is typically assumed – nearly 15 years ago, Grant et al. (2006) produced a comprehensive review of the role of stress in child and adolescent psychopathology in which they documented numerous examples of a single variable acting as a moderator in one set of studies and then also as a mediator in another set of studies. However, although it is quite common for the same variable to be conceptualized as a moderator and a mediator in separate studies or by separate groups of researchers, whether a variable functions as both a moderator and a mediator *simultaneously* is virtually never examined in a single analytic model. Thus, the

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**Cite this article:** Goldstein BL, Finsaas MC, Olino TM, Kotov R, Grasso DJ, Klein DN (2023). Three-variable systems: An integrative moderation and mediation framework for developmental psychopathology. *Development and Psychopathology* **35**: 12–23. https://doi.org/10.1017/S0954579421000493

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https://doi.org/10.1017/S0954579421000493 Published online by Cambridge University Press

overarching goal of this paper is to assist researchers in advancing the study of vulnerability factors by highlighting scenarios in which a mediator is also a moderator.

We first begin by defining the three most common theories of vulnerability factor–psychopathology relationships and how they are analyzed. We then discuss how each of these three vulnerability factor types may be complementary rather than mutually exclusive, and describe an integrative analytic framework discussed by statisticians (Hayes, 2015; Preacher et al., 2007), epidemiologists (Valeri & VanderWeele, 2013), and in some applied contexts (Kraemer et al., 2002) but rarely implemented in developmental psychopathology. We then review findings from several specific areas of research to illustrate when this integrative approach may apply. We also discuss possible reasons why this type of moderated mediation model has not gained more widespread use and address criticisms of the model. Next, we provide recommendations about when to use this model, including the timing for when to measure variables and how to select the correct model, and briefly discuss sample size. We also point to existing statistical tools for testing moderation and mediation in a three-variable model. Finally, we discuss important caveats, limitations, advanced analytic approaches, and considerations for developmentally informed designs.

## Basic Conceptual Perspectives and Analytic Approaches for Vulnerability Factors

"Risk factor" is a generic term referring to a variable that is believed to increase the probability of experiencing a negative outcome; for extensive discussions of risk factors see the works of Kraemer et al. (1997), Lenzenweger (2013) and Glahn et al. (2014). Conceptually, vulnerability factors are thought to lead to symptoms or disorders primarily via one of three ways: (a) as a direct predictor, (b) in conjunction with a moderator, or (c) through a mediator. The conceptual and statistical models corresponding to these three types of vulnerability factors are shown in Figure 1.

The direct predictor is the simplest model – a risk factor predicts a subsequent outcome without requiring other variables (Figure 1a). Studies of direct effect predictors such as these minimally require a longitudinal design with two assessments, where the risk factor is measured at the first time point and the outcome is measured at the second time point. Often in these designs, researchers also include the outcome variable at the first time point as a covariate to show that the risk factor predicts the outcome at the second time point over and above the way the outcome is predicted by its prior level.

An alternative model posits that a vulnerability factor is *moderated* by another variable to increase symptoms (Figure 1b). That is, two variables statistically interact to predict later psychopathology. The "third variable" in this model is often termed a moderator, but can also be thought of as a vulnerability factor in its own right.[1] Moderation can operate in several different ways. In some cases, the moderator variable is described as a catalyst that interacts with an underlying vulnerability leading to psychopathology. In this way, symptoms only increase when the vulnerability and moderator are both present. This is the pattern described in the classic diathesis stress model (Monroe & Simons, 1991). Another possibility is known as the differential susceptibility model (Belsky & Pluess, 2009); this occurs when high levels of the moderator increase risk for psychopathology (e.g., the association between the vulnerability factor and psychopathology is positive), but low levels of the moderator actually decrease risk for psychopathology (the direction of the association between the vulnerability factor and psychopathology is negative). Another version, known as the dual vulnerability model (e.g., Morris, Ciesla, & Garber, 2008), describes a situation in which high levels of either the vulnerability factor or the moderator can lead to psychopathology, but psychopathology will not occur when both the vulnerability factor and moderator are low. With regard to timing, the moderator and vulnerability factor are often measured contemporaneously and psychopathology is measured in a follow-up assessment. Issues concerning timing of variables are discussed in a later section.

Lastly, in a mediation framework, a vulnerability factor may be associated with an increase in symptoms via its effect on the third variable (Figure 1c). In these models, it is common that a vulnerability factor predicts the mediator (path *a* in Figure 1c), which in turn predicts psychopathology (path *b* in Figure 1c).[2] There are several directions in which the mediation may manifest. It is possible that the original vulnerability factor may increase or decrease the mediator, and the mediator may also increase or decrease psychopathology (when the effect of the mediator is to decrease psychopathology, it is considered a protective mediator).

## A Third Variable that is Both a Moderator and a Mediator

While there has been considerable attention paid to distinguishing moderators from mediators (Kraemer et al., 2008) – and there is good reason to clearly describe these terms (Baron & Kenny, 1986) – there may also be instances in which a variable functions simultaneously as both a moderator and a mediator (Figure 2). From an empirical perspective, there are many instances when this might occur. For example, Grant et al. (2006) reviewed hundreds of moderation and mediation studies examining the links between stressors and psychopathology in children and adolescents, and found numerous variables (e.g., coping skills, social support, and familial functioning) and various cognitive processes (e.g., attributional style and maladaptive beliefs) that were shown to be moderators in one study but mediators in another. However, moderators and mediators are rarely tested within the same analytic model. Instead of viewing moderation and mediation as distinct, we can instead consider them to reflect different components of the associations within a "three-variable system" that can be examined not only within a single study, but within the same analytic model.

When moderation and mediation occur in a three-variable system, the implication is that the indirect effect of $M$ linking $X$ to $Y$ is not uniform across the full range of values of $X$ and $M$. In other

[1]We often view moderators as a distinct class of variables, but they can be risk factors in the same way as the "primary" risk factor in the model. For example, stressful life events are a common moderator in psychopathology research when studied alongside other risk factors; however, in the absence of any other risk factor we have no qualms about calling stressful events a risk factor in their own right. The fact that moderators can be risk factors themselves, on equal footing with a primary predictor, has implications that are discussed in a later section of the paper.

[2]A considerable amount has been written describing the various assumptions required and the statistical methods to test mediation (Baron & Kenny, 1986; Hayes, 2009; Shrout & Bolger, 2002; Zhao, Lynch, & Chen, 2010). We follow the perspective of others that the key to supporting mediation is that the product of the indirect effect has an asymmetric confidence interval that does not include zero (MacKinnon et al., 2002; Shrout & Bolger, 2002). This perspective differs from other approaches that emphasize changes in the magnitude of the $X$ and $Y$ relationship (c path) when the indirect pathways are included versus when they are excluded. However, as described later on in the paper, there are several ways to interpret the special case of moderation and mediation in a three-variable system.

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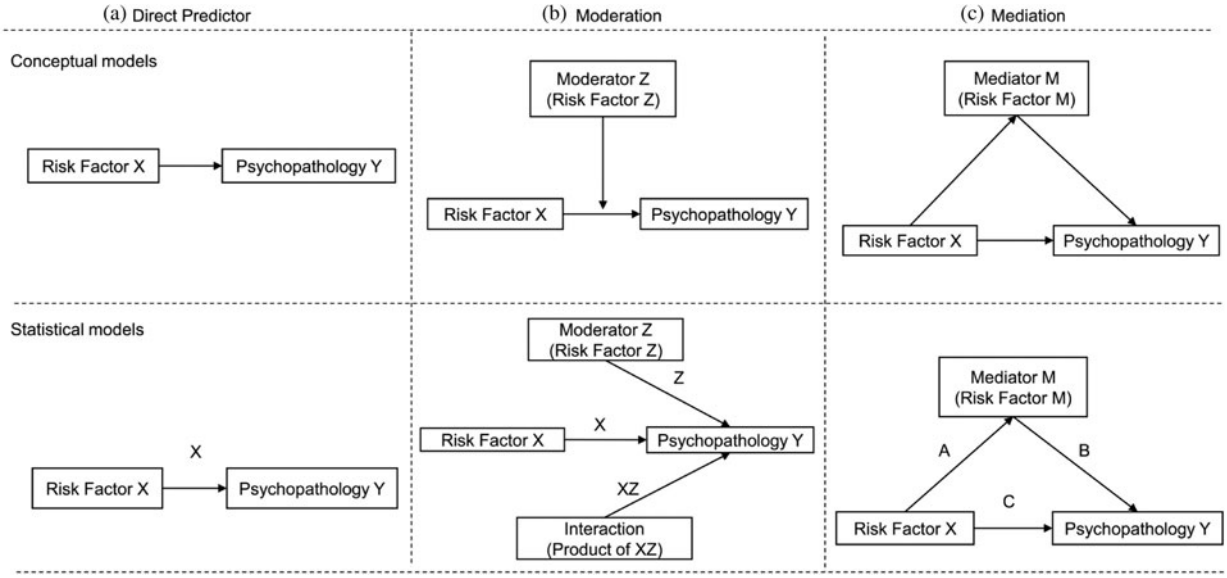


**Figure 1.** Theoretical and statistical diagrams of common risk factor–pathology relationships.

words, the indirect effect varies for the sample depending on the levels of *X* and *M*. When mediation is examined without an interaction between *X* and *M*, we are only able to capture the indirect effect for the sample on average, but it is plausible that the indirect effect may not be uniform across the entire sample. One example of this is when high and low values of *X* and *M* differentially influence the magnitude of the indirect effect, such that the effect is higher when *X* and *M* are high relative to when *X* and *M* are low. Conversely, the mediation effect is lower when the vulnerability factors *X* and *M* are low. This will be clearer when considering the examples in subsequent sections. This model is particularly relevant to developmental psychopathology when two vulnerability factors not only relate to an outcome, but also relate to each other via a developmental process in which one vulnerability factor (*X*) influences the development of the second vulnerability factor (*M*). From a more mechanistic and process-oriented approach, it is important to acknowledge that the degree of risk imposed by a vulnerability factor on an adverse outcome can be influenced by associations with one or more other vulnerability factors.

