HHS Public Access

Author manuscript

Early Interv Psychiatry. Author manuscript; available in PMC 2015 June 17.

Published in final edited form as:

Early Interv Psychiatry. 2010 May ; 4(2): 143–152. doi:10.1111/j.1751-7893.2010.00177.x.

Mediators and moderators in early intervention research

Nicholas J. K. Breitborde[1], **Vinod H. Srihari**[2], **Jessica M. Pollard**[3], **Donald N. Addington**[4], and **Scott W. Woods**[2]

[1]Department of Psychiatry, University of Arizona, Tucson, Arizona, USA

[2]Department of Psychiatry, Yale University, New Haven, Connecticut, USA

[3]Acadia Hospital, Bangor, Maine, USA

[4]Department of Psychiatry, University of Calgary, Calgary, Alberta, Canada

Abstract

Aim—The goal of this paper is to provide clarification with regard to the nature of mediator and moderator variables and the statistical methods used to test for the existence of these variables. Particular attention will be devoted to discussing the ways in which the identification of mediator and moderator variables may help to advance the field of early intervention in psychiatry.

Methods—We completed a literature review of the methodological strategies used to test for mediator and moderator variables.

Results—Although several tests for mediator variables are currently available, recent evaluations suggest that tests which directly evaluate the indirect effect are superior. With regard to moderator variables, two approaches ('pick-a-point' and regions of significance) are available, and we provide guidelines with regard to how researchers can determine which approach may be most appropriate to use for their specific study. Finally, we discuss how to evaluate the clinical importance of mediator and moderator relationships as well as the methodology to calculate statistical power for tests of mediation and moderation.

Conclusion—Further exploration of mediator and moderator variables may provide valuable information with regard to interventions provided early in the course of a psychiatric illness.

Keywords

early intervention; mediators; methodology; moderators; statistics

The goal of early intervention in psychiatry is to reduce and/or prevent the morbidity and mortality that often accompanies psychiatric illnesses.[1] Using current nomenclature for the different levels of prevention strategies in public health,[2] this work can range from 'health promotion' in which one attempts to reduce or eliminate the presence of risk factors for a disease in the environment to 'primary prevention' in which one attempts to reduce the incidence rate of a disease among healthy individuals who possess one or more major risk

Corresponding author: Dr Nicholas J. K. Breitborde, Department of Psychiatry, University of Arizona, 1501 N. Campbell Ave., PO Box 245002, Tucson, AZ 85724-5002, USA. breitbor@email.arizona.edu.

factor for developing the disease to 'secondary prevention' in which one attempts to prevent or minimize the loss of functioning among individuals already diagnosed with a disease. Although early intervention has been a mainstay within most disciplines of medicine, psychiatry has only more recently come to embrace an early intervention perspective.[3]

Given the relative recency of early intervention in psychiatry, it is not surprising that most studies to date have focused on what Guralnick[4] has referred to as 'first-generation research' – efficacy and effectiveness research designed to demonstrate that early intervention is associated with positive outcomes with regard to the course of mental illness (e.g. reduced rates of hospitalization, cost-savings, etc.). Completion of such first-generation research is critical in that it establishes a sufficiently large evidence base demonstrative of the benefits of early intervention.

As the evidence in support of early intervention grows, there is increasing interest in moving beyond the completion of additional efficacy/effectiveness studies to the exploration of new, more complex topics. For example, researchers may now wonder *why* specific early intervention strategies work (i.e. what are the underlying mechanisms) and *for whom* and *under what circumstances* will early intervention produce the greatest clinical benefits.[4–6] Questions such as these represent what Guralnick[4] refers to as 'second-generation research' – questions that examine the mechanisms through which interventions produce their benefit and attempt to identify which specific interventions will work best for specific individuals. Ultimately, the shift within early intervention research from first to second-generation research is a natural step in the maturation of the field and may increase the public health impact of early intervention programs.[4,7] Specifically, clarifying the mechanisms underlying the benefits of validated treatments may facilitate the refinement of existing interventions while simultaneously providing insight into the underlying disease processes that are unfolding early in the course of a mental illness.[5–7] Likewise, increasing our knowledge of patient specific factors that determine whether or not early intervention will be beneficial will help practitioners personalize treatment recommendations.

Hopwood[8] has noted that the transition from first-generation to second-generation research is associated with changes in the research designs and statistical analyses that are typically utilized. Specifically, whereas first-generation research seeks to identify whether there is an association between a specific intervention and a desired outcome, second-generation research seeks to clarify the factors that may underlie or influence this association. Two examples of such underlying/influential factors are mediator and moderator variables. It is these variables which address the fundamental questions of second-generation research, that is, how does a specific intervention produce clinical benefits (i.e. what variable(s) mediate the effect of the intervention) and when and for whom will a specific intervention work best (i.e. what variable(s) moderate the effect of the intervention).[6,9]

Thus, the goal of this paper is to provide clarification with regard to the nature of mediator and moderator variables and the statistical methods used to test for them. Ultimately, we hope that this clarification will promote greater exploration of mediator and moderator variables within early intervention studies – thereby facilitating the continued transition to second-generation research within the field of early intervention in psychiatry.

