

## How Do Risk Factors Work Together? Mediators, Moderators, and Independent, Overlapping, and Proxy Risk Factors

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**Objective:** The authors developed a methodological basis for investigating how risk factors work together. Better methods are needed for understanding the etiology of disorders, such as psychiatric syndromes, that presumably are the result of complex causal chains.

**Method:** Approaches from psychology, epidemiology, clinical trials, and basic sciences were synthesized.

**Results:** The authors define conceptually and operationally five different clinically important ways in which two risk factors may work together to influence an outcome: as proxy, overlapping, and inde-

pendent risk factors and as mediators and moderators.

**Conclusions:** Classifying putative risk factors into these qualitatively different types can help identify high-risk individuals in need of preventive interventions and can help inform the content of such interventions. These methods may also help bridge the gaps between theory, the basic and clinical sciences, and clinical and policy applications and thus aid the search for early diagnoses and for highly effective preventive and treatment interventions.

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The disorders of greatest medical, research, and policy concern today, particularly in psychiatry, are likely to be complex. Such disorders may have not a single cause but a causal chain, or multiple such causal chains. These chains may involve genetic, environmental, social, and biological risk factors. The effect of no one of these risk factors can be fully understood except in the context of all the others. Yet insufficient attention has been devoted to helping both the clinical researcher and the clinician with the appropriate methodological tools to provide this information. Whether the emphasis is placed on the decision-making process of intervention or on research questions such as the role of genetics or imaging in predicting the development of disorder, an understanding of how risk factors work together is crucial.

Thus, important as the study of individual risk factors is, such studies only initiate the process of fully elucidating the causes of most disorders. Accumulating risk factors and either counting or scoring them does little to increase the understanding of etiologic processes or of how interventions might be optimally timed, constructed, or delivered to prevent or treat psychiatric conditions. Costly and time-consuming randomized clinical trials that manipulate risk factors often produce disappointing results. Time and energy are wasted on fruitless and often misleading arguments about “nature” versus “nurture” risk factors. Medical journals and the public media frequently feature reports of the finding of new risk factors, reports that often conflict with each other—confusing clinicians, the lay

public, policy makers, and researchers and promising medical advances that frequently do not materialize.

Much of this confusion results from the imprecision with which technical terms have come to be used in risk research (1, 2). These terms include “risk” (the probability of an outcome), “correlate” (a measure somehow associated with the outcome), “risk factor” (a correlate shown to precede the outcome), and “causal risk factor” (a risk factor that, when changed, is shown to change the outcome). Because so many factors are evaluated in cross-sectional studies (3), requiring terminological precision in research discussion (1, 2, 4) would lead to the setting aside of many factors that are correlates, signs and symptoms, concomitants, or even consequences of a disorder but that are not risk factors and certainly not causal risk factors. Nevertheless, there would still likely be a multitude of risk factors left for any disorder, playing very different roles in the etiologies of different disorders.

Some of these roles, specifically those of mediators (intermediate variables) or moderators (effect modifiers), have already been considered in psychology (5–9) and in epidemiology (10, 11). There is a proliferation of terminology, often not defined in a way that can be operationalized, and an assumption of knowledge typically not available (e.g., of causal relationships). Finally, both outcome and predictors are often assumed to have properties (e.g., those of a multivariate normal distribution) that seldom apply in risk factor research. While these discussions are

incomplete, they form the conceptual basis of the present discussion.

To give some flavor of the problem, consider the following. An “intermediate factor,” defined as synonymous with “contingent variable,” “intervening [causal] variable,” and “mediator variable,” is “a variable that occurs in a *causal* pathway from an independent to a dependent variable. It *causes* variation in the dependent variable, and itself is *caused* to vary by the independent variable” (11, p. 87, emphasis added). Even though this definition indicates that a mediator occurs after that which it mediates and before the outcome, in epidemiology these are frequently assessed in cross-sectional studies where temporal patterns cannot be documented. Then a “confounder” is defined as “a variable that can *cause* or *prevent* the outcome of interest, is not an intermediate variable, and is associated with the factor under investigation” (11, p. 35, emphasis added). Clearly, knowledge of causal associations is necessary to implement both these definitions. Moreover, a variable may be labeled in one study as a confounder and in another study of the same outcome in the same population as a moderator or mediator, depending on which factor is the focus of each investigation. Finally, an “effect modifier,” synonymous with “moderator” (11, p. 52), “refers to variation in the magnitude of a measure of exposure effect across levels of another variable” (10, p. 254). Since a mediator, as defined in the preceding, should also produce such variation, the difference between a mediator and a moderator is ambiguous.