To illustrate moderation and mediation in a three-variable system, we consider the widely discussed phenomena of Gene × Environment interaction (G × E) and Gene by Environment correlation (*r*GE) as they relate to psychopathology (Rutter, Moffitt, & Caspi, 2006). Suppose a gene interacts with an environmental stressor to increase risk for psychopathology (G × E); however, the gene also predicts the environmental stressor with which it interacts (*r*GE). While candidate genes studies are being increasingly replaced with polygenic risk score approaches, we can consider a candidate gene as an example for illustrative purposes, focusing on the dopamine D2 receptor gene (*DRD2*), parenting, and anxious–depression symptoms in childhood (Hayden et al., 2010). Hayden et al. (2010) found evidence that the a1 allele of *DRD2* exhibited a significant association with anxious–depression symptoms (path *x* or path *c* in Figure 1). Furthermore, a significant interaction emerged between *DRD2* and intrusive parenting to predict anxiety–depression (path *xz* in Figure 1b). At the same time, *DRD2* also predicted intrusive parenting (path *a* in Figure 1c). In this example, the environmental variable – intrusive parenting – is clearly acting simultaneously as moderator and mediator of the gene–psychopathology relationship. This is because parenting interacts with the candidate gene while, at the same time, parenting is being predicted by the very same gene. More forcefully stated, it is not conceptually reasonable to separate the moderating and mediating effect of the environment on a gene–disorder relationship when both contribute to risk (Lau & Eley, 2008; Price & Jaffee, 2008). However, cases in which moderation and mediation co-occur are not restricted to G × E interplay, but can generalize to a wide range of scenarios with vulnerability factors at different levels of analysis. A similar example can be found at the level of a gene, physiology, and psychopathology. Goodyer, Bacon, Ban, Croudace, and Herbert (2009) found that the short allele of the serotonin transporter gene was associated with higher morning cortisol (an *a* path) and, at the same time, the short allele and morning cortisol interacted to predict depression onset (an *xz* path). Unfortunately, such examples are rarely reported, although exceptions can be found (Cole, Zapp, Fettig, & Pérez-Edgar, 2016; Gerhart, Baker, Hoerger, & Ronan, 2014; Maniates, Stoop, Miller, Halberstadt, & Wolf, 2018). However, by merging Figure 1b and Figure 1c together, we can see that simultaneously testing the three primary types of risk factor–psychopathology relationships can be readily achieved within a single model.

We believe that examining moderation and mediation in the same three-variable system is potentially beneficial for advancing the study of vulnerability factors. We depict this model in Figure 2. This approach allows for simultaneous evaluation of each of the three common vulnerability factor–disorder relationships within a single statistical model. This approach has advantages over a piecemeal approach in which each variant is tested separately. We believe that failing to test for both moderation and mediation limits theory development and slows research progress. Let us imagine a scenario in which the same vulnerability factor, disorder, and a third variable are examined in two separate studies. The first research group tests only moderation and finds a significant effect. The second research group tests only mediation and also finds a significant effect. While it is possible that both results are correct and complement one another, we cannot be

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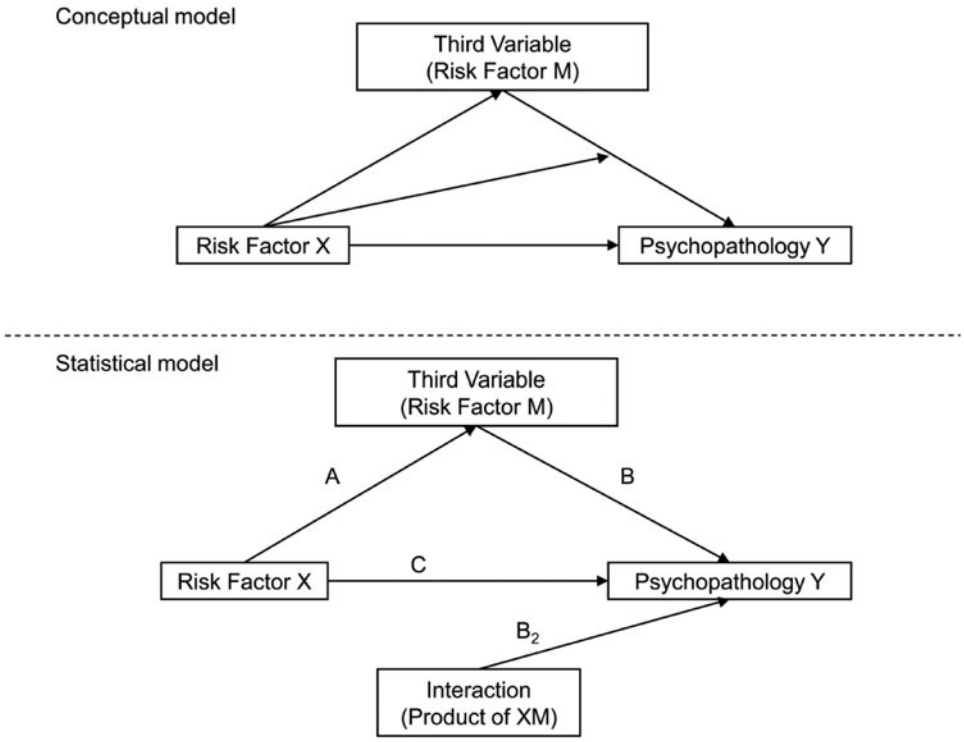


**Figure 2.** Moderation and mediation in a three-variable system. Comparing the conceptual model to the statistical model is illustrative for several purposes, but especially for demonstrating that the interaction is its own term that is not "acting" upon path *c* or path *b*. The significant product $ab_2$ (one that does not include zero in the 95% confidence interval) supports moderation and mediation in a three-variable system.

sure. It could be that both research groups tested moderation and mediation, but one group elected to report only moderation and the other group elected to report only mediation (each group possibly reporting only the model they found to be statistically significant). In other words, each report might have concealed a failed replication of the other research group's finding. This is not to say that simultaneous moderation and mediation should always be tested in a three-variable system – specific suggestions for when this model is most sensible are given later in this article – but there may be many scenarios in which we fail to conduct or report critical tests and this, in turn, may have deleterious repercussions for theory and reproducibility. We are not advocating that researchers always "test everything," but that when theory dictates this approach, researchers using the three-variable system are inherently encouraged to report everything, regardless of what ends up being significant. In the following sections, we review two vulnerability factor literatures in which moderated mediation is plausible, but – to the best of our knowledge – has yet to been tested within a single analytic model.

### *Parental externalizing psychopathology, harsh parenting, and offspring externalizing*

Moderation and mediation in a three-variable system may be relevant to the intergenerational transmission of psychopathology. One example is the relationships among parents with externalizing histories, harsh or abusive parenting, and externalizing behavior of their offspring. Moderation and mediation in a three-variable system hypothesis for this scenario might be that the indirect effect of harsh parenting on the relationship between parental externalizing and child externalizing is larger for those with higher levels of harsh parenting, but that the indirect effect is small or nonsignificant when harsh parenting is not present. Parental history of externalizing behavior (Chassin, Rogosch, & Barrera, 1991; Chronis et al., 2003; Hicks, Foster, Iacono, & McGue, 2013; Hicks, Krueger, Iacono, McGue, & Patrick, 2004) and harsh parenting (Deater-Deckard & Dodge, 1997; Pinquart, 2017) are both a robust predictor of externalizing problems in offspring.