Mediator variables

> In the absences of a concern for such mediating or intervening mechanisms, one ends up with facts, but with incomplete understanding.
>
> –Rosenberg, 1968, p. 63[10] (see Footnote 1)

Definition and application to early intervention research

A mediator is an intervening variable which is thought to account for the relationship between the predictor variable and outcome variable.[11,12] Conceptually, mediator models assume that the predictor variable causes changes in the mediator variable, and the mediator variable then causes changes in the outcome variable. This relationship is displayed in Fig. 1, where α represents the effect of the predictor variable on the mediator variable, β represents the effect of the mediator variable on the outcome variable, τ represents the effect of the predictor variable on the outcome variable in the absence of the mediator, and τ' represents the effect of the predictor variable on the outcome variable after adjusting for the mediator.

The identification of mediating variables may be a particularly important endeavour in early intervention research. Clarifying the mechanisms through which early intervention programs produce positive clinical benefits may allow for the refinement of these programs to maximize their effectiveness.[6] Additionally, in certain instances, identifying the mechanisms of change may also shed light on the underlying progressive disruption in brain circuitry that accompanies the development of mental illnesses[7] as well as the factors that could potentially reduce or eliminate this disruption. Such work has the potential to address one of the key goals in modern psychiatry – shifting treatment from a model of palliative care to a model of preventative and/or curative treatment.[13]

Statistical methodology

We describe the statistical methodology used to test for mediation in the context of linear regression. However, it is important to note that the method recommended below can also be applied when using logistic or probit regression as well as structural equation modelling (SEM).[8,11,14,15] For a more thorough discussion, the reader is referred to MacKinnon.[11]

In their review of mediator variables in social psychology, Baron and Kenney[12] note that most social phenomena have multiple causes and, as such, single mediator models are likely an oversimplification of the mechanisms underlying these phenomena. A similar statement could be made with regard to psychiatric illnesses. As our knowledge of the etiological factors underlying these illnesses grows, we are becoming more aware of the multiple biopsychosocial processes that contribute to the development of psychiatric illnesses. Consequently, although we describe only the methodology to test single mediator models, we strongly encourage researchers to explore the possibility of multiple mediators in their research. For a description of the methodology used to test multiple mediator models, see MacKinnon[11] and Preacher and Hayes[16]

[1]We were first introduced to this quote by MacKinnon.[11]

As a general statistical practice, independent and mediator variables (as well as any covariates) should always be centred prior to completing the analyses described below. Centring involves 'shifting' the distribution of a variable to facilitate improved interpretability of the results of the subsequent analyses. For instance, continuous variables are often 'mean centred' by subtracting the mean score for the variable from each individual data point. This process shifts the mean of the newly centred variable to zero. The reader is directed to Kraemer and Blasey[17] for a more thorough discussion of centring data.

Although several tests for mediation are currently available,[18] recent evaluations suggest that tests which directly evaluate the indirect effect in a mediational model (path αβ in Fig. 1) outperform other methods with regard to both Type I and Type II error.[18,19] The logic underlying these tests is that if variable M mediates the relationship between the predictor variable and the outcome variable then both path α and β will not be zero and, consequently, the multiplicative product αβ will not be zero either.[20]

To calculate the indirect effect, one needs to complete two regression equations. First, an estimate of α is obtained by completing a regression analysis with the predictor variable as the independent variable and the mediator variable as the dependent variable. In this equation, α is the unstandardized regression coefficient for the predictor variable. Second, an estimate of β is obtained by completing a regression analysis with the mediator variable as the independent variable (with the predictor variable as a covariate) and the outcome variable as the dependent variable, where β is the unstandardized regression coefficient for the mediator variable. The indirect effect (αβ) is then calculated by multiplying these two regression coefficients:

Recent reviews advocate the use of asymmetric confidence intervals in evaluating the statistical significance of the indirect effect.[11,20,21] Consequently, these tests of mediation are often referred to as 'distribution of the product strategies' as they evaluate the estimated range of possible values of the multiplicative product αβ. Two equally effective strategies are currently available to calculate these confidence intervals.[21] First, MacKinnon and colleagues[21] have developed a Fortran program called PRODCLIN, which calculates asymmetric confidence intervals for the indirect effect. Values for the asymmetric confidence intervals can also be obtained using bootstrap methodology using macros developed by Preacher and Hayes.[22]

Effect size and tests of mediation

In addition to evaluating the statistical significance of a mediational relationship, researchers may be interested in exploring the 'practical significance' or 'clinical importance' of their findings.[23] Evaluation of the effect size of the mediational relationship (i.e. a measure of the magnitude of the effect) is one strategy through which researchers may accomplish this goal. Several effect size measures have been proposed for evaluating the magnitude of the indirect effect in mediational analyses. For example, one of the most commonly used effect size indices is the percentage of the relationship between the predictor variable and the outcome variable that is accounted for by the indirect effect (P_M). This can be calculated using the following formula[24]:

$$P_M = (\alpha\beta)/\tau \quad (1)$$

Unfortunately, this measure is problematic in that it is unstable in samples less than 500 and, as noted by Preacher and Hayes,[20] is not a proper proportion 'as it is not necessarily bounded by 0 and 1' (p. 37).