In this report we first focus on the simplest possible case, where A and B are two binary measures (presence/absence of some trait or event) both already demonstrated to be risk factors for the binary outcome (O). Integrating approaches from psychology, epidemiology, clinical trials, and the basic sciences, we synthesize an approach specifically designed for the risk research context. We will define and differentiate five different and clinically important ways in which two risk factors may work together to influence an outcome: as mediating, moderating, independent, overlapping, and proxy risk factors. Then, for observational risk studies, we extend this approach beyond that of two binary risk factors. While the same principles hold for seeking moderators and mediators of treatments in a randomized clinical trial, we will leave the full discussion of the implementation of these principles in randomized clinical trials for a future report. Finally, we will then focus on extending this approach beyond that of two binary risk factors for observational risk studies.

Such issues relate to all of the literature on risk factors but are particularly of interest in psychiatry. The issues discussed here bear on why it is so difficult to establish a genetic basis for psychiatric disorders; why, when linked genes are found, it is so difficult to replicate or confirm the results; why, even when genetic results are replicated, progress in using this information to prevent the disorder is so slow. The same problems occur with identifying en-

**TABLE 1. Three Linear Models Applied to the Same Population With Binary Risk Factors A and B for Binary Outcome O, With the Interaction Term for Each Model<sup>a</sup>**

Variable	Equation for Linear Model	Probability of Outcome O (p) in Each Subgroup		
		Linear Model: p	Logistic Model: ln [p/(1-p)]	Log Linear Model: ln p
Presence of A, B (1=present, 0=absent)				
1, 1	$\mu+\alpha+\beta+\gamma$	0.40	-0.405	-0.916
1, 0	$\mu+\alpha$	0.30	-0.847	-1.204
0, 1	$\mu+\beta$	0.20	-0.223	-1.609
0, 0	$\mu$	0.10	-2.197	-2.303
Interaction effect		0.00	-1.532	-0.406

<sup>a</sup> Use of risk difference as an effect size is associated with the linear approach, the odds ratio is associated with the logistic model, and the risk ratio is associated with the log linear model.

vironmental, social, or other biological causes of psychiatric disorders. Finally, the issues also bear on why so many treatments of psychiatric disorders have circumscribed effects.

## Rethinking Standard Approaches

There are precursors in the current research literature to all five ways we propose that risk factors can work together: proxy, overlapping, independent, mediating, and moderating. There are, however, inconsistencies and ambiguities with all of these precursors.

First, there is a long history of philosophical and scientific debate about what “cause” means and how to demonstrate that “A causes O” (12–18). All minimally require demonstration that A is a risk factor for O, i.e., all causal factors are risk factors, but many risk factors are not causal. Empirical demonstration of causality (e.g., by a randomized clinical trial) is usually costly and thus typically a late step in the risk research process, appropriate when more easily accessible information forms a strong case for a hypothesized causal process. As our focus is on forming that strong case, operational definitions that require prior demonstrations of causal relationships, often seen in the psychology and epidemiology literature, will not be used here.

Then, what we here call “working together” is often termed “interaction.” However, we mean something broader than statistical interaction, which is defined narrowly as nonadditivity of the effects of A and B on outcome O in a particular linear model. Consider the hypothetical population and the two risk factors A and B for outcome O described in Table 1. In this case, if one applied a linear model to the probabilities (in which the measure of association is a risk difference), there would be zero statistical interaction, but in a logistic model (measure of association: odds ratio) or log linear model (measure of association: risk ratio) there would be nonzero statistical interaction. Yet whatever is happening to the subjects in the population has not changed. Only the model has changed,

**TABLE 2. Illustration of the Effect of Measurement Error When A and B Are Two Different Measurements of the Same Construct Used as Risk Factors for Outcome O<sup>a</sup>**

Presence of A, B (1=present, 0=absent)	True Prevalence (%)	True Risk (%)	Observed Prevalence (%)	Observed Risk (%)
1, 1	20	100	18	98
1, 0	0		4	20
0, 1	0		10	20
0, 0	80	0	68	0
Total population	100	20	100	20

<sup>a</sup> For A, sensitivity=90%, specificity=95%, kappa=0.67. For B, sensitivity=95%, specificity=90%, kappa=0.59.

and each of these linear models fits the data perfectly. In short, statistical interaction is a property of which linear model the researcher selects, not a property of the population, risk factors, or outcome. “Working together” to produce an outcome may or may not produce a statistical interaction in a particular linear model. Thus, when we talk about “working together,” we intend the term to reflect how the risk factors are affecting the subjects.