Several studies have found evidence for moderation, reporting that harsher (or less warm) parenting moderates the effect of parent externalizing on offspring symptoms (Conners-Burrow et al., 2013, 2015; DeGarmo, 2010; Keller, Cummings, Davies, & Mitchell, 2008; although see Frick et al., 1992 for negative findings). At the same time, some others find evidence of mediation. For instance, parent–child conflict and harsh parenting mediates the association between parental externalizing/alcoholism and child externalizing behaviors (Bailey, Hill, Oesterle, & Hawkins, 2009; Loukas, Fitzgerald, Zucker, & Von Eye, 2001). Thus, there is some indication that both moderation and mediation may be present in this three-variable system. In addition, while we focused specifically on parental and offspring externalizing, it is worth nothing that parenting practices may exhibit similar moderating and mediating functions in explaining the link between other types of parental psychopathology and child problems (Callender, Olson, Choe, & Sameroff, 2012; Kane & Garber, 2009). Studies in this area also suggest important developmental considerations with regard to harsh parenting, including the recency of exposure, the accumulation of exposure, and when exposures occur during the course of development (Dunn et al., 2018). Whether future studies find support of moderation and mediation may differ depending on these issues.

https://doi.org/10.1017/S0954579421000493 Published online by Cambridge University Press


**Figure 3.** Four-variable moderated mediation examples. These models are examples of four-variable moderated mediation that are useful to consider when thinking about the validity of the three-variable system. We argue that the three-variable system is most comparable to second-stage moderated mediation.

### *Neuroticism, stressful life events, and depression*

Neuroticism, stressful life events, and their relationship to depression is another example of moderation and mediation in a three-variable system. Neuroticism and stressful life events prospectively predict depression (Dougherty et al., 2011; Goldstein, Kotov, Perlman, Watson, & Klein, 2018; Hakulinen et al., 2015; Jeronimus, Kotov, Riese, & Ormel, 2016; Keller, Neale, & Kendler, 2007; Kendler, Karkowski, & Prescott, 1998; Monroe, Rohde, Seeley, & Lewinsohn, 1999; Vrshek-Schallhorn et al., 2015). Some studies support the possibility of moderation between neuroticism and stressful life events (Kendler, Kuhn, & Prescott, 2004; Van Os & Jones, 1999; Vinkers et al., 2014); others, however, do not (Goldstein, Perlman, Eaton, Kotov, & Klein, 2019; Mineka et al., 2020; Spinhoven et al., 2011). There is also evidence that stressful life events may mediate the relationship between neuroticism and depression in youth (Goldstein et al., 2019; Kercher, Rapee, & Schniering, 2009; Wetter & Hankin, 2009); this is often referred to as the stress generation model (Hammen, 1991). Considering both sets of findings suggests the possibility that moderation and mediation may exist within a three-variable system. However, examining stressful life events as both a moderator and mediator of the neuroticism–depression relationship has rarely been reported within a single sample, let alone in the same analytic model (Goldstein et al., 2019; Spinhoven et al., 2011). It is also noteworthy that neuroticism and depression exhibit varying degrees of stability across development (Roberts & DelVecchio, 2000; Salk, Hyde, & Abramson, 2017) – mediation by stressful life events has only been found in young samples, not in older adults (Ormel, Oldehinkel, & Brilman, 2001). As a result, the developmental period in question is likely to be an important consideration when evaluating moderation and mediation in this three-variable system.

## Myths about Moderation and Mediation

Despite the examples provided above, researchers may be skeptical about whether a variable can simultaneously serve as a moderator and a mediator in a three-variable system for several reasons, and this hesitancy may partially explain why this model is so rarely tested. The first issue is that, in the three-variable system, it may be unclear how the moderator is related to the indirect effect. The second issue involves assumptions for when to consider a variable as a moderator or a mediator. The third is concerns about statistical power.

Regarding the first issue, it is useful to compare the three-variable system to what we more typically see in moderation and mediation with four variables, which is illustrated in Figure 3. In four-variable models, the roles of moderator and mediator are represented by different constructs and there are two variants of this model that are particularly relevant. In one version, the moderator can influence the magnitude of the indirect effect by its effect on the *X* to *M* path (path *a*); this is called first-stage moderated mediation. The second version is when the moderator influences the *M* to *Y* path (path *b*); this is called second-stage moderated mediation (Edwards & Lambert, 2007). In these four-variable models, the way the moderator and mediator relate to *X* and *Y* is unambiguous. In the three-variable system, the moderating and mediating effects are less intuitive. Up until now, we have largely discussed the *M* variable as influencing the indirect effect in the three-variable system. However, in the case of the three-variable system, it may at first glance appear that the moderator does not influence the indirect effect so it cannot be a valid model. The *M* variable cannot be moderating the effect that *X* has on path *a* (first-stage moderated mediation) as the product of *X* and *M* predicts *Y*, not *M*. Moreover, we are accustomed to conceptual diagrams of the simple case of moderation, such as the upper panel of Figure 1b, which gives the impression that *M* is acting upon the *X* to *Y* path. Therefore, one might be tempted to conclude that the moderation effect in the three-variable system is unrelated to the indirect effect because *M* appears to be moderating the direct effect (*X* to *Y* path) in the model rather than the *M* to *Y* path.

In our view, this issue is related to an important misconception of moderating effects as "acting" on pathways. Methodologists have long noted that the only difference between a moderator and a "primary predictor" is conceptual and that, from a mathematical standpoint, the moderator and primary predictor are equivalent (e.g., Bauer & Curran, 2005; Finsaas & Goldstein, 2021). Figure 1b shows how it may be arbitrary to label *M* or *X* as a moderator. The top panel of Figure 1b illustrates the theoretical model in which the moderator is depicted as acting on the *X* and *Y* paths; however, what is actually estimated in the statistical model appears in the lower panel, where it is clear that there is no mathematical difference between *X* and *Z*.[3] There is nothing novel about this statistical depiction of moderation – it is the very same diagram that is shown in the classic paper by Baron and Kenny (1986) – but, perhaps because the conceptual model is what is often used to depict moderation, moderators are incorrectly believed to be acting on a pathway. This issue is compounded by how researchers typically present moderation analyses by including simple slope follow-up tests at specific values of the

[3]The mathematical equivalence of the moderator and primary predictor can also be seen from looking at a regression equation with an interaction term and in considering the computational steps of how those regression models are fitted to data.

https://doi.org/10.1017/S0954579421000493 Published online by Cambridge University Press

moderator. While there is nothing incorrect about these follow-up tests, they carry interpretive value and are often written in a way that reinforces the perception that there is something special about the moderating variable when, in reality, simple slopes can be calculated with either *M* or *X* as the moderator (Finsaas & Goldstein, 2021).

This is relevant to the three-variable system because if the selection of a moderator is arbitrary from a mathematical standpoint, we can view the *X* variable as the *moderator* in just the same way as the *M* variable. The equations to estimate the model are identical using either conceptual framework. Instead of viewing the variable that is assessed in the intermediate period (labeled *M* in Figure 2) as the mediator and moderator (e.g., parenting practices, stressful life events), we can instead view *M* as only a mediator and the initial predictor, risk factor *X* (e.g., parental externalizing or neuroticism), as the moderator. Others writing about a three-variable system with moderation and mediation have referred to this model as an "independent variable as moderator" model or a model with an "Exposure × Mediator interaction" (independent variable and exposure meaning the initial vulnerability factor) (Hayes, 2015; Muthén, Muthen, & Asparouhov, 2016). If we consider *X* to be the moderator, the three-variable system more closely resembles a variant of second-stage moderated mediation (Edwards & Lambert, 2007), since the moderator *X* influences the *M* to *Y* path (path *b* in Figure 2). Stated using the more traditional language of moderated mediation, in the case of the three-variable system, the indirect effect of *X* to *Y* via *M* will vary in magnitude as a function of *X*.

Instead, we argue that neither *M* nor *X* needs to hold the label of moderator, and that the term "moderated mediation" may confuse more than clarify in this instance. We prefer to view this model as a case in which moderation and mediation effects are both present, and the inclusion of both best explains the relationships among the three variables. Stated another way, by including mediation and moderation, we are able to provide the fullest account of the outcome variable *Y* (in statistical terms, by including moderation within a mediation model when both types of effects are present will lead to a greater reduction in the unexplained variance of *Y*). In addition, we can take an agnostic view in how to think of this model by describing it as a three-variable system with mediation and an *interaction*, as described similarly by Muthén et al. (2016). This word choice highlights that, in moderation analyses, we need not be concerned with whether *M* influences the direct effect (size of *X* and *Y*) *per se*, but instead can think of an interaction as reflecting that two variables multiplicatively combine to predict an outcome. In other words, moderation analysis tests whether the effect of two variables on the outcome is greater than the sum of their independent contributions, which is consistent with the notion that allowing the interaction of *X* and *M* will reveal how their joint contribution on the indirect effect is not uniform at all levels of *X* or *M*.