More recently, Fairchild and colleagues[23] have proposed an R^2 effect size measure for the mediated effect (R^2_{med}). This value indicates the amount of the variance in the outcome variable that is attributable to the indirect effect and is calculated as:

$$R^2_{med} = r^2_{MY} - (R^2_{Y,MX} - r^2_{XY}) \quad (2)$$

where r^2_{MY} is the squared correlation between the mediator and outcome variable, $R^2_{Y,MX}$ is the overall R^2 obtained from a linear regression model in which the predictor and moderator variables are both entered as predictors of the outcome variable, and r^2_{XY} is the squared correlation between the predictor variable and outcome variable.

Unfortunately, R^2_{med} is unstable in samples less than 100 and may not be appropriate to use outside of the context of linear regression.[23]

Mediation and causality

Of note, care must be taken in inferring causality and directionality in mediational relationships.[25,26] For instance, the statistical procedures used to test for the existence of a mediator variable are the same procedures that would be used to test for proxy risk factors – a relationship in which hypotheses with regard to causality and directionality in the interrelationships between the variables differ from mediational relationships.[27] A proxy risk factor is a variable which appears to be a risk factor for a specific outcome only because this variable is strongly correlated with a true risk factor for the outcome and not because this variable actually influences the outcome variable.[25] This relationship is shown in Fig. 1 alongside a mediator model. *A priori* theoretical evidence, longitudinal evaluation of the direction of the relationship between the predictor variable and mediator variable, and follow-up experimental studies can provide a researcher with stronger evidence with regard to the assumed directionality and causality in mediational analyses.[25,26]

Statistical power

Kraemer and colleagues[6] have suggested that decisions with regard to the completion of mediational analyses should ideally be made *a priori* during the design of a clinical trial. In such situations, researchers will ultimately be concerned with how many subjects will need to be included in their study to maintain sufficient statistical power. To assist in this endeavour, Fritz and MacKinnon[19] have produced a table which lists the number of subjects that would be required to maintain a statistical power of 0.80 for a mediational analysis using various tests of mediation at varying levels of effect size for the α and β paths. For instance, in a situation in which both the α and β paths were each of a medium effect size

(using Cohen's[28] definition) and the researcher planned to use the PRODCLIN program developed by MacKinnon and colleagues[21] to test for mediation, 74 subjects would be required to achieve a power of 0.80.

Of note, given our relatively limited (but growing) knowledge of mental illnesses,[29] it would be presumptuous to assume that researchers will always possess *a priori* hypotheses with regard to mediator variables when designing studies. As such, *post hoc* identification and testing of these variables may be a necessary and valuable component of the research enterprise and should not be viewed disparagingly as 'data-dredging' or 'fishing expeditions'.[6] More specifically, these analyses have the potential to generate new and valuable hypotheses that may provide insight into the etiology of mental illness as well as how best to treat these devastating illnesses.[6,25] Consequently, we recommend as a general practice that all early intervention studies recruit sufficient subjects so as to possess sufficient statistical power to test mediational hypotheses even if such hypotheses are not known prior to the start of the study. At the same time, when testing several mediational models, researchers should consider the use of multiple comparison procedures (e.g. correcting for false discovery rate[30]) to reduce the likelihood of incorrectly concluding that there is a statistically significant mediational relationship in situations in which there is not.

Moderator variables

> If we want to know how well we are doing in the biological, psychological, and social sciences, an index that will serve us well is how far we have advanced in our understanding of the moderator variables of our field.
>
> –Hall and Rosenthal, 1991, p. 447[31]

Definition and application to early intervention research

In their seminal article on mediation and moderation, Baron and Kenny[12] define a moderator as 'a qualitative (e.g. sex, race, class) or quantitative (e.g. level of reward) variable that affects the direction and/or strength of the relation between an independent variable and a dependent or criterion variable' (p. 1174). Thus, unlike mediator variables, moderators do not *account* for the relationship between a predictor variable and an outcome variable; rather moderators *influence the nature* of the relationship between the predictor variable and the outcome variable. In statistical terms, such a relationship is often referred to as an 'interaction'. There is also a key temporal difference between mediator and moderator variables. Specifically, whereas changes in or exposure to the mediator variables must temporally follow changes in or exposure to the predictor variable, levels of a moderators variable must be present prior to or at the same time as changes in or exposure to the predictor variable[6,25] (see footnote 2). A moderator relationship is displayed visually in Fig. 2.

[2]There is also a temporal difference between a mediator variable and the previously described proxy risk factor. As noted, changes in or exposure to a mediator variable must temporally follow changes in or exposure to the predictor variable. On the other hand, a change in or exposure to proxy risk factor can either temporally proceed or occur simultaneously with changes in or exposure to a true risk factor.