In psychology, the most common operational definitions of “mediation” and “moderation” (5) are based on such linear models. For example, it is suggested that one first fit a linear regression of the outcome variable while using A and B as independent variables, then fit the same linear regression model while using only A as the independent variable. If the regression coefficient of A in the first model differs from that in the second model, then B is said to mediate A. Since the absence of any A×B statistical interaction is here assumed, that definition can only be applied with the linear model in Table 1. But then it can be shown that with this definition, B will mediate A only if A and B are uncorrelated (noncollinear) in the population. In that case, A mediates B as well. This is certainly not in accord with the *conceptual* definition of “mediation,” but it is the necessary result of the preceding *operational* definition.

The conceptual definition of “B mediates A” in both psychology (5) and epidemiology (10, 11) suggests that B explains how and why A works to produce O. If so, logically A must temporally precede B in order that B mediate A. The very term “mediator” (or “intermediate variable”) suggests that the mediator stands between that which it mediates and the outcome. The ambiguity of the directionality of mediation is immediately remedied if demonstration of temporal precedence is required.

To make matters more complex, to demonstrate that A moderates B, the operational approach suggested in the literature (5, 10) is to fit a linear regression, as in the preceding, but now with A, B, and the A×B interaction as independent variables. Then A is said to moderate B if there is nonzero interaction. In Table 1, if one fits the linear model, A does not moderate B, but if one fits either other model, A does moderate B (and, again, B moderates A).

In the psychology literature, a distinction is often made between the situation in which A directly influences B (in

which case, mediation is claimed) and that in which A influences the association between B and O (in which case, moderation is claimed). However, if A is a risk factor for B, there can be no indication from statistical analysis alone of exactly how A influences B. The only situation in which it can be clear that A influences the association between B and O, without influencing B itself, is when A precedes B but is not correlated with B. This brings us one step closer to the goal of this report: to suggest how to differentiate clearly and unambiguously between a moderator and mediator. In what follows, the correlation between A and B, as well as temporal precedence, become important considerations in clarifying how risk factors work together.

Furthermore, the preceding situation is even more confused by misinterpretation of statistical hypothesis testing (19–25). For example, instead of defining mediation as some property of the population (e.g., by a population effect size, such as the regression coefficients referred to earlier, or a potency measure), some define it by the p value of a statistical test relating to some null hypothesis concerning that population property. Then, since the p value is a statistic that depends on sample size and other design decisions that affect power, as well as the effect of interest, any low-powered study is likely to show that there is no mediation, and a higher-powered study is likely to show that there is mediation. If the p value defines the relationship, both these contradictory conclusions would be technically correct. When the definition is population based, it should be clear that a nonsignificant result does not prove the null hypothesis, for it may reflect either small effect size or inadequate power. The effect size that is statistically significant should be further checked for clinical or policy significance.

Finally, few measurements of risk factors or outcomes have perfect reliability (R.H. Hoyle and D.A. Kenny, unpublished paper, 1998). Underlying each observed and measured risk factor is some usually unknown latent construct. Yet the relationship one sees between the observed risk factor and the outcome depends both on the association between the latent construct and the outcome and on the errors in their measurement.

Consider Table 2. This involves a hypothetical population in which there is only one binary latent construct, measured independently by both A and B with different sensitivities and specificities (e.g., depression as indicated by the Hamilton and Beck scales). The observed prevalence of the risk factors and the observed risk of outcome in each risk factor group do not correspond to their true values. This is a phenomenon long known in epidemiology (26–32). Some prevalences are biased upward, some downward; the bias is totally determined by the balance between the sensitivities and specificities of A and B. This is not a problem resolved by getting larger samples, for larger samples only provide more precise estimators of the wrong parameters. Any definition of types of relations between risk factors and outcome should be based on pa-

rameters relatively robust to the effects of misclassification: here precedence, correlation, and potency.

## Conceptual Bases of a New Risk Factor Approach

The basic idea here is to envision what underlying processes relating the latent risk factors are of interest in the population, then to identify specific relationships between risk factors that would be observed in the data were those underlying processes actually going on. For reasons already indicated, the three features on which we focus are temporal precedence (of A and B, which comes first?), correlation (are A and B correlated?), and dominance.