A second source of skepticism about this model is related to confusion about the independence and timing criteria for when to assess moderators versus mediators. With regard to timing variables, methodologists widely agree that a mediator should occur after the initial vulnerability factor *X*, but before the outcome *Y* (Fairchild & MacKinnon, 2009; Kraemer et al., 2008; MacKinnon, Lockwood, Hoffman, West, & Sheets, 2002); however, the independence and timing of moderators have been debated. Baron and Kenny (1986) did not provide requirements or address the timing of moderators, although they suggested that it might be desirable for a moderator to be independent of vulnerability factor *X*. In contrast, a second widely utilized framework – the MacArthur approach, developed by Kraemer et al. (2002) – specifies that a moderator must be measured *before* the vulnerability factor and that the moderator should be independent of initial variable *X* (Kraemer et al., 2008). The issue of independence matters because if *X* and *M* must be independent, then the *a* path in mediation would be zero. Because of the issue of variable timing and the requirement of independence between *X* and *M* in moderation, Kraemer et al. (2002, 2008) go so far as to state that a variable cannot be both a moderator and mediator at the same time. There are certainly some scenarios where temporal ordering and independence of the moderator could be appropriate and may even be advantageous. However, this is likely to be the case primarily in randomized clinical trials, which is the context in which Kraemer et al. (2008) developed their guidelines (Karazsia & Berlin, 2018). In clinical trials, temporal ordering of moderators is important if researchers want to examine whether symptom severity prior to treatment is a moderator of outcome. In addition, in treatment research, variables assessed *after* the first session(s) or doses could theoretically be influenced by the differential effectiveness of the treatment group (path *a*) and therefore might be more appropriate to be treated as a mediator rather than a moderator. Requiring that a moderator be strictly independent of the other predictor is also important in clinical trials as a way of ensuring proper random assignment (Kraemer et al., 2008). For instance, in clinical trials, some of the moderators of interest may be time invariant (e.g., race), which would not logically be assumed to be mediators.[4]

However, in observational research, vulnerability factors are almost never orthogonal (Walker, Downey, & Nightingale, 1989); hence, this requirement is neither necessary nor feasible. As it is often impossible (and unethical) to randomly assign participants to exposure to vulnerability factors and because the temporal ordering of vulnerability factors is not always entirely clear, our position is that claiming the moderator must be first in time is not useful. We mention the issues of timing and independence of moderators in clinical research to highlight that there are some approaches that make stricter assumptions about moderators and it is possible that this might partially explain why researchers are hesitant to consider a variable as both a moderator and mediator; however, these assumptions are by no means mandatory requirements for all types of research or disciplines interested in vulnerability factor research.

However, if one wanted to conserve the rule that a moderator must temporally precede the independent variable, it is important to recall that assigning a variable to be the moderator can be somewhat arbitrary, as discussed above. By calling the initial vulnerability factor *X* the moderator in this model we are, in essence, preserving the temporal criteria of having a moderator be measured first, since *X* must come before *M* according to the stricter MacArthur rules of moderation. Similarly, we also described how the term "interaction" can be used to help highlight that the vulnerability factor and the third variable are actually on an even footing with one another, consistent with how this model has been referred to as a mediation model with an Exposure × Mediator interaction (Muthén et al., 2016; Valeri & VanderWeele, 2013).

[4]In clinical trials, demographic variables would not logically be mediators for two reasons. The first is that they fail to meet the time criteria for mediators because they are clearly established before the trial begins and the second is that they should not have an association with the treatment group because of random assignment. However, in risk factors research, demographic variables could be considered as the *X* risk factor in a three-variable system.

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In summary, a researcher can consider *M* to function as both a mediator and a moderator (Figure 2). At the same time, a researcher could treat *X* as the moderator of the *M* to *Y* relationship and *M* as the mediator of *X* to *Y*. Whether *M* is conceptually viewed as both a moderator and mediator, or if *X* is viewed as the moderator instead of *M*, is a matter of theory and the researcher's specific question. Both are valid ways of considering this model and neither conceptualization would change the way the model is estimated.

A third concern about this model relates to power. Researchers may assume that because more paths are estimated within the model, the power to detect effects is lower. However, the power to detect significant relationships in the three-variable system is identical to the power to detect a significant interaction with correlated predictors. In moderation-only models, the correlation between *X* and *M* is factored into the model's power and impacts the variance explained in *Y*, even if that correlation is not reported (Asparouhov & Muthén, 2020). In the three-variable system, the correlation of *X* and *M* is derived as a regression coefficient (to capture path *a* in the *X* to *M* relationship). The correlation is the same as the standardized regression coefficient, which is why the power for the three-variable system is the same as in a moderation-only model. As a result, the sample size requirements for moderation and mediation in a three-variable system are no different from those of a moderation-only model with correlated predictors (for details, see Asparouhov & Muthén, 2020), though we acknowledge that moderation models in general require large samples, especially when the interaction effect is small.

## Recommendations for Simultaneously Testing Moderation and Mediation in a Three-Variable System

What then are our recommendations regarding the special case of a three-variable system with moderation and mediation? Because selecting a *de facto* moderator is not always sensible in developmental psychopathology, we do not believe that the timing of the "moderator" is a critical determinant in applying this model. Even if one still held to the "moderator must be measured" first criterion, we would argue that because the primary predictor (e.g., parental externalizing, reward processing) and the moderating variable (e.g., parenting, stress) are treated the same mathematically, the vulnerability factor can instead be thought of as moderating the *relationship* between the mediating variable and the outcome in the three-variable system, as discussed by others (Hayes, 2015; Muthén et al., 2016; Valeri & VanderWeele, 2013).

Like others, we agree that the mediator should occur temporally after the initial vulnerability factor and before the outcome because temporal ordering is critical for demonstrating mediation. If we want to claim that vulnerability factor *X* contributes to mediator *M*, then that vulnerability factor must temporally precede the mediator. However, there can be greater flexibility regarding the timing of the mediator relative to the outcome. While it is ideal for the mediator to be assessed before the outcome (to clearly establish that the mediator is a prospective predictor of the psychopathology outcome), there may be many cases where the mediator can be measured at the same time as the outcome. This would only be allowed if the temporal ordering of the mediator and outcome variables can be reliably determined despite assessing them contemporaneously. For instance, a well-validated stressful life event interview that assesses events occurring in the period *between* the vulnerability factor and outcome could be administered at the same assessment wave as the outcome variable under two conditions. First, the outcome measure (e.g., symptoms) must focus on a very brief window (e.g., the past 2 weeks), and the level of that outcome in the previous wave can be included as a covariate. Second, researchers must be able to clearly date the occurrence of the mediator (e.g., a stressful life event or life transition) or clearly describe the timescale properties of the mediator.

Another consideration for developmental psychopathologists is whether the *a* path should be significant. Strictly speaking, from a statistical perspective, this path does not need to be significant in order to infer mediation (e.g., Hayes & Rockwood, 2017; MacKinnon et al., 2002; Rucker, Preacher, Tormala, & Petty, 2011). However, we believe that the *a* path should be significant if a theory makes explicit hypotheses about this path, and that this path is conceptually relevant to many theories in developmental psychopathology. Specifically, one of the appeals of this model is that the vulnerability factor *X* can be thought of as relevant to the development of *M*, which is supported when the *a* path is significant (as was the case in our examples described above; i.e., stress generation explicitly states that neuroticism should predict stress – an *a* path). Moreover, the conceptual roots of this model are based on G × E and *r*GE effects, with the latter relationship being defined by a significant *a* path. In extending this analytic model more broadly to developmental psychopathology, we think it is sensible for the *a* path to be significant in many cases, although it is not strictly required. Instead, we urge developmental psychopathology researchers to consider the theoretical implications of this model when the *a* path is or is not significant.

Lastly, we suggest and outline a specific set of steps for researchers to follow when deciding between whether their data are best represented by a regular regression model, a moderation-only or mediation-only model, or the three-variable system model. Researchers should fit the three-variable system model to the data and examine the significance of the *X* to *M* mediation path and the *XM* to *Y* interaction path (see section Guides for Statistical Implementation for details). If these paths are significant, there is a high likelihood that it is the correct model. If the product of these paths ($ab_2$) is significant then the three-variable system model is clearly superior to models that exclude these paths. However, if only the moderation effect is significant, but *X* to *M* is not (and $ab_2$ is not), researchers can then test a moderation-only model. Similarly, if the first leg of mediation is significant, but *XM* to *Y* is not, researchers could then test mediation alone. When neither of these paths are significant and the product $ab_2$ is not significant, it is likely that the best model would be a regression model with only direct, independent predictive effects (*X* to *Y* and *M* to *Y*).

Overall, our recommendations build upon existing guidance about moderation and mediation. For the three-variable system these recommendations can be summarized as follows.

(a) A moderation and mediation three-variable system should be measured with a minimum of three time points (although, for an exception see point (c)).
(b) The sequence of when to measure the components in the model is as follows: the primary vulnerability factor at Time 1, the third variable *M* at Time 2, and the outcome at Time 3.
(c) In some circumstances, two time points may be sufficient. In these cases, the primary vulnerability factor must be assessed at Time 1 and both the third variable *M* and the outcome are assessed at Time 2. However, this depends on whether it is

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possible to establish with confidence that the third variable temporally preceded the outcome variable (e.g., *M* occurred or measures a process that takes place during the interval between Time 1 and Time 2).

(d) When a given theory explicitly hypothesizes that vulnerability factor *X* may contribute to the development of vulnerability factor *M*, there should be a significant predictive association from vulnerability factor *X* to vulnerability factor *M* (a significant *a* path).

(e) When the comprehensive moderation and mediation in a three-variable system model is fit, the indirect effect (mediation), and interaction effect (moderation) are significantly different from zero it can generally be concluded that the moderation and mediation model is superior to either a regular regression, moderation-only, or mediation-only model. While there are several ways for reporting and evaluating this model, we encourage users to test the index of moderated mediation (Hayes, 2015), the product $ab_2$, which is a straightforward and simple metric (illustrated in greater detail in the next section).

## Guides for Statistical Implementation

Our goal here was not to develop a new statistical model, but rather to call attention to the underappreciation and potential value of considering moderation and mediation in a three-variable system. This model has been mentioned for over a decade in widely cited papers (Kraemer et al., 2008, 2002) and there are several papers discussing this model, with practical guides, by methodologists and statisticians (Hayes, 2015; Muthén et al., 2016; Valeri & VanderWeele, 2013). However, it has received little attention in developmental psychopathology research.

When interpreting effects in a model that contains significant moderation and mediation examined simultaneously, they should be interpreted together rather than as distinct effects. Researchers can report findings following the approach of Hayes (2015), referred to as the index of moderated mediation. Briefly, this index characterizes how the magnitude of the indirect effect changes depending on the value of a moderator. For the index of moderated mediation in the three-variable system, the initial vulnerability factor is treated as the moderator of the indirect effect of *X* to Y through *M*. In the case we have described, it is calculated as follows, based on the path coefficient labels in Figure 1, where *X* indicates the value of vulnerability factor *X*:

$$\text{Indirect effect magnitude} = ab + ab_2(X)$$

In this equation, the index of the moderated mediation effect is the coefficient $ab_2$ as it represents how much the indirect effect will change; details about the index of moderated mediation, statistical significance, and graphical depiction are provided by Hayes (2015). There are several other ways of evaluating this model. One approach, which may be familiar to more researchers, is similar to the simple slopes approach, but in this case the "simple slopes" are conducted with respect to the indirect effect at small, medium, and large values of the moderator (Stride, Gardner, Catley, & Thomas, 2015). This approach gives the same interpretative information as the index of moderated mediation and is not necessary to include if the index of moderated mediation is also reported.

Another approach for interpretation that is gaining traction as a possible best practice is the derivation of counterfactuals (Valeri & VanderWeele, 2013; VanderWeele, 2014). Counterfactuals may not be as well known to developmental psychopathologists, but they have the advantage of isolating the components of the effect on the outcome variable so researchers can report the proportion of the effect that is attributable to the interaction/moderation effect alone, the mediation effect alone, and the combination of the moderation and mediation effect. A counterfactual relevant to the interaction plus indirect effect will be quite similar to the index of moderated mediation.

Fortunately, for researchers interested in applying this model, there are statistical tools for doing so. Moderation and mediation can be tested in three-variable systems using macros for SAS, SPSS (Valeri & VanderWeele, 2013), and R packages lavaan (Rosseel, 2012) or Mplus (Muthén & Muthén, 2017). The SAS and SPSS macros have been developed for testing these models with a counterfactual approach by Valeri and VanderWeele (2013). Mplus syntax for this model has been posted online (Stride et al., 2015) and is also described in detail by Muthén et al. (2016). Mplus also includes features for implementing the counterfactual approach (Muthén & Asparouhov, 2015). Given the existing guidance on how to evaluate three-variable system models statistically and the availability of tools to do so, there are few roadblocks for implementing this model. Calculating the index of moderated mediation is also relatively straightforward, and syntax has been developed for that approach as well (Hayes, 2015).

## Important Considerations, Limitations, and Alternative Models

We have argued that, in many situations, researchers should consider testing moderation and mediation in a single analytic model. However, we should emphasize the caveat that this model should only be considered when there are reasonable theoretical reasons to do so. Furthermore, there are several issues that require additional discussion, including mediation analysis in nonexperimental contexts, the often low replicability of interactions, theoretical considerations of developmental processes, and advanced analytic models that may be more appropriate for a given research question.

It is important to acknowledge some challenges in mediation analyses in general as they are also inherently present in testing mediation and moderation in a three-variable system. First, studies of mediation should not be equated with causation or mechanism (Tryon, 2018). It may be tempting to claim that because *X* comes before and predicts *M*, it must be causing *M*, but this is an oversimplification. Instead, mediation should be thought of as a necessary, but not sufficient, statistical technique to demonstrate that something may be a mechanism. Causation is better supported by experimental study designs, and statistical tests cannot substitute for random assignment and manipulation of variables. However, making causal claims about mediators can be difficult even when experimental designs are used (Bullock, Green, & Ha, 2010). For instance, if experimental manipulation of mediator *M* unintentionally impacts another mediator $M_2$ (even one that is not observed in the model), it is unclear whether the manipulated change in *M* or $M_2$ is contributing to a change in *Y*, and this unintentional manipulation could bias the indirect effect through *M*. Second, even if we can manipulate the mediator, it may not always be possible to manipulate all study participants in the same way (e.g., if the study involves a negative mood induction, some participants might not be impacted by the manipulation). As a result of not knowing which subjects are actually

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changing due to the manipulation, there is a good likelihood that the estimation of the indirect effect will be biased (e.g., those assigned to the manipulation who respond in an atypical fashion will alter estimation of the indirect effect). Regardless of whether the study is observational or experimental, failure to include additional mediator variables when they are present can lead to an overestimation of the indirect effect when testing a mediation model (Fritz, Kenny, & MacKinnon, 2016; Muthén et al., 2016). Third, measurement error can lead to biases in the indirect effect (Fritz et al., 2016).

Just like with mediation, many of the concerns with interactions are also present when examining moderation and mediation in a three-variable system. Importantly, interactions are difficult to replicate and replicate less often than main effects (Amir & Sharon, 1990; Open Science Collaboration, 2015). As noted previously, sample size consideration for moderation and mediation in a three-variable system is largely determined by the power to detect interactions. Estimation of the power to detect an interaction is more complex than the power for main effects in traditional regression analyses and these complexities, such as the correlation between predictors, may not always be properly considered when planning a study, leading to inadequate sample size (Aguinis & Stone-Romero, 1997; McClelland & Judd, 1993). At the same time, effect sizes for interactions may be smaller than anticipated, which could lead researchers to select samples that are underpowered, leading to spurious type II errors (Aguinis, Beaty, Boik, & Pierce, 2005). Similar to the issues discussed with mediation, measurement error is also an issue for interactions (Altmejd et al., 2019; McClelland & Judd, 1993). In addition, lower variance of *X* and *M* (or restrictions of their variance) can substantially lower power. Lastly, and in part as a result of the issues just mentioned, interactions that are tested in observational studies are less likely to be detected than in experimental studies (McClelland & Judd, 1993). Given that it is often impossible to use experimental designs in developmental psychopathology, researchers should pay even greater attention to sample size, select reliable measures, and – when possible – sample from the population in a way that increases the variances of *X* and *Z*.

Perhaps most importantly, developmental theory must be carefully considered when applying the three-variable system or any statistical model (Selig & Preacher, 2009). The three-variable system that we have described is not inherently a developmental model. What makes a model developmental depends on the nature of the question and the constructs investigated, how they are measured, and when they are measured. Selig and Preacher (2009) describe several issues and provide guidance when testing mediation in longitudinal models. For instance, researchers must consider the lag between time points so as not to miss a true effect. If the lag is too short, a process may not have had sufficient time to unfold. If the lag is too long, the effects may have diminished. In addition, researchers need to consider whether or how their constructs change. The simple linear models that we have used as examples throughout this paper are not designed to capture change. While moderation and mediation in a three-variable system can be tested with as few as two time points, the use of three or more time points allows for testing the possibility that moderation and mediation influence change over time or are specific to one or multiple periods of time, which may be informative. Another consideration is the direction of effects. Each of the examples and figures presented here to illustrate moderation and mediation in a three-variable system have been unidirectional (vulnerability factor, third variable, and outcome), but it is possible that bidirectional effects may be present. Furthermore, when researchers already have good evidence to suggest that additional variables may play a moderating or mediating role they should also be included in the model (e.g., a hybrid of Figures 2 and 3; for other examples see Hayes, 2015, 2018).

Finally, simultaneous testing of moderation and mediation may be incorporated into more complex developmental models. While we have focused on testing the three-variable system in Figure 2, we also encourage researchers to test moderation and mediation simultaneously in a family of developmental models that are receiving increased attention for their ability to examine two or more co-developmental processes. Some of these models are well known, such as the parallel growth curve model (Cheong, MacKinnon, & Khoo, 2003; Muthén & Curran, 1997) and the trait–state–occasion model (Cole, Martin, & Steiger, 2005). Others are perhaps less widely used, such as the random-intercept cross-lagged panel design (the successor to traditional cross-lagged models), which may have a wide range of applications for researchers interested in teasing apart between-person and longitudinal within-person change and would fit well as an extension of the path model shown in Figure 2 (Berry & Willoughby, 2017; Hamaker, Kuiper, & Grasman, 2015). Another hybrid model is the autoregressive latent trajectory model with structured residuals, which includes elements of linear growth and cross-lagged models (Grimm, Ram, & Estabrook, 2016; Mund & Nestler, 2019). Still others, such as the dual change score model, can be particularly flexible and capable of testing a variety of development relationships (Grimm et al., 2016; Mund & Nestler, 2019). While it is well beyond the scope of a single article to describe the full range of models that apply to developmental research, our point is that testing moderation and mediation simultaneously can be incorporated into many developmental analyses and researchers should not feel constrained to testing only the simple version that we used for illustration.

## Conclusions

We have made the case for testing an integrated moderation–mediation model when working with three-variable systems in developmental psychopathology. This model is intuitive and can be applied to a variety of vulnerability factor–psychopathology relationships. This model is not a new concept, but is underappreciated and underutilized. We believe that this model holds promise for advancing developmental psychopathology by providing a framework that more comprehensively tests the three-variable vulnerability factor and outcome scenarios. As we have described, the three-variable system avoids a piecemeal approach to theory building about vulnerability factor–disorder relationships by testing the three common types of relationships simultaneously. In addition, this approach can speed up the process by which we are able to determine the replicability of moderation and mediation effects in vulnerability factor research.

We have illustrated the conceptual value of this model by giving a hypothetical example with genetics as well as describing several instances from diverse corners of the research literature where this model might help clarify discrepancies and improve theory. This integrative framework is of value for furthering progress in research domains that are well established and accelerating knowledge in emerging areas. We have also provided suggestions for testing this model using longitudinal designs. Ideally, there should be at least three waves of assessments, but in some situations this model can be applied with only two time points. However, we

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caution that this model should not be applied cavalierly, but that researchers should consider the nature and timing of the data they include in these models as well as the use of more advanced models that can accommodate testing moderation and mediation in a single analysis.

Overall, we believe that on conceptual and statistical grounds there is good reason to apply moderation and mediation simultaneously using a three-variable system when conducting developmental psychopathology research. Choosing to test only moderation or only mediation, in the absence of a compelling rationale, may limit theory development and slow research progress. Instead, when rather simple assessment timing criteria are met, simultaneously testing moderation and mediation in three-variable risk (or resilience) factor–outcomes systems should be considered as a first-line research strategy rather than an afterthought.

**Funding Statement.** This work was supported by National Institute of Mental Health training grant T32-MH-013043 (MCF) and National Institute of Mental Health grants R01-MH-107495 (TMO), R01-MH-093479 (RK), and U01-MH-113390 (DJG).

**Conflicts of Interest.** None.

## References

Aguinis, H., Beaty, J. C., Boik, R. J., & Pierce, C. A. (2005). Effect size and power in assessing moderating effects of categorical variables using multiple regression: A 30-year review. *Journal of Applied Psychology*, *90*, 94–107. doi:10.1037/0021-9010.90.1.94

Aguinis, H., & Stone-Romero, E. F. (1997). Methodological artifacts in moderated multiple regression and their effects on statistical power. *Journal of Applied Psychology*, *82*, 192–206. doi:10.1037/0021-9010.82.1.192

Altmejd, A., Dreber, A., Forsell, E., Huber, J., Imai, T., Johannesson, M., … Camerer, C. (2019). Predicting the replicability of social science lab experiments. *PLoS One*, *14*, 1–18. doi:10.1371/journal.pone.0225826

Amir, Y., & Sharon, I. (1990). Replication research: A "must" for the scientific advancement of psychology. *Journal of Social Behavior and Personality*, *5*, 51.

Asparouhov, T., & Muthén, B. (2020). Bayesian estimation of single and multilevel models with latent variable interactions. *Structural Equation Modeling*, *28*, 314–328. doi:10.1080/10705511.2020.1761808

Bailey, J. A., Hill, K. G., Oesterle, S., & Hawkins, J. D. (2009). Parenting practices and problem behavior across three generations: Monitoring, harsh discipline, and drug use in the intergenerational transmission of externalizing behavior. *Developmental Psychology*, *45*, 1214–1226. doi:10.1037/a0016129

Baron, R. M., & Kenny, D. A. (1986). The moderator–mediator variable distinction in social psychological research: Conceptual, strategic, and statistical considerations. *Journal of Personality and Social Psychology*, *51*, 1173–1182.

Bauer, D. J., & Curran, P. J. (2005). Probing interactions in fixed and multilevel regression: Inferential and graphical techniques. *Multivariate Behavioral Research*, *40*, 373–400. doi:10.1207/s15327906mbr4003_5

Belsky, J., & Pluess, M. (2009). Beyond diathesis stress: Differential susceptibility to environmental influences. *Psychological Bulletin*, *135*, 885–908.

Berry, D., & Willoughby, M. T. (2017). On the practical interpretability of cross-lagged panel models: Rethinking a developmental workhorse. *Child Development*, *88*, 1186–1206. doi:10.1111/cdev.12660

Bullock, J. G., Green, D. P., & Ha, S. E. (2010). Yes, but what's the mechanism? (don't expect an easy answer). *Journal of Personality and Social Psychology*, *98*, 550–558. doi:10.1037/a0018933

Callender, K. A., Olson, S. L., Choe, D. E., & Sameroff, A. J. (2012). The effects of parental depressive symptoms, appraisals, and physical punishment on later child externalizing behavior. *Journal of Abnormal Child Psychology*, *40*, 471–483. doi:10.1007/s10802-011-9572-9

Chassin, L., Rogosch, F., & Barrera, M. (1991). Substance use and symptomatology among adolescent children of alcoholics. *Journal of Abnormal Psychology*, *100*, 449–463. doi:10.1037/0021-843X.100.4.449

Cheong, J. W., MacKinnon, D. P., & Khoo, S. T. (2003). Investigation of mediational processes using parallel process latent growth curve modeling. *Structural Equation Modeling*, *10*, 238–262. doi:10.1207/S15328007SEM1002_5

Chronis, A. M., Lahey, B. B., Pelham, W. E., Kipp, H. L., Baumann, B. L., & Lee, S. S. (2003). Psychopathology and substance abuse in parents of young children with attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*, *42*, 1424–1432. doi:10.1097/00004583-200312000-00009

Cicchetti, D., & Toth, S. L. (2009). The past achievements and future promises of developmental psychopathology: The coming of age of a discipline. *Journal of Child Psychology and Psychiatry*, *50*, 16–25.

Cole, D. A., Martin, N. C., & Steiger, J. H. (2005). Empirical and conceptual problems with longitudinal trait-state models: Introducing a trait-state-occasion model. *Psychological Methods*, *10*, 3–20. doi:10.1037/1082-989X.10.1.3

Cole, C. E., Zapp, D. J., Fettig, N. B., & Pérez-Edgar, K. (2016). Impact of attention biases to threat and effortful control on individual variations in negative affect and social withdrawal in very young children. *Journal of Experimental Child Psychology*, *141*, 210–221. doi:10.1016/j.jecp.2015.09.012

Conners-Burrow, N. A., McKelvey, L., Pemberton, J. R., Lagory, J., Mesman, G. R., & Whiteside-Mansell, L. (2013). Moderators of the relationship between maternal substance abuse symptoms and preschool children's behavioral outcomes. *Journal of Child and Family Studies*, *22*, 1120–1129. doi:10.1007/s10826-012-9674-1

Conners-Burrow, N. A., McKelvey, L. M., Pemberton, J. R., Mesman, G. R., Holmes, K. J., & Bradley, R. H. (2015). Buffering the negative effects of maternal alcohol problems on child behavior. *Journal of Family Psychology*, *29*, 576–584. doi:10.1037/fam0000121

Deater-Deckard, K., & Dodge, K. A. (1997). Externalizing behavior problems and discipline revisited: Nonlinear effects and variation by culture, context, and gender. *Psychological Inquiry*, *8*, 161–175. doi:10.1207/s15327965pli0803_1

DeGarmo, D. S. (2010). Coercive and prosocial fathering, antisocial personality, and growth in children's postdivorce noncompliance. *Child Development*, *81*, 503–516. doi:10.1111/j.1467-8624.2009.01410.x

Dougherty, L. R., Bufferd, S. J., Carlson, G. A., Dyson, M., Olino, T. M., Durbin, C. E., & Klein, D. N. (2011). Preschoolers' observed temperament and psychiatric disorders assessed with a parent diagnostic interview. *Journal of Clinical Child and Adolescent Psychology*, *40*, 295–306. doi:10.1080/15374416.2011.546046

Dunn, E. C., Soare, T. W., Raffeld, M. R., Busso, D. S., Crawford, K. M., Davis, K. A., … Susser, E. S. (2018). What life course theoretical models best explain the relationship between exposure to childhood adversity and psychopathology symptoms: Recency, accumulation, or sensitive periods? *Psychological Medicine*, *48*, 2550–2561. doi:10.1017/S0033291718000181

Edwards, J. R., & Lambert, L. S. (2007). Methods for integrating moderation and mediation: A general analytical framework using moderated path analysis. *Psychological Methods*, *12*, 1–22. doi:10.1037/1082-989X.12.1.1

Fairchild, A. J., & MacKinnon, D. P. (2009). A general model for testing mediation and moderation effects. 87–99. doi:10.1007/s11121-008-0109-6

Finsaas, M. C., & Goldstein, B. L. (2021). Do simple slopes follow-up tests lead us astray? Advancements in the visualization and reporting of interactions. *Psychological Methods*, *26*, 38–60. doi:10.1037/met0000266

Frick, P. J., Lahey, B. B., Loeber, R., Stouthamer-Loeber, M., Christ, M. A. G., & Hanson, K. (1992). Familial risk factors to oppositional defiant disorder and conduct disorder: Parental psychopathology and maternal parenting. *Journal of Consulting and Clinical Psychology*, *60*, 49–55. doi:10.1037/0022-006X.60.1.49

Fritz, M. S., Kenny, D. A., & MacKinnon, D. P. (2016). The combined effects of measurement error and omitting confounders in the single-mediator model. *Multivariate Behavioral Research*, *51*, 681–697. doi:10.1080/00273171.2016.1224154

Gerhart, J. I., Baker, C. N., Hoerger, M., & Ronan, G. F. (2014). Journal of contextual behavioral science experiential avoidance and interpersonal problems: A moderated mediation model. *Journal of Contextual Behavioral Science*, *3*, 291–298. doi:10.1016/j.jcbs.2014.08.003

Glahn, D. C., Knowles, E. E. M., McKay, D. R., Sprooten, E., Raventós, H., Blangero, J., … Almasy, L. (2014). Arguments for the sake of

https://doi.org/10.1017/S0954579421000493 Published online by Cambridge University Press

endophenotypes: Examining common misconceptions about the use of endophenotypes in psychiatric genetics. *American Journal of Medical Genetics, Part B: Neuropsychiatric Genetics*, *165*, 122–130. doi:10.1002/ajmg.b.32221

Goldstein, B. L., Kotov, R., Perlman, G., Watson, D., & Klein, D. N. (2018). Trait and facet-level predictors of first-onset depressive and anxiety disorders in a community sample of adolescent girls. *Psychological Medicine*, *48*, 1282–1290. doi:10.1017/S0033291717002719

Goldstein, B. L., Perlman, G., Eaton, N. R., Kotov, R., & Klein, D. N. (2019). Testing explanatory models of the interplay between depression, neuroticism, and stressful life events: A dynamic trait-stress generation approach. *Psychological Medicine*, 1–10. doi:10.1017/S0033291719002927

Goodyer, I. M., Bacon, A., Ban, M., Croudace, T., & Herbert, J. (2009). Serotonin transporter genotype, morning cortisol and subsequent depression in adolescents. *British Journal of Psychiatry*, *195*, 39–45. doi:10.1192/bjp.bp.108.054775

Grant, K E, Compas, B E, Thurm, A E, Mcmahon, S D, Gipson, P Y, Campbell, A J…Westerholm, R I. (2006). Stressors and child and adolescent psychopathology: Evidence of moderating and mediating effects. *Clinical psychology review*, *26*(3), 257–283. https://doi.org/10.1016/j.cpr.2005.06.011.

Grimm, K. J., Ram, N., & Estabrook, R. (2016). Growth *modeling*: Structural *equation and multilevel modeling approaches*. New York, NY: Guilford Press.

Hakulinen, C., Elovainio, M., Pulkki-Råback, L., Virtanen, M., Kivimaki, M., Jokela, M., … Jokela, M. (2015). Personality and depressive symptoms: Individual participant meta-analysis of 10 cohort studies. *Depression and Anxiety*, *32*, 461–470. doi:10.1002/da.22376

Hamaker, E. L., Kuiper, R. M., & Grasman, R. P. P. P. (2015). A critique of the cross-lagged panel model. *Psychological Methods*, *20*, 102–116. doi:10.1037/a0038889

Hammen, C. (1991). Generation of stress in the course of unipolar depression. *Journal of Abnormal Psychology*, *100*, 555–561.

Hayden, E. P., Klein, D. N., Dougherty, L. R., Olino, T. M., Laptook, R. S., Dyson, M. W., … Singh, S. M. (2010). The dopamine D2 receptor gene and depressive and anxious symptoms in childhood: Associations and evidence for gene-environment correlation and gene-environment interaction. *Psychiatric Genetics*, *20*, 304–310. doi:10.1097/YPG.0b013e32833adccb

Hayes, A. F. (2009). Beyond Baron and Kenny: Statistical mediation analysis in the new millennium. *Communication Monographs*, *76*, 408–420.

Hayes, A. F. (2015). An index and test of linear moderated mediation. *Multivariate Behavioral Research*, *50*, 1–22. doi:10.1080/00273171.2014.962683

Hayes, A. F. (2018). *Introduction to mediation, moderation, and conditional process analysis: A regression-based approach* (2nd ed.). New York, NY: Guilford Press.

Hayes, A. F., & Rockwood, N. J. (2017). Regression-based statistical mediation and moderation analysis in clinical research: Observations, recommendations, and implementation. *Behaviour Research and Therapy*, *98*, 39–57. doi:10.1016/j.brat.2016.11.001

Hicks, B. M., Foster, K. T., Iacono, W. G., & McGue, M. (2013). Genetic and environmental influences on the familial transmission of externalizing disorders in adoptive and twin offspring. *JAMA Psychiatry*, *70*, 1076–1083. doi:10.1001/jamapsychiatry.2013.258

Hicks, B. M., Krueger, R. F., Iacono, W. G., McGue, M., & Patrick, C. J. (2004). Family transmission and heritability of externalizing disorders: A twin-family study. *Archives of General Psychiatry*, *61*, 922–928. doi:10.1001/archpsyc.61.9.922

Jeronimus, B. F., Kotov, R., Riese, H., & Ormel, J. (2016). Neuroticism's prospective association with mental disorders halves after adjustment for baseline symptoms and psychiatric history, but the adjusted association hardly decays with time: A meta-analysis on 59 longitudinal/prospective studies with 443 313 participants. *Psychological Medicine*, *46*, 2883–2906. doi:10.1017/S0033291716001653

Kane, P., & Garber, J. (2009). Parental depression and child externalizing and internalizing symptoms: Unique effects of fathers' symptoms and perceived conflict as a mediator. *Journal of Child and Family Studies*, *18*, 465–472. doi:10.1007/s10826-008-9250-x

Karazsia, B. T., & Berlin, K. S. (2018). Can a mediator moderate? Considering the role of time and change in the mediator–moderator distinction. *Behavior Therapy*, *49*, 12–20. doi:10.1016/j.beth.2017.10.001

Keller, P. S., Cummings, E. M., Davies, P. T., & Mitchell, P. M. (2008). Longitudinal relations between parental drinking problems, family functioning, and child adjustment. *Development and Psychopathology*, *20*, 195–212. doi:10.1017/S0954579408000096

Keller, M. C., Neale, M. C., & Kendler, K. S. (2007). Association of different adverse life events with distinct patterns of depressive symptoms. *American Journal of Psychiatry*, *164*, 1521–1529. doi:10.1176/appi.ajp.2007.06091564

Kendler, K. S., Karkowski, L. M., & Prescott, C. A. (1998). Stressful life events and major depression: Risk period, long-term contextual threat, and diagnostic specificity. *The Journal of Nervous and Mental Disease*, *186*, 661–669.

Kendler, K. S., Kuhn, J., & Prescott, C. A. (2004). The interrelationship of neuroticism, sex, and stressful life events in the prediction of episodes of major depression. *American Journal of Psychiatry*, *161*, 631–636. doi:10.1176/appi.ajp.161.4.631

Kercher, A. J., Rapee, R. M., & Schniering, C. A. (2009). Neuroticism, life events and negative thoughts in the development of depression in adolescent girls. *Journal of Abnormal Child Psychology*, *37*, 903–915. doi:10.1007/s10802-009-9325-1

Kraemer, H. C., Kazdin, A. E., Offord, D. R., Kessler, R. C., Jensen, P. S., & Kupfer, D. J. (1997). Coming to terms with the terms of risk. *Archives of General Psychiatry*, *54*, 337–343.

Kraemer, H. C., Kiernan, M., Essex, M., & Kupfer, D. J. (2008). How and why criteria defining moderators and mediators differ between the Baron & Kenny and MacArthur approaches. *Health Psychology*, *27*, 101–108. doi:10.1037/0278-6133.27.2(Suppl.).S101

Kraemer, H. C., Wilson, G. T., Fairburn, C. G., & Agras, W. S. (2002). Mediators and moderators of treatment effects in randomized clinical trials. *Archives of General Psychiatry*, *59*, 877–883. doi:10.1001/archpsyc.59.10.877

Lau, J. Y. F., & Eley, T. C. (2008). Disentangling gene-environment correlations and interactions on adolescent depressive symptoms. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, *49*, 142–150. doi:10.1111/j.1469-7610.2007.01803.x

Lenzenweger, M. F. (2013). Endophenotype, intermediate phenotype, biomarker: Definitions, concept comparisons, clarifications. *Depression and Anxiety*, *30*, 185–189. doi:10.1002/da.22042

Loukas, A., Fitzgerald, H. E., Zucker, R. A., & Von Eye, A. (2001). Parental alcoholism and co-occurring antisocial behavior: Prospective relationships to externalizing behavior problems in their young sons. *Journal of Abnormal Child Psychology*, *29*, 91–106. doi:10.1023/A:1005281011838

MacKinnon, D. P., Lockwood, C. M., Hoffman, J. M., West, S. G., & Sheets, V. (2002). A comparison of methods to test mediation and other intervening variable effects. *Psychological Methods*, *7*, 83–104. doi:10.1037/1082-989X.7.1.83

Maniates, H., Stoop, T. B., Miller, M. W., Halberstadt, L., & Wolf, E. J. (2018). Stress-generative effects of posttraumatic stress disorder: Transactional associations between posttraumatic stress disorder and stressful life events in a longitudinal sample. *Journal of Traumatic Stress*, *31*, 191–201. doi:10.1002/jts.22269

McClelland, G. H., & Judd, C. M. (1993). Statistical difficulties of detecting interactions and moderator effects. *Psychological Bulletin*, *114*, 376–390. doi:10.1037/0033-2909.114.2.376

Mineka, S., Williams, A. L., Wolitzky-Taylor, K., Vrshek-Schallhorn, S., Craske, M. G., Hammen, C., & Zinbarg, R. E. (2020). Five-year prospective neuroticism–stress effects on major depressive episodes: Primarily additive effects of the general neuroticism factor and stress. *Journal of Abnormal Psychology*, *129*, 646.

Monroe, S. M., Rohde, P., Seeley, J. R., & Lewinsohn, P. M. (1999). Life events and depression in adolescence: Relationship loss as a prospective risk factor for first onset of major depressive disorder. *Journal of Abnormal Psychology*, *108*, 606–614. doi:10.1037/0021-843X.108.4.606

Monroe, S. M., & Simons, A. D. (1991). Diathesis-stress theories in the context of life stress research: Implications for the depressive disorders. *Psychological Bulletin*, *110*, 406. doi:10.1037/0033-2909.110.3.406

Morris, M. C., Ciesla, J. A., & Garber, J. (2008). A prospective study of the cognitive-stress model of depressive symptoms in adolescents. *Journal of Abnormal Psychology*, *117*, 719–734. doi:10.1037/a0013741

https://doi.org/10.1017/S0954579421000493 Published online by Cambridge University Press

Muller, D., Descartes, P., Judd, C. M., & Yzerbyt, V. Y. (2005). When moderation is mediated and mediation is moderated. *89*, 852–863. doi:10.1037/0022-3514.89.6.852

Mund, M., & Nestler, S. (2019). Beyond the cross-lagged panel model: Next-generation statistical tools for analyzing interdependencies across the life course. *Advances in Life Course Research*, *41*, 100249. doi:10.1016/j.alcr.2018.10.002

Muthén, B., & Asparouhov, T. (2015). Causal effects in mediation modeling: An introduction with applications to latent variables. *Structural Equation Modeling*, *22*, 12–23. doi:10.1080/10705511.2014.935843

Muthén, B. O., & Curran, P. J. (1997). General longitudinal modeling of individual differences in experimental designs. *Psychological Methods*, *2*, 371–402.

Muthén, L. K., & Muthén, B. O. (2017). *Mplus user's guide (version 8.0)*. Los Angeles, CA: Muthén & Muthén.

Muthén, B. O., Muthen, L. K., & Asparouhov, T. (2016). *Regression and mediation analysis using Mplus*. Los Angeles, CA: Muthén & Muthén.

Open Science Collaboration. (2015). Estimating the reproducibility of psychological science. *Science*, *349*, 4716. doi:10.1126/science.aac4716

Ormel, J., Oldehinkel, A. J., & Brilman, E. I. (2001). The interplay and etiological continuity of neuroticism, difficulties, and life events in the etiology of major and subsyndromal, first and recurrent depressive episodes in later life. *American Journal of Psychiatry*, *158*, 885–891. doi:10.1176/appi.ajp.158.6.885

Pinquart, M. (2017). Associations of parenting dimensions and styles with externalizing problems of children and adolescents: An updated meta-analysis. *Developmental Psychology*, *53*, 873–932. doi:10.1037/dev0000295

Preacher, K. J., Rucker, D. D., & Hayes, A. F. (2007). Addressing moderated mediation hypotheses: Theory, methods, and prescriptions. *Multivariate Behavioral Research*, *42*, 185–227. doi:10.1080/00273170701341316

Price, T. S., & Jaffee, S. R. (2008). Effects of the family environment: Gene-environment interaction and passive gene-environment correlation. *Developmental Psychology*, *44*, 305–315. doi:10.1037/0012-1649.44.2.305

Roberts, B. W., & DelVecchio, W. F. (2000). The rank-order consistency of personality traits from childhood to old age: A quantitative review of longitudinal studies. *Psychological Bulletin*, *126*, 3.

Rosseel, Y. (2012). Lavaan: An R package for structural equation modeling and more. Version 0.5-12 (beta). *Journal of Statistical Software*, *48*, 1–36.

Rucker, D. D., Preacher, K. J., Tormala, Z. L., & Petty, R. E. (2011). Mediation analysis in social psychology: Current practices and new recommendations. *Social and Personality Psychology Compass*, *5*, 359–371. doi:10.1111/j.1751-9004.2011.00355.x

Rutter, M., Moffitt, T. E., & Caspi, A. (2006). Gene-environment interplay and psychopathology: Multiple varieties but real effects. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, *47*, 226–261. doi:10.1111/j.1469-7610.2005.01557.x

Salk, R. H., Hyde, J. S., & Abramson, L. Y. (2017). Gender differences in depression in representative national samples: Meta-analyses of diagnoses and symptoms. *Psychological Bulletin*, *143*, 783–822.

Selig, J. P., & Preacher, K. J. (2009). Mediation models for longitudinal data in developmental research. *Research in Human Development*, *6*, 144–164. doi:10.1080/15427600902911247

Shrout, P. E., & Bolger, N. (2002). Mediation in experimental and nonexperimental studies: New procedures and recommendations. *Psychological Methods*, *7*, 422–445. doi:10.1037/1082-989X.7.4.422

Spinhoven, P., Roelofs, K., Hovens, J. G. F. M., Elzinga, B. M., van Oppen, P., Zitman, F. G., & Penninx, B. W. J. H. (2011). Personality, life events and the course of anxiety and depression. *European Journal of Personality*, *25*, 443–452.

Stride, C. B., Gardner, S. E., Catley, N., & Thomas, F. (2015). Mplus code for mediation, moderation and moderated mediation models (1 to 80). Retrieved from http://www.offbeat.group.shef.ac.uk/FIO/mplusmedmod.htm

Tryon, W. W. (2018). Mediators and mechanisms. *Clinical Psychological Science*, *6*, 619–628. doi:10.1177/2167702618765791

Valeri, L., & VanderWeele, T. J. (2013). Mediation analysis allowing for exposure–mediator interactions and causal interpretation: Theoretical assumptions and implementation with SAS and SPSS macros. *Psychological Methods*, *18*, 474–474. doi:10.1037/a0035596

VanderWeele, T. J. (2014). A unification of mediation and interaction: a four-way decomposition. *Epidemiology*, *25*, 749–761. doi:10.1097/EDE.0000000000000121.A

Van Os, J., & Jones, P. B. (1999). Early risk factors and adult person–environment relationships in affective disorder. *Psychological Medicine*, *29*, 1055–1067.

Vinkers, C. H., Joëls, M., Milaneschi, Y., Kahn, R. S., Penninx, B. W. J. H., & Boks, M. P. M. (2014). Stress exposure across the life span cumulatively increases depression risk and is moderated by neuroticism. *Depression and Anxiety*, *31*, 737–745. doi:10.1002/da.22262

Vrshek-Schallhorn, S., Stroud, C. B., Mineka, S., Hammen, C., Zinbarg, R. E., Wolitzky-Taylor, K., & Craske, M. G. (2015). Chronic and episodic interpersonal stress as statistically unique predictors of depression in two samples of emerging adults. *Journal of Abnormal Psychology*, *124*, 918–932. doi:10.1037/abn0000088

Walker, E., Downey, G., & Nightingale, N. (1989). The nonorthogonal nature of risk factors: Implications for research on the causes of maladjustment. *Journal of Primary Prevention*, *9*, 143–163. doi:10.1007/BF01325209

Wetter, E. K., & Hankin, B. L. (2009). Mediational pathways through which positive and negative emotionality contribute to anhedonic symptoms of depression: A prospective study of adolescents. *Journal of Abnormal Child Psychology*, *37*, 507–520. doi:10.1007/s10802-009-9299-z

Zhao, X., Lynch, J. G. Jr, & Chen, Q. (2010). Reconsidering Baron and Kenny: Myths and truths about mediation analysis. *Journal of Consumer Research*, *37*, 197–206.

https://doi.org/10.1017/S0954579421000493 Published online by Cambridge University Press