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Mediation Analysis in Psychosomatic Medicine Research

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Abstract

This article presents an overview of statistical mediation analysis and its application to psychosomatic medicine research. The article begins with a description of the major approaches to mediation analysis and an evaluation of the strengths and limits of each. Emphasis is placed on longitudinal mediation models, and an application using latent growth modeling is presented. The article concludes with a description of recent developments in mediation analysis and suggestions for the use of mediation for future work in psychosomatic medicine research.

Keywords

statistical mediation; mediation analysis; mechanism; indirect effect

INTRODUCTION

Mediation analysis is a valuable tool for researchers because it can help explain the transmission of effects between two variables. In psychosomatic medicine research, the relation between psychosocial and physiological processes is often more clearly explained by mediating variables, such as health behaviors or interpersonal relationships (1,2). As a result, mediating variables are central to many questions in psychosomatic medicine:

- Does socioeconomic status affect cortisol levels through psychosocial distress (3)?
- Does an intervention designed to decrease anxiety result in lower mortality rates (4)?
- Does childhood intelligence quotient predict locus of control, and does locus of control predict adult overweight and obesity risk (5)?

Questions like these suggest that psychosocial and biological variables may exist in an ordered chain of relations, in which one variable is thought to cause changes in a second variable, which then causes changes in a third variable. Mediation analysis is one way to investigate these processes.

Within the psychosomatic medicine literature, the importance of identifying mediating processes was expressed nearly 50 years ago, "... the question as to the mediating mechanisms remains one of the greatest puzzles of medicine" (6) and continues today, "prospective studies are needed to examine the behavioral mechanisms mediating the relationship between psychosocial factors and HIV disease progression" (1). In response, mediation studies have become more common. In this journal, more than 60 empirical articles tested some form of mediation since 1999, compared with the 23 articles of the prior

decade. This surge in popularity has coincided with increasingly advanced methods to test mediating effects, which can complicate substantive researchers' analysis decisions. This article is a guide to the major mediation approaches with a specific application to psychosomatic medicine research. First, we present statistical definitions of mediation, along with applications of the single mediator model and multiple mediator model. Second, we build on these basic models with a description of longitudinal mediation models and applications to experimental research. Finally, we discuss new methods for categorical data, person-centered approaches, and experimental approaches, and we conclude with limitations and future directions of mediation analysis.

Model-Building Considerations and Definitions

Like any statistical analysis, a significant mediation effect in a sample of data may or may not reflect a true underlying mediation relation. Thus, mediation analysis must be combined with research literature and sound theory to provide incremental evidence for mediation relations. This foundation is critical in the selection of mediating variables and their hypothesized relations to outcomes. Consider, for example, the relationship between exposure to neighborhood violence and overweight in adolescents. The links between exposure to neighborhood violence and elevation of blood pressure (7) and between blood pressure and body fat (8) suggest that blood pressure may be a mediator in the relationship between neighborhood violence and overweight. Researchers also use theory to guide their selection of mediators. For example, social cognitive theory can help generate a mediation model for a program to prevent falls in older populations (9). Self-efficacy, a central component of social cognitive theory, is thought to increase the likelihood that an individual will confidently perform a given task, such as physical exercise. Thus, a program designed to increase mobility among older adults could specifically target self-efficacy to increase mobility and reduce falls. In this case, self-efficacy is the mediator between the program and mobility.

In its simplest form, mediation is the extent to which a variable, *M*, is intermediate in a causal relationship between an independent variable *X* and dependent variable *Y*. The addition of this third variable suggests a causal chain, in which *X* causes *M* and *M* causes *Y*: $X \rightarrow M \rightarrow Y$. Mediation is conceptually distinct from other types of third variable relationships (10). For example, a third variable, *Z*, could cause both *X* and *Y*, such that excluding *Z* would lead to an incorrect inference of the relationship between *X* and *Y*. In this case, *Z* is a confounding variable. Confounding variables are independent from the causal process and can include stable characteristics (e.g., gender) or malleable variables (e.g., dietary behaviors) (11). Mediation and confounding effects are statistically equivalent yet conceptually clearly distinct (12). Thus, it is critical that researchers consider the potential for confounding effects by thoughtfully integrating theory, design, and prior research to construct a model representing a causal sequence.