The question of dominance in risk research is this: If one could use A and/or B to predict O, which decision would yield the greatest potency: A alone, B alone, or one of the two combinations of A and B? If the maximal potency among these four rules is achieved by using A alone, we will say that A dominates B. If maximal potency is achieved by using B alone, then B dominates A. Finally, if maximal potency is achieved by using A and B simultaneously (either "A and B" or "A or B" defining the high-risk group), then A and B codominate. For example, in Table 2, if the potency measure selected (4) were Cohen's kappa (percentage of agreement corrected for chance), if one used only A, kappa would be 81.9%; if one used only B, kappa would be 75.1%. If one used A or B (i.e., a person would be at high risk if she or he had a value of 1 for either A or B), kappa would be 89.2%. If one used A and B (i.e., a person would be high risk if she or he had a value of 1 for both A and B), kappa would be 69.9%. Thus, in this case, A and B codominate since the highest value of kappa would be achieved by requiring both A and B connected here by an "or" rule.

We assume that A and B are established risk factors for O in a population. The design of the study in which A, B, and O are measured must assure the independence of their errors of measurement (i.e., objective or blinded assessment of A, B, and O). This is necessary in order that correlations between the observed variables can be interpreted as indicating correlation between the latent constructs they measure, rather than the expectations or biases of the observers.

## Proposed Definitions

Now, using these principles, let us define and discuss the five proposed ways risk factors can work together.

### *B Is a Proxy Risk Factor for A*

Any correlate of a strong risk factor may also appear to be a risk factor for the same outcome, even though the only connection between that correlate and the outcome lies in the strong risk factor correlated with both. Any small component of a strong global causal factor may itself be a risk factor. A global factor, only one component of which is a causal factor, may itself be a risk factor. A correlation of this type has been called a "pseudocorrelation."

We propose to call a risk factor of this type a "proxy risk factor." In this case, B is a proxy risk factor for A for the outcome O if A and B are correlated, if there is no temporal precedence of either A or B or if A precedes B, and if, in either case, A dominates.

Inadequate parenting has been shown to be a risk factor for attention deficit hyperactivity disorder (ADHD). Any component of inadequate parenting (e.g., parental physical abuse) is likely to be a risk factor for ADHD as well. A risk factor that is a small part or an indicator of a more global risk factor is likely to be a proxy risk factor for the global risk factor. When there are multiple risk factors, all proxy risk factors for one global risk factor, they should be *aggregated* to gain clearer understanding of what the causal processes might be.

Conversely, if inadequate access to health and educational resources, and not parental education, income, occupational status, or any other component of socioeconomic status, were the causal factor for ADHD, socioeconomic status would be a proxy risk factor for that access for ADHD. In many cases, *disaggregation* of a complex global measure such as socioeconomic status would be important in improving our understanding of the causal process and, thus, informing the development of effective preventive measures.

In fact, prospective, longitudinal studies (33, 34) have shown that socioeconomic status relates to later psychiatric dysfunction in children. Breakdown of the variable has shown that low parental educational attainment, family dysfunction, harsh child-rearing practices, limited parental warmth, single-parent family status, peer group instability (moving the child to multiple child care facilities), and exposure to aggressive behavior in the home are correlated with socioeconomic status. Each also predicts later psychiatric dysfunction in children.

It should be emphasized that proxy risk factors *are* risk factors. They may ultimately prove to be incidental to the causal processes, but they are often useful as indicators of profitable directions for the search for causal factors (by substitution, aggregation, or disaggregation). Researchers are often reluctant to label a risk factor a proxy risk factor. Yet not setting aside proxy risk factors from consideration once the risk factor for which they are proxy is identified can confuse, mislead, and impede the understanding of the potential causes of disorders and the formulations of effective prevention and treatment interventions.

### *A and B Are Overlapping Risk Factors*

When (as in Table 2) one has two measures that strongly tap into the same construct, what will be observed is that neither A nor B has temporal precedence, A and B are correlated, and A and B are codominant, i.e., they are overlapping risk factors. Generally, when A and B are overlapping risk factors, combining the measures A and B "steps up" the reliability of the measure of the shared construct by combining the information in both measures (35, 36) and,



**TABLE 3. Proposed Definitions of How Risk Factors A and B Work Together to Affect Outcome O<sup>a</sup>**

Condition	Status			
	Yes	No	Yes	No
Correlation of A and B	Yes	No	Yes	No
Temporal precedence	Yes	Yes	No	No
Domination				
A dominates	B proxy risk factor	B proxy risk factor	B proxy risk factor	
Codomination	B mediates (total)	A moderates	Overlapping	Independent
B dominates	B mediates (partial)		A proxy risk factor	

<sup>a</sup> Three cases (indicated by empty cells) are theoretically impossible when A and B are both risk factors for O but may be observed in practice because of misclassification.

thus, the potency of the combined risk factors. The issue then remains of the portions of A or B unrelated to the shared construct.

For example, if one uses two different moderately reliable indicators of depression, e.g., a high Hamilton scale score (A) and a high Beck scale score (B) as risk factors for subsequent suicide attempt (O), the conclusion is likely to suggest that A and B are overlapping risk factors. In such cases, A and B might best be combined to obtain a risk factor that more reliably taps the shared construct (here, depression).

**A and B Are Independent Risk Factors**

We propose to call A and B “independent risk factors” if there is no temporal precedence of A or B, A and B are uncorrelated, and A and B are codominant.

For example, female gender (A) and nonwhite ethnicity (B) are both risk factors for obesity (O), clearly there is no temporal precedence, and they are uncorrelated. If both nonwhite ethnicity and female gender simultaneously help predict obesity, these factors would be independent risk factors for this outcome. Thus, being both female and African American or Hispanic American might define the high-risk group for obesity in subsequent analysis.

**B Is a Mediator of A**

According to Baron and Kenny (5) as well as Rothman and Greenland (10), conceptually, a mediator variable (B) is one that explains how or why another variable (A) affects the outcome (O). This kind of relationship is fundamental to the development of causal chains. Operationally, one would document temporal precedence (with A preceding B), correlation between A and B, and when one considered A and B jointly, either domination of A by B (total mediation) or codomination by A and B (partial mediation). Although the ideal posits causal association between the constructs, we cannot infer causality from observation of association in a sample, particularly when using nonexperimental data. We can usually only say that what we observe is consistent with what we would expect to see if a causal path leading from A to B to O were in force. Just as all causal risk factors are risk factors, but not all risk factors are causal, all causal chains consist of mediators, but not all mediators will eventually prove to be links of some causal chain.

For example, illicit intravenous drug use (A), unprotected sex (A), multiple blood transfusions (A), and being born to an HIV-positive mother (A) might all be totally or

partially mediated by positive HIV status (B) in their relationships to AIDS (O). Another illustration is that the gene for phenylketonuria is mediated by the phenylketonuria enzyme in its effects on IQ.

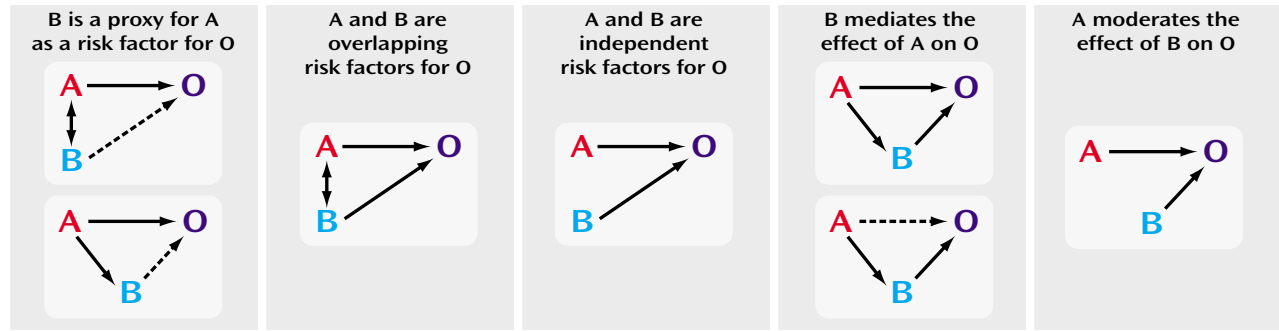
**A Is a Moderator of B**

According to Baron and Kenny (5), conceptually a moderator (A) specifies on whom or under what conditions another variable (B) will operate to produce the outcome (O). A moderator (A) is supposed to affect the relationship between the other variable (B) and the outcome (O), whereas a mediator (B) is supposed to be influenced by the other variable (A) directly.

As already noted, the current operational definition of “A moderates B” is so imprecise that almost any two risk factors, given a judicious choice of linear model and a large enough sample, could be found to simultaneously moderate each other. Yet the conceptual definition in both psychology and epidemiology is a vitally important one, not covered by the situations already discussed. Consequently, we will try to effect suitable redefinition, not of the concept, but of its operationalization.

The crucial situation not covered is when A precedes B and identifies two subpopulations, say A<sub>1</sub> and A<sub>0</sub>, in which the distribution of B is the same (i.e., B is not correlated with A). Thus, A does not influence B directly. However, the potency of B as a risk factor for O may be different in A<sub>1</sub> and A<sub>0</sub>. In short, A somehow changes the relationship between B and O without directly affecting the level or probability of B. This situation, in which A precedes B, A and B are not correlated, and A and B codominate, defines “A moderates B.” This is an important situation, for it suggests the possibility that in distinct subpopulations (defined by A) different causal chains operate, or one causal chain operates differently. Terms such as “susceptibility” or “resiliency” or “buffering factors” may correspond to moderators.

For example, female gender (A) and early puberty (B) may be risk factors for panic disorder (37). Here, gender temporally precedes early puberty and is uncorrelated with it. The evidence suggests that early puberty matters more for females than for males with reference to panic disorder. If so, gender moderates the effect of early puberty on panic disorder, here defining on whom B operates as a risk factor. In a rat model (38), it has been shown that genotype moderates the effect of maternal deprivation on the presence or absence of schizophrenic-like be-

FIGURE 1. Five Ways Risk Factors A and B Can Work Together to Affect Outcome O<sup>a</sup>

<sup>a</sup> Left to right positioning indicates temporal order. A solid arrow indicates a correlation. A dotted arrow indicates a correlation that weakens or disappears when the other risk factor is considered.

haviors. In humans, it has been shown that genotype moderates the relative effectiveness of certain drugs (39). These and other such examples are important in that they illustrate that a genotype associated with a disorder may not indicate any genetic role in the causal pathway to the disorder but may identify who is or is not susceptible to an environmental causal factor. If so, prevention would require not gene manipulation but environmental manipulation for genetically at-risk individuals.

A summary of these definitions appears in tabular form in Table 3 and schematically in Figure 1. The three missing cases in Table 3 are ones theoretically not possible when A and B are individually binary risk factors for O. In practice, because of misclassifications, these situations sometimes occur. It is important to note that under these proposed definitions, the same factor cannot be both a moderator and a mediator of a target risk factor for a particular outcome in a population. Moreover, the directionality, i.e., which risk factor mediates or moderates which other risk factor, is unambiguous. Finally, specifically what must be demonstrated in order to claim that each relationship exists is explicit.

### Extension to More Complex Situations

The two major difficulties in attempting to extend these principles to other than binary risk factors are the related problems of 1) establishing precedence and 2) evaluating potency. In a randomized clinical trial, the onset and end of treatment are determined by the investigators. Random assignment to treatment and control groups guarantees that all prandomization variables precede the choice of treatment and are uncorrelated with it and are thus potential moderators of treatment. Any change or event that occurs during treatment that is associated with treatment is a potential mediator of treatment. The outcome of treatment, which may be binary or ordinal, is determined at the end of the treatment period. Thus, establishing precedence in seeking moderators and mediators of treatment in a randomized clinical trial is straightforward. Finally, the effect sizes used in randomized clinical trials are different from those used as measures of potency in risk as-

essment studies. Thus, we will leave detailed further discussion of application of these principles in randomized clinical trials to another report. We here focus on the more difficult problem of risk factor studies, where the outcome is binary (onset of disease or not, presence of disease or not), the studies are typically observational, and determining whether the putative risk factor or the outcome came first is a challenge.

Suppose, for example, A is a dimensional depression score and B is a dimensional anxiety score. How would one establish the precedence of A or B, when both may vary within an individual over time and at every point of time one can measure both depression and anxiety on every subject in the population? If one cannot establish precedence, one cannot begin to demonstrate causal effects or causal chains. Clearly, which of two risk factors is measured first, which is entered into a hierarchical or stepwise analysis first, or which has greater potency does not establish temporal precedence.

One solution is to define an event based on the risk factor, by defining a threshold that is crossed at some point in time. One could then establish when each subject first passed the set threshold on the anxiety scale, when she or he first passed the set threshold on the depression scale, and which came first. The threshold should not be set arbitrarily. It should at least correspond to the particular optimal dichotomization that determined the potency of each risk factor used (4).

Moreover, the time at which such a threshold is passed is an event with important clinical and policy implications. If depression is measured at 20 years of age, but the score reflects a situation in place since the age of 10, an intervention designed to manipulate the construct underlying the depression score may be much too late by the age of 20. The primary clinical or policy value of risk research lies in the ability to identify high-risk subjects for whom an appropriate intervention can be designed and to whom and when that intervention would be delivered in order to prevent the disorder, requiring just such a dichotomization.

There are also limitations to interpreting analytic results in the absence of dichotomization. Some of these points are articulated in arguments supporting different choices of potency measures for risk factors (4). Suffice it here to show how misleading it may be to use the commonly used product moment correlation coefficient ( $r$ ) with a nondichotomized risk factor and a binary outcome for clinical and policy judgments.

Let us suppose that a scaled risk factor ( $X$ ) has normal distributions in both the subpopulations with and without the outcome, with different means but the same standard deviation (the model that underlies the two-sample  $t$  test). The effect size commonly used here is Cohen's  $d$  (the standardized mean difference between groups) (40). The sensitivity and specificity for optimal dichotomization are at a cutoff point halfway between the two means. Then, for example, if  $r=0.1$ , which most would consider trivial, Cohen's  $d$  might be 3.2 (when  $p=0.001$ ), and the sensitivity and specificity equal to a very high 94%, or Cohen's  $d$  might be 0.20 (when  $p=0.5$ ) and the sensitivity and specificity equal to a trivial 54%. One cannot tell from  $r$  alone whether a factor is of clinical or research value for the purposes a risk factor must serve.

Yet any recommendation for dichotomization is bound to be contentious. Part of the long and controversial history of mediator/moderator research in psychology (6) is the struggle between those advocating moderated subgroups analysis (as here) versus multiple regressions (based on linear models, often appropriate in randomized clinical trials but problematic in risk studies). It is widely and uniformly recommended not to dichotomize *unnecessarily* (41–43), a recommendation that has been inappropriately translated to a fiat that one should *never* dichotomize. However, in the risk research context, to establish temporal precedence and to evaluate potency in a way that most clearly establishes clinical and policy significance, as already indicated, dichotomization seems necessary. The arguments concerning dichotomization often reflect a struggle between those primarily interested in statistical significance and those primarily interested in clinical or policy significance.

If we accept the necessity of dichotomization to establish clinical or policy significance in risk studies, extension to the situation with more than two binary risk factors poses little problem, for all the risk factors can be examined pairwise in temporal order. We recommend the following steps.

1. Each factor for which there might be some question of status as a risk factor for the outcome (because of questions about precedence or potency) should be set aside. This may happen because of the nature of the population the sample represents, because of the unreliability of that factor in that population or sample, or because the study was underpowered, but the documentation of risk factor status on such a basis would be questionable.

2. Each pair of risk factors in which there is no temporal precedence might be examined. Proxy risk factors would

then be set aside, and independent and overlapping risk factors would be optimally combined.

3. The remaining risk factors might then be organized in terms of temporal precedence, and each such pair of risk factors that are temporally ordered can now be classified as mediating, moderating, or proxy risk factors, moving from the earliest in time to the latest. Once again, proxy risk factors would be set aside.

At any point that a moderating risk factor is identified, the population is split into two subpopulations (in which the pursuant causal processes might differ). Subsequent analysis would check for risk factors and interactions between risk factors separately in the two subpopulations.

Any chain of mediating relationships within a population or subpopulation across time is now the empirical basis of a hypothesis of a causal chain that can be evaluated in a randomized trial.

## Discussion

Why is all this so important to elucidating the etiologic processes and informing preventive and treatment interventions for psychiatric disorders? First, designing an intervention to be tested in a randomized clinical trial that manipulates correlates that are not risk factors or risk factors that are not causal either because they cannot be changed (fixed markers) or because, when changed, they do not change the risk of the outcome (variable markers) is a waste of time (2). When there are chains of causal risk factors (all mediators), addressing only one link of that chain may result in treatment effects of minor clinical or policy significance. In the same situation, sequential interventions addressing each link in turn may succeed. Currently, most prevention programs are aimed at multiple risk factors at the same time in a blunderbuss fashion. This is not a substitute for understanding how and when individual influences operate. Indeed, blunderbuss interventions, almost by definition, focus on a variety of influences, some of which are fixed or variable markers or proxy risk factors that dilute or divert from intervention effects that derive from changing causal risk factors. At the same time, ignoring strong moderators of treatment response may mean inclusion of many subjects for whom the interventions are not appropriate, perhaps are even harmful, and both reduced power for statistical testing and attenuated effect sizes.

A recent report (44) presented the results of an multisite randomized clinical trial comparing the relative effectiveness of a medical management treatment, a behavioral management treatment, a combination treatment, and treatment as usual in the community for treatment of ADHD. The major contrast was between the two treatments involving the medical management protocol and the two treatments not using this protocol. This report was immediately followed by consideration of moderators and mediators of treatment response according to the model

presented here (45). Comorbid anxiety disorder at baseline (affecting about 34% of the ADHD children) was shown to moderate the effect of treatments. The children with anxiety disorders appeared to benefit more from behavioral management than did those without anxiety disorders. Adequate compliance with the treatments (by standards set a priori) was shown to mediate the treatment effects. Those in the medical management treatments evidenced greater compliance with treatment, and response to treatment was more strongly associated with compliance in those groups than in the others. More work on identifying both moderators and mediators of treatment effects is currently underway. When this work is completed, in future research in this area it would be prudent to consider stratifying samples by the strongest moderators and to consider what further manipulations to the protocols for treatments are suggested by the mediators. In general, it is possible that the weak effects associated with various treatments for psychiatric disorders may be due to lack of information on moderators and mediators of treatment.

At the same time, genetic risk factors working with environmental risk factors may well obviate some of the old nature-nurture conflicts. As already noted, a gene may moderate environmental risk factors (46), the gene not causing the outcome but identifying people susceptible to the environmental causal risk factor.

It is easy to underestimate the importance of this effect. Take a hypothetical example. Suppose that 20% of the population have genotype A, that 10% of the population are exposed to a toxic environment B, and that A and B are totally independent. Finally, suppose that people with genotype A who are exposed to environment B are 99% sure of getting the disorder, while everyone else has only a 5% change of that disorder (A moderates B). The odds ratio comparing those with both A and B versus all others would be  $1,881 - (0.99 \cdot 0.95) / (0.01 \cdot 0.05)$ —easy to detect with only a moderate sample size. However, if we know about only the gene, those with genotype A (without consideration of environment B) have a 14.4% risk of the disorder versus 5.0% of those without genotype A, an odds ratio of 3.2 (versus 1,881). If we know about only the environment, those with environment B (without consideration of genotype) have a 23.8% risk versus 5.0% in those without environment B, an odds ratio of 5.9 (versus 1,881). It would take a large sample and careful assessment of A or B separately to establish that either is a risk factor, and even if one did, neither variable alone would account for much of the disorder.

Moreover, a gene may be mediated by environmental causal factors, helping explain how the gene works to produce the outcome, e.g., the phenylketonuria gene mediated by the phenylketonuria enzyme in its effect on IQ. A gene may be a proxy risk factor for an environmental risk factor, or vice versa, one or the other ultimately irrelevant to causal chains leading to the disorder. For instance,

genes associated with skin color may be proxy risk factors for poor access to health and educational resources in their effect on IQ. As others have noted (47, 48), it is fallacious to try to ascribe some distinct percentage of any outcome to either genes or environment separately or to interpret “heritability” as necessarily indicating a genetic cause. It has been very difficult in psychiatry, despite great expenditures of effort and funds, to find genetic bases of psychiatric disorders. Many reported results have remained unreplicated and unconfirmed, and many have been disconfirmed. It is possible that not attending to the points discussed herein has contributed to this situation.

Risk moderators and risk mediators are analogous to neurotransmitters, neuromodulators, and neurohormones in that understanding them depends on understanding their activity and the loci of their effects (49, p. 4). While hardly novel, the idea of building a model step by step, checking each new building block before it is set in place, is less familiar in risk research. In biobehavioral risk research, an entire complex theoretical model, often involving concomitants and consequences as well as risk factors, is put to test as a whole, by using complex linear regression models (e.g., structural equation modeling). If the model is not rejected, it may be that the test or the test power is inadequate. If it is rejected, it is not known specifically which particular building block of the model failed.

The point of risk research is to promote understanding of the possibly multiple causal paths, some involving complex chains of causal risk factors, leading to disorders. Then the goal is to use that information to decide correctly for whom, when, and how to intervene to prevent the onset of disorders or to facilitate recovery. For such goals, this careful step-by-step approach may provide a powerful avenue leading from theory, through basic and clinical research results, to results of direct clinical and policy significance.

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