With regard to early intervention research (and treatment research in general), a greater understanding of moderator variables will help to answer what Paul has identified as the fundamental question for treatment research: '**What** treatment, by **whom**, is most effective for **this** individual with **that** specific problem, and under **which** set of circumstances' (p. 111).[32] For instance, in psychiatric care, clinicians are often faced with the challenge of determining which of the many validated psychosocial and pharmacological interventions to prescribe to a specific client.[33] As evidence in support of these interventions comes from aggregate data obtained from heterogeneous populations, there is limited information to guide decisions with regard to what treatment(s) to prescribe to a specific client who possesses a unique set of strengths and weaknesses as well as a specific constellation of symptoms. Clarifying the moderating variables that influence the magnitude or direction of the effect of a specific therapeutic intervention may help to facilitate the development of guidelines with regard to personalized treatment programs for individuals early in the course of a psychiatric illness – as well as all individuals with a mental illness in general.[6,7,29]

Statistical methodology

We will describe the statistical methodology for testing for moderator variables in both multiple linear and logistic regression. A more thorough discussion of these topics can be found elsewhere,[34,35] including strategies to test for moderator variables in the context of ANOVA[36] and SEM[37]. Of note, multiple factors may influence the relationship between a predictor variable and outcome variable – in fact this may be the norm in psychiatry where various outcomes are often influenced by multiple biopsychosocial factors. Below, we described situations in which there is only one moderator variable but direct the reader to Cohen *et al*.[34] and Preacher *et al*.[38] for a discussion of testing models with multiple moderating variables

As noted earlier, continuous predictor and moderator variables (as well as any covariates) should be centred prior to completing the analyses. However, in certain situations, it may be more appropriate to code categorical predictor variables and moderator variables using other strategies (e.g. dummy coding, weighted means) depending on the specific question that the researcher is interested in testing. Cohen and colleagues[28] review the specific situations in which different coding systems for categorical predictor and moderator variables should be used.

Testing for a moderational relationship involves two steps. First, the researcher tests for the existence of a statistically significant interaction between the predictor variable and moderator variable with regard to the outcome variable. Second, if there is evidence that such a statistically significant interaction is present, *post hoc* probing of the interaction is completed to clarify the nature of how the moderator variable influences the relationship between the predictor variable and outcome variable[15,39] (e.g. to specify the type – enhancing/buffering/antagonistic – of moderated relationship that is present).

Step 1: testing for a statistically significant interaction

In Step 1, the researcher calculates two regression equations, using linear regression when the dependent variable is continuous or logistic regression when the dependent variable is

categorical. In the first regression equation, the predictor variable and moderator variable are entered as independent variables in a regression equation (along with any covariates) with the outcome variable as the dependent variable. This produces the regression equation:

$$\hat{Y}=B_0+B_1P+B_2M+\sum(B_iC_i) \quad (3)$$

In this equation, B_0 is the regression coefficient for the constant term, B_1 is the regression coefficient for the predictor variable (*P*), B_2 is the regression coefficient for the moderator variable (M), and $\Sigma(B_iC_i)$ represents the regression coefficients (*B*) and variable value (*C*) for any covariates included in the regression equation. The regression coefficients for the predictor variable and moderator variable can be interpreted as the effect of the predictor variable or moderator variable on the outcome variable when the other variable (i.e. predictor or moderator) is zero.[39] If the variables were mean centred prior to completing the analyses, these regression coefficient can be interpreted as the effect of the predictor variable or moderator variable on the outcome variable when the other variable (i.e. predictor or moderator) is at its mean value.[17] (see Footnote 3 for a description of $\hat{Y}$ in this equation).

It is important to note that the regression coefficients of the predictor variable and moderator variable in Equation 3 are not equivalent to main effects in ANOVA (i.e. the effect of an independent variable on the dependent variable). Rather, these values are more accurately described as 'conditional effects' (i.e. the effect of one independent variable on the dependent variable after partialing out the effect of the other independent variable on the dependent variable).

In the second regression equation, the interaction term (i.e. multiplicative product) of the predictor variable and moderator variable is entered as a variable in the regression equation along with the predictor variable, moderator variable and any covariates. This produces the regression equation

$$\hat{Y}=B_0+B_1P+B_2M+B_3(P*M)+\sum(B_iC_i) \quad (4)$$

In this equation, B_3 is the regression coefficient for the interaction term (*P***M*). If the interaction term is a statistically significant predictor of the outcome variable, there is

[3]Of note, in linear regression, $\hat{Y}$ is the predicted value of the outcome variable, whereas in logistic regression $\hat{Y}$ is the log(odds) of the outcome of interest where:

$$\log(odds)=\ln\left(\frac{prob_{Y*}}{1-prob_{Y*}}\right)$$

In this equation, $prob_{Y*}$ is the probability of the outcome of interest. For example, in a study testing factors that predict the occurrence of hospitalization in which hospitalization is coded as a two-level dummy variable (0 = no hospitalization and 1 = hospitalization), the probability of the outcome of interest is the probability that a hospitalization will occur.

evidence suggesting that the moderator variable influences the relationships between the predictor variable and the outcome variable.

Step 2: *post hoc* probing of the interaction

If there is evidence suggesting that the moderator variable influences the relationship between the predictor and outcome variables (i.e. the regression coefficient for the interaction term in Equation 4 is statistically significant), the next step is to clarify the nature of the moderated relationship using *post hoc* probing.[15,34,39] We will review the two currently recommended strategies available for completing this *post hoc* probing: 'pick-a-point' and regions of significance.

'Pick-a-Point' approach

Ragosa[40] has referred to the first strategy to probe the nature of the moderated relationship as the 'pick-a-point' approach. In this approach, the researcher evaluates the nature of the moderational relationship by examining the relationship between the predictor and outcome variables at several values (i.e. points) of the moderator value. We will review the statistical methodology behind this approach in the context of linear regression (i.e. continuous dependent variable), but recommend the use of available statistical programs[38] and macros for SPSS and SAS[35] when completing these analyses.

Following the protocol outlined by Cohen and colleagues,[34] we first note that Equation 4 can be re-written as:

$$\hat{Y} = P(B_1 + B_3M) + (B_0 + B_2M + \sum(B_iC_i)) \quad (5)$$

Using Equation 5, one can graph the simple regression equation of the relationship between the predictor and outcome variables at a specific value of the moderator variable where (B_1 + B_3M) is the slope and (B_0 + B_2M + $\Sigma(B_iC_i)$) is the y-intercept of the simple regression equation. To complete these graphs, one calculates the value of the outcome variable ($\hat{Y}$) for two values of the predictor variable (P). Typically, the two values of P are $\bar{P} \pm \sigma_{\hat{P}}$, where $\bar{P}$ is the mean value of the predictor variable in the sample, and $\sigma_{\hat{P}}$ is the standard deviation of the predictor variable in the sample. The simple regression equation can be displayed by connecting these two points to form a straight line. This process is typically repeated for three different values of the moderator variable so as to produce three simple regression equations (i.e. three separate lines). Following the suggestion of Cohen and Cohen,[41] the values of the moderator variable that are typically used are $\bar{M} - \sigma_{\hat{M}}$ (low), $\bar{M}$ (mean) and $\bar{M} + \sigma_{\hat{M}}$ (high), where $\bar{M}$ is the mean value of the moderator variable in the sample and $\sigma_{\hat{M}}$ is the standard deviation of the moderator variable in the sample. The nature of the interaction can then be displayed by plotting these three simple regression equations.

Of note, in certain situations, one may wish to test the relationship between the predictor variable and outcome variable at different values of the predictor and/or moderator variable than described above. For instance, using an example described by Preacher,[42] if the predictor or moderator variable in a study were subjects' scores on the Beck Depression Inventory, it may be preferable to graph the simple regression equations using clinical cut-

off scores for depression or dysthymia as opposed to the values described above. Ultimately, one must consider what values of the predictor and moderator variables will provide the most useful information when evaluating the simple regression equations.

Next, one examines whether the respective slopes of the simple regression equations are significantly different from zero. As noted earlier, the slope of the simple regression equation is ($B_1 + B_3M$). Dividing the slope by its standard error produces a *t*-score with degrees of freedom equal to *n*-*k*-1 where n is the sample size and *k* is the number of predictors in the model.[34] If this *t*-score is determined to be statistically significant, one can conclude that the slope of the simple regression equation is significantly different from zero. The standard deviation for the slope at a specific value of the moderator variable (e.g. low, mean or high) is equal to[34]:

$$s_{slope_M} = \sqrt{\sigma^2_{B_{11}} + 2M\mathrm{cov}_{B_{13}} + M^2\sigma^2_{B_{33}}} \quad (6)$$

Where $\sigma^2_{B_{11}}$ is the variance of the regression coefficient B_1, M is the specific value of the moderator variable (e.g. low, mean or high) that was used in the calculation of the slope of the simple regression equation, cov_{B13} is the covariance between the regression coefficients B_1 and B_3, and $\sigma^2_{B_{33}}$ is the variance of the regression coefficient B_3.

Holmbeck[39] has proposed a slightly modified version of the 'pick-point strategy' for the situation in which the moderator is a two-level categorical variable. The key difference involves the calculation of the slope of the simple regression equations. This strategy draws on the fact that within multiple regression, regression coefficients are calculated for situations in which the other non-outcome parameters are equal to zero. For example, in a situation in which the moderator variable was gender of the study participant (male/female), one would calculate the regression equation outlined in Equation 6 two times. In the first regression equation, males would be coded as 0 and females would be coded as 1. As males were coded as 0 for gender, the regression coefficients for the predictor variable and interaction term obtained from this analysis would provide information with regard to slope of the simple regression equation for male subjects. In the second regression equation, females would be coded as 0 and males would be coded as −1. This second set of regression coefficients for the predictor variable and interaction term obtained from this analysis provides information with regard to slope of the simple regression equation for female subjects. The statistical significance of the slope of the simple regression equation for each gender can be evaluated using the same procedures as described above.

Regions of significance approach

Several scholars have criticized the 'pick-a-point' approach for failing to identify the specific value(s) of the moderator for which there is a statistically significant relationship between the predictor and outcome variables.[35,38,43] To address this concern, Bauer and Curran[43] have developed the test of 'regions of significance' which is an extension of the Johnson-Neyman technique[44] to multiple regression. The benefit of this test is that it identifies the specific value(s) of the moderator variable at which the relationship between

the predictor and outcome variable reaches criteria for statistical significance. A program[38] and macro for SPSS or SAS[35] to complete these analyses are currently available online.

Although it is inappropriate to use the regions of significance test in situations in which the moderator is a categorical variable, we believe that, in the absence of *a priori* hypotheses, the greater specificity provided by this approach relative to the 'pick-a-point' approach makes the test of regions of significance the best strategy to use when probing interactions with continuous mediator variables. However, in situations in which researchers possess *a priori* hypotheses with regard to specific values of the moderator variable at which the relationship between the predictor and outcome variables may change, it may be more appropriate to use the 'pick-a-point' strategy.

Effect size and tests of moderation

After identifying a statistically significant interaction, researchers may wish to evaluate the 'practical significance' of the interaction (i.e. moderating relationship). Although several effect size measures are available (e.g. squared semi-partial correlation for the interaction term in linear regression and odds ratio for the interaction term in logistic regression), oftentimes these measures are difficult to interpret from a clinical or policy perspective.

With regard to intervention studies, the 'number needed to treat' (NNT) statistic may provide an especially useful measure of how much the effect of an intervention is influenced by a moderator variable. NNT provides an estimate of the number of individuals that would need to receive a treatment to prevent the occurrence of one additional adverse event.[45] A smaller NNT is indicative of a more clinically effective intervention. To clarify the practical significance of a factor which moderates the effect of a specific intervention, one could calculate the NNT for the intervention at different levels of the moderator variable. For example, an investigator may discover that receipt of a specific intervention predicts reduced rates of hospitalization among individuals with first-episode psychosis and that gender moderates this relationship. More specifically, in this hypothetical situation, the clinical benefits of this intervention are found to be greater among women then men. Using NNT to clarify the practical significance of this finding, this scholar may discover that the NNT to prevent one hospitalization among men was 50, whereas among women the NNT is only 10.

Statistical power

Similar to mediator variables, decisions with regard to the incorporation of moderator variables in a study should ideally be made *a priori*.[6,29] Consequently, when designing a study, it may be important to plan to recruit sufficient subjects so as to possess adequate power to test moderator hypotheses. To complete these analyses, the researcher would calculate the number of subjects required to detect an interaction term of a specific effect size at a specific level of statistical power (typically 0.80) in a model in which both the predictor and moderator variables are included (as well as any covariates). Although generic effect sizes can be used in these calculations (e.g. Cohen's criteria for small, medium and large effect sizes[28]), ideally, one would use an effect size that translated to a specific and meaningful real world goal (e.g. using an effect size equivalent to a 20% increase in full time employment within a sample).

Of note, it may be unrealistic to assume that hypotheses with regard to moderator variables will always be known *a priori*. Consequently, we recommend that all early intervention studies recruit sufficient subjects so as to possess sufficient power to test moderational hypotheses even if such hypotheses are not known prior to the start of the study. At the same time, when testing several potential moderator variables, researchers should consider the use of multiple comparison procedures to reduce the likelihood of falsely rejecting the null hypothesis.

CONCLUSION

There is great potential for early intervention to positively influence the course of psychiatric illnesses and ultimately to force a paradigm shift in mental health care in which existing systems would shift from a model of palliative care to one of preventive medicine. However, demonstrations of the efficacy and effectiveness of early intervention alone are unlikely to be sufficient to usher in such a radical change in the delivery of mental health services. Rather, this paradigm shift will likely require the development of a more comprehensive knowledge base in which the mechanisms underlying both psychiatric disorders and their treatments are clarified and guidelines for the personalized, case by case, deployment of psychiatric interventions are available. In this regard, greater attention to mediator and moderator variables within the field of early intervention in psychiatry may be a critical step in promoting the advancement of the field.

Acknowledgments

We would like to thank Steven R. López for his helpful comments with regard to this manuscript. Funding for this research was provided by State of Connecticut, Department of Mental Health and Addiction Services as well as by a grant from the Patrick and Catherine Weldon Donaghue Medical Research Foundation.

References

1. Christodoulou GN, Christodoulou NG. Early intervention in psychiatry. Early Interv Psychiatry. 2007; 1:7–8. [PubMed: 21352103]
2. Mensah GA, Dietz WH, Harris VB, et al. Prevention and control of coronary heart disease and stroke – nomenclature for prevention approaches in public health. A statement for public health practice from the Centers for Disease Control and Prevention. Am J Prev Med. 2005; 29:152–7. [PubMed: 16389142]
3. McGorry P. Welcome to Early Intervention in Psychiatry. Early Interv Psychiatry. 2007; 1:1–2. [PubMed: 21352100]
4. Guralnick MJ. Second generation research on the effectiveness of early intervention. Early Educ Dev. 1993; 4:366–78.
5. Hinshaw SP. Moderators and mediators of treatment outcome for youth with ADHD: understanding for whom and how interventions work. J Pediatr Psychol. 2007; 32:664–75. [PubMed: 17264086]
6. Kraemer HC, Wilson T, Fairburn CG, Agras WS. Mediators and moderators of treatment effects in randomized clinical trials. Arch Gen Psychiatry. 2002; 59:877–83. [PubMed: 12365874]
7. Insell TR. Translating scientific opportunity into public health impact: a strategic plan for research on mental illness. Arch Gen Psychiatry. 2009; 66:128–33. [PubMed: 19188534]
8. Hopwood CJ. Moderation and mediation in structural equation modeling: applications for early intervention research. J Early Interv. 2007; 29:262–72.
9. Frazier PA, Tix AP, Barron KE. Testing moderator and mediator effects in counseling psychology research. J Couns Psychol. 2004; 51:115–34.

10. Rosenberg, M. The Logic of Survey Analysis. New York: Basic Books; 1968.
11. MacKinnon, DP. Introduction to Statistical Mediation Analysis. New York: Lawrence Erlbaum; 2008.
12. Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. J Pers Soc Psychol. 1986; 51 :1173–82. [PubMed: 3806354]
13. Insell TR. The arrival of preemptive psychiatry. Early Interv Psychiatry. 2007; 1:5–6. [PubMed: 21352102]
14. MacKinnon DP, Lockwood CM, Brown CH, Wang W, Hoffman JM. The intermediate endpoint in logistic and probit regression. Clin Trials. 2007; 4:499–513. [PubMed: 17942466]
15. Holmbeck GN. Toward terminological, conceptual, and statistical clarity in the study of mediators and moderators: examples from the child-clinical and pediatric psychology literatures. J Consult Clin Psychol. 1997; 65:599–610. [PubMed: 9256561]
16. Preacher KJ, Hayes AF. Asymptotic and resampling strategies for assessing and comparing indirect effects in multiple mediator models. Behav Res Methods. 2008; 40:879–91. [PubMed: 18697684]
17. Kraemer HC, Blasey CM. Centring in regression analyses: a strategy to prevent erros in statistical inference. Int J Methods Psychiatr Res. 2004; 13:141–51. [PubMed: 15297898]
18. MacKinnon DP, Lockwood CM, Hoffman JM, West SG, Sheets V. A comparison of methods to test mediation and other intervening variable effects. Psychol Methods. 2002; 7:83–104. [PubMed: 11928892]
19. Fritz MS, MacKinnon DP. Required sample size to detect the mediated effect. Psychol Sci. 2007; 18:233–9. [PubMed: 17444920]
20. Preacher, KJ.; Hayes, AF. Contemporary approaches to assessing mediation in communication research. In: Snyder, LB., editor. The Sage Sourcebook of Advanced Data Analysis Methods for Communication Research. Thousand Oaks, CA: Sage; 2008. p. 13-54.
21. MacKinnon DP, Fritz MS, Williams J, Lockwood CM. Distribution of the product confidence limits for the indirect effect: program PRODCLIN. Behav Res Methods. 2007; 39:384–9. [PubMed: 17958149]
22. Preacher KJ, Hayes AF. SPSS and SAS procedures for estimating indirect effects in simple mediation models. Behav Res Methods Instrum Comput. 2004; 36:717–31. [PubMed: 15641418]
23. Fairchild AJ, MacKinnon DP, Taborga MP, Taylor AB. R^2 effect-size measures for mediation analysis. Behav Res Methods. 2009; 41:486–98. [PubMed: 19363189]
24. MacKinnon DP, Dwyer JH. Estimating mediated effects in prevention studies. Eval Rev. 1993; 17:144–58.
25. Kraemer HC, Stice E, Kazdin A, Offord D, Kupfer D. How do risk factors work together? Mediators, moderators, and independent, overlapping, and proxy risk factors. Am J Psychiatry. 2001; 158:848–56. [PubMed: 11384888]
26. Shrout PE, Bolger N. Mediation in experimental and nonexperimental studies: new procedures and recommendations. Psychol Methods. 2002; 7:422–45. [PubMed: 12530702]
27. MacKinnon DP, Krull JL, Lockwood CM. Equivalence of the mediation, confounding and suppression effect. Prev Sci. 2000; 1:173–81. [PubMed: 11523746]
28. Cohen, J. Statistical Power Analysis for the Behavioral Sciences. Hillsdale, NJ: Lawrence Erlbaum; 1988.
29. Kraemer HC, Frank E, Kupfer DJ. Moderators of treatment outcomes: clinical, research, and policy importance. JAMA. 2006; 296:1286–9. [PubMed: 16968853]
30. Benjamini Y, Hochberg Y. Controlling the false dicovery rates: a practical and powerful approach to multiple testing. J R Stat Soc B. 1995; 57:289–300.
31. Hall JA, Rosenthal R. Testing for moderator variables in meta-analysis issues and methods. Commun Monogr. 1991; 58:437–48.
32. Paul GL. Strategy of outcome research in psychotherapy. J Consult Psychol. 1967; 31:109–18. [PubMed: 5342732]
33. Insell TR. Beyond efficacy: the STAR*D trial. Am J Psychiatry. 2006; 1631:5–7.

34. Cohen, J.; Cohen, P.; West, SG.; Aiken, LS. Applied Multiple Regression/Correlation Analysis for the Behavioral Sciences. 3. Mahwah, NJ: Lawrence Erlbaum; 2003.

35. Hayes AF, Matthes J. Computational procedures for probing interactions in OLS and logistic regression: SPSS and SAS implementations. Behav Res Methods. 2009; 41:924–36. [PubMed: 19587209]

36. Jaccard, J. Interaction Effects in Factoral Analysis of Variance. Thousand Oaks, CA: Sage; 1997.

37. Jaccard, J.; Wan, CK. LISERL Approaches to Interaction Effects in Multiple Regression. Thousand Oaks, CA: Sage; 1996.

38. Preacher KJ, Curran PJ, Bauer DJ. Computational tools for probing interaction effects in multiple linear regression, multilevel modeling, and latent curve analysis. J Educ Behav Stat. 2006; 31:437–48.

39. Holmbeck GN. Post-hoc probing of significant moderational and mediational effects in studies of pediatric populations. J Pediatr Psychol. 2002; 27:87–96. [PubMed: 11726683]

40. Ragosa D. Comparing nonparallel regression lines. Psychol Bull. 1980; 88:307–21.

41. Cohen, J.; Cohen, P. Applied Multiple Regression/Correlation Analysis for the Behavioral Sciences. Hillsdale, NJ: Lawrence Erlbaum; 1983.

42. Preacher, KJ. A Primer on Interaction Effects in Multiple Linear Regression. [Updated August 10, 2006; cited June 1, 2009.] Available from URL: http://people.ku.edu/~preacher/interact/interactions.htm

43. Bauer DJ, Curran PJ. Probing interactions in fixed and multilevel regression: inferential and graphical techniques. Multivariate Behav Res. 2005; 40:373–400.

44. Johnson PO, Fay LC. The Johnson-Neyman technique, its theory and application. Psychometrika. 1950; 15:349–67. [PubMed: 14797902]

45. Laupacis A, Sackett DL, Roberts RS. An assessment of clinically useful measures of the consequence of treatment. N Engl J Med. 1988; 318:1728–33. [PubMed: 3374545]

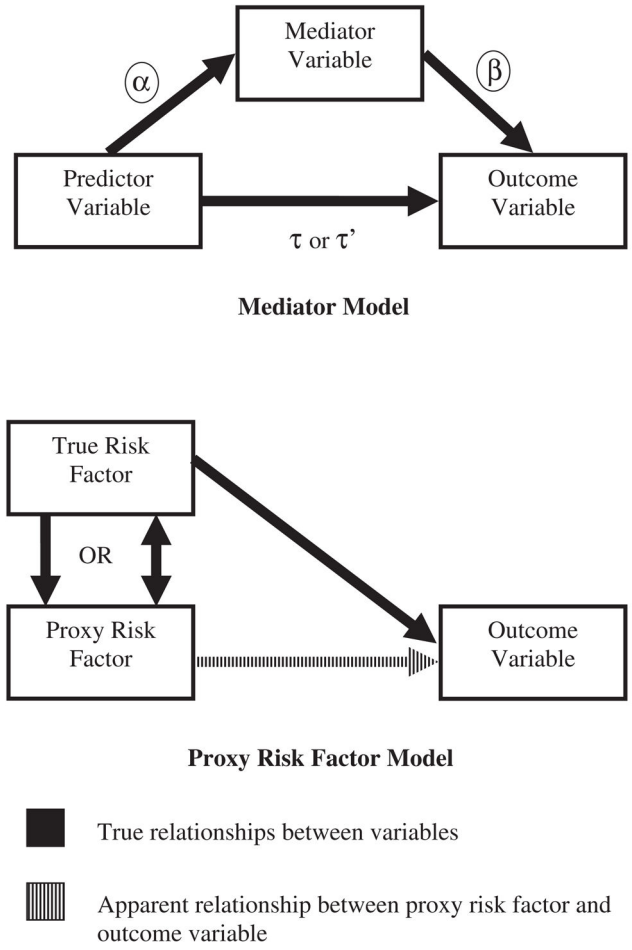

FIGURE 1.
Mediator model and proxy risk factor.

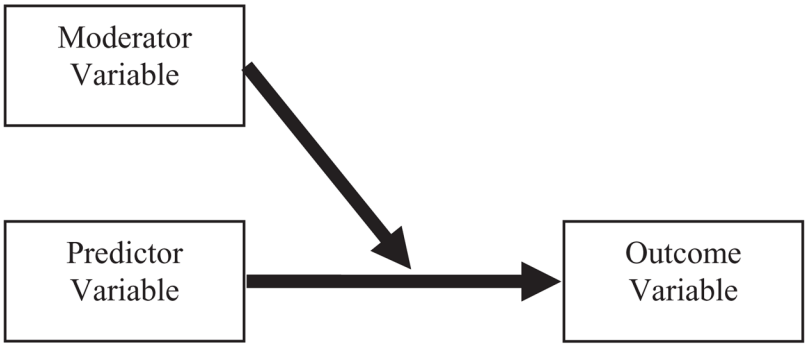

FIGURE 2.
Moderator model.