Another third variable relationship that is different from mediation is a covariate, in which the information about variable *Z* improves the ability of *X* to predict *Y* but does not substantially change the relationship between *X* and *Y*. Finally, a third variable, *Z*, can moderate the relationship between *X* and *Y*, such that the relationship of *X* to *Y* differs at different values of *Z*. Unlike mediators, moderators, confounders, and covariates are not part of a causal sequence. The distinction between mediation and moderation has been the subject of much discussion and research (13–16). There are more detailed distinctions among several of these third variable measures (17), but these major distinctions are useful for organizing most applications of third variable effects.

In mediation models, the *X* variable can be continuous or categorical. Gale and colleagues (5) found that a continuous measure of childhood intelligence quotient (*X*) predicted internal

locus of control (M), which predicted health outcomes. Chesney and associates (18) randomly assigned patients with human immunodeficiency virus to a treatment or control condition (X), which predicted changes in coping efficacy (M), which then predicted psychological distress (Y). Randomized treatment studies, in which the X variable represents treatment or control conditions, are advantageous because the researcher manipulates the timing of the X variable, such that X precedes M and Y, making causal interpretation of results clearer. However, the use of X variables that do not represent randomization to conditions is often a necessity in psychosomatic research, for example, socioeconomic status, religiosity, or stressful life events. In these situations, a body of research and evidence from many sources must be brought to bear to claim mediation relations.

Mediation Regression Equations and Statistical Mediation Analysis

The following three regression equations provide the information for the most commonly used approaches to statistical mediation analysis:

$$Y = i_1 + cX + e_1 \quad (1)$$

$$Y = i_2 + c'X + bM + e_2 \quad (2)$$

$$M = i_3 + aX + e_3 \quad (3)$$

where i_1 and i_2 and i_3 are intercepts, e_1 , e_2 , and e_3 are residuals, Y is the dependent variable, X is the independent variable, M is the mediator, and c is the coefficient relating the independent variable and the dependent variable in the first equation. Equations 2 and 3 are represented in a diagram of the mediation model in Figure 1, where c' is the coefficient relating the independent variable to the dependent variable adjusted for the mediator, b is the coefficient relating the mediator to the dependent variable adjusted for independent variable, and a is the coefficient relating the independent variable to the mediator. Because the mediating variable, M, is both a dependent variable (Eq. 3) and an independent variable (Eq. 2), identifying mediation relations are often challenging.

A review of empirical articles in *Psychosomatic Medicine* from the years 1999 to 2008 revealed 66 studies, which tested for mediation (Appendix). Of these articles, over half ($n = 36$) used the causal steps approach outlined in the classic work of Baron and Kenny (13,19) and Judd and Kenny (20,21). With this approach, four requirements must be met to establish mediation. First, the independent variable must be significantly related to the dependent variable in Equation 1. Second, a significant relation of the independent variable to the hypothesized mediating variable is required in Equation 3. Third, the mediating variable must be significantly related to the dependent variable when both the independent variable and mediating variable are predictors of the dependent variable in Equation 2. Fourth, the coefficient relating the independent variable to the dependent variable must be larger than the coefficient relating the independent variable to the dependent variable in the regression model with both the independent variable and the mediating variable predicting the dependent variable. The requirement of a significant X to Y relationship substantially reduces the power to find a true mediated effect (22,23). For example, the Baron and Kenny (13) causal steps test requires >20,000 subjects to detect mediation with 0.8 power when the effects of the a and b paths in the model are small and $X \rightarrow Y$ is completely mediated through M (a typical finding in psychology data) (23). Low statistical power is important in practice, because it leads to Type 2 errors, or the failure to find true mediated effects.

The mediated effect in the single mediator model (Fig. 1) may be calculated as either a product ($\hat{a}\hat{b}$) or a difference ($\hat{c} - \hat{c}'$) between coefficients (24) if both M and Y are continuous variables. The product of coefficients method involves estimating Equations 2 and 3 and computing the product of $\hat{a}$ and $\hat{b}$, $\hat{a}\hat{b}$, to form the mediated or indirect effect (25). The rationale behind this method is that mediation depends on the extent to which X changes the mediator (M), represented by the coefficient a , and the extent to which the mediator affects the outcome variable, the coefficient b . The mediated or indirect effect is the change in Y when X is fixed and M is changed to the level it would have had when X is increased by one unit. To test for significance, the product is then divided by the standard error of the product, and the ratio is compared with a standard normal distribution. Many studies only require $\hat{c}'$ to be less than $\hat{c}$ when testing mediation, but the significance of this drop should be tested to assess whether the reduction of $\hat{c}$ to $\hat{c}'$ is consistent with chance.

The difference in the coefficients, $\hat{c} - \hat{c}'$, from Equations 1 and 2, is the reduction in the effect of the independent variable on the dependent variable adjusted for the effect of the mediator. To test for significance, the difference is then divided by the standard error of the difference, and the ratio is compared with a standard normal distribution. The $\hat{a}\hat{b}$ and $\hat{c} - \hat{c}'$ measures of mediation are algebraically equivalent (26) for normal theory ordinary least squares and maximum likelihood estimation of the mediation equations. This equivalence does not always hold for logistic or probit regression; transformation is required to achieve similar results (24).

In the mediation approaches described above, a mediation effect is obtained by dividing the effect by its standard error and comparing the resulting ratio to a table of the normal distribution (27,28). If the absolute value of the observed Z statistic is greater than 1.96, then it is concluded that the effect would occur 5% of the time or less by chance alone. However, in the mediation model, statistical power and Type I error rates are too low for most tests of significance based on the normal distribution (22), and confidence limits are imbalanced (22,26). An explanation for these findings is that the product of two normally distributed random variables, such as the ab product estimator of the mediated effect, is not itself normally distributed (29,30). Asymmetric confidence limits for the mediated effect based on the distribution of the product (31) are more accurate than those based on the normal distribution. A new program, PRODCLIN (MacKinnon, Fritz, Williams, and Lockwood, 2007; program available at <http://www.public.asu.edu/~davidpm/ripl/Prodclin/>), estimates critical values of the distribution of the product and computes confidence limits for the mediated effect.

Computer intensive methods, such as bootstrapping and other resampling methods, make fewer assumptions and may be more accurate in this case because of the nonnormal distribution of the product. Fritz and MacKinnon (23) compared single-sample methods (such as the distribution of the product) to several computer intensive methods to test mediation in the single mediator model. This work showed that bootstrapping and distribution of the product were most accurate. Further work (32) has shown similar results for more complex mediation models that incorporate multiple independent and dependent variables.

Model Assumptions

Mediation analysis rests on several statistical and design assumptions that extend beyond the usual assumptions of regression models (10). First, the model assumes inclusion of relevant variables and reliable and valid measures of constructs (33–35). For example, it is assumed that measurement error in any of the measures is not large enough to affect results. Measurement error in the mediator, for example, is likely to reduce estimates of the mediated effect (36). Second, the residuals in Equations 2 and 3 are assumed to be

independent and that M and the residual in Equation 2 are assumed to be independent for the mediated effect, $\hat{a}\hat{b}$ (35,37). Third, it is assumed that the functional form relating variables is correct. Most applications of mediation relations assume linear relations among variables but nonlinear relations among variables may be also be valid. Fourth, the model assumes no XM interaction, although the presence of such an interaction can be tested. Finally, it is assumed that the model is correctly specified with regard to causal ordering and direction of effects (e.g., $X \rightarrow M \rightarrow Y$ rather than $Y \rightarrow M \rightarrow X$ without bidirectional effects). There are several complicating aspects of this assumption that form most new developments in mediation analysis. For example, the model is considered self-contained with no outside or omitted influences that would alter the relations in the model. In many situations, it is likely that there are other influences, so researchers often include covariates and other variables to form more comprehensive mediation models. Additionally, the role of the mediator as both a dependent and independent variable creates ambiguities in the causal interpretation of mediation relations. There are several new approaches that attempt to distinguish types of mediation relations, such as those that are at fixed values of variables versus those relations obtained by controlling for variables (38). Most of these new approaches are based on counterfactual consideration of all possible conditions any one participant may serve in, as well as the actual condition in which the participant served. This ambiguity of interpretation of the $M \rightarrow Y$ relation in even the simplest mediation model highlights the need to evaluate carefully this relation in many forms of study, including experimental research designs, qualitative data, and replication studies. To date, these models have focused on the three-variable mediation model described above and have not yet incorporated longitudinal data. The specification of mediation relations with longitudinal data seeks to clarify the temporal precedence of variables in the mediation model, consistent with changes in X preceding changes in M, and changes in M preceding changes in Y (10,39). In light of the challenges of identifying true mediation relations, it is best to focus on building evidence for a mediation relation with a variety of qualitative, statistical, theoretical, and empirical evidence that is tested in new designs and different contexts (10).

Multiple Mediator Model

For psychosomatic medicine, models with multiple mediators likely provide a more accurate assessment of mediation effects. For example, a cardiovascular disease program may target multiple mediators, such as diet, exercise, and stress management. Models with more than one mediator are straightforward extensions of the single mediator case (40). Several standard error formulas for comparing different mediated effects are given by MacKinnon (10,40).

Effect Size Measures

Effect size measures of the mediated effect provide information about the size and meaningfulness of the mediated effect. These measures can be applied to individual paths (e.g., $X \rightarrow M$) or for the entire mediated effect ($\hat{a}\hat{b}$). Details of effect size measures of individual paths are documented elsewhere (10); here we describe the most common effect size measures of the mediated effect. To illustrate, we use a study (41) from ATHENA (Athletes Targeting Healthy Exercise and Nutrition Alternatives), a preventive intervention designed to promote healthy eating and exercise habits among 1,668 adolescent female athletes. This program targeted several mediators and social norms (i.e., beliefs about the extent to which magazine advertisements are true), which were expected to be positively associated with intentions to engage in unhealthy weight control behaviors, such as diet pills or vomiting.

Proportion Mediated and Ratio Measures—The proportion of the total effect that is mediated ($\hat{a}\hat{b}/\hat{c}$) is one of the most common methods for assessing the effect size of the

mediated effect. One mediation test in the ATHENA analysis showed that social norms mediated the relationship between treatment condition and intentions to use unhealthy weight control behaviors, with a proportion mediated of 0.45. Thus, the mediated effect explains 45% of the total effect of the program on unhealthy weight control intentions. One limitation of this method is its lack of stability for sample sizes less than 500 (26,42). Additionally, inconsistent mediation models, in which the mediated effect and the direct effect have opposite signs, may result in nonsensical values, such as a proportion greater than one or a negative value (12). For the inconsistent mediation model case, the absolute values of the coefficients can be used (25).

The ratio effect size measure, $(\hat{a}\hat{b}/\hat{c}')$, compares the mediated effect to the direct effect. To take the ATHENA example, the mediated effect through social norms was $(0.219 \times 0.234)/(0.006) = 8.5$ times larger than the direct effect of program condition on intentions. This method is also limited by instability in sample sizes less than 500 (26).

R² Measures—R² measures divide the observed variance in the dependent variable into the part attributable to the direct effect, to the mediated effect, and the part that is not explained by either effect. For example, one measure represents the amount of variance in Y explained by M specific to the mediated effect. R² measures have shown minimal bias for smaller sample sizes (14,43,44).

Longitudinal Mediation Models

The complex relationship between biological and psychological processes often calls for research questions that not only examine mediating mechanisms at a given time point but that also document changes in these mechanisms over time. Longitudinal data provide a closer representation of the temporal precedence assumption of the mediation model. It should be emphasized, however, that longitudinal data do not remove the need for models that are constructed based on theory and/or prior research; mediation relations may be missed due to a discrepancy in the timing of measurement and the timing of the mediated effect. Models with 3 or more waves, although they are complicated and may require large sample sizes, are often preferable because they likely increase the accuracy of the estimated relations among variables. For the longitudinal models described below, we turn away from the regression procedures discussed thus far and present mediation models that require a covariance structure program, such as SAS, Mplus (45), or LISREL (46).

Autoregressive Models—Autoregressive mediation models are path models in which contemporaneous and longitudinal relations among X, M, and Y across 3 or more time points can be tested. Large coefficients indicate high stability in the rank order among subjects; individual differences in growth are not modeled with this method. The basic three-wave autoregressive mediation model is a path model in which relations among variables one lag (wave) apart are considered, the stability of measures is assessed over time, and only longitudinal relations consistent with longitudinal mediation are considered (47,48). Figure 2 shows the basic autoregressive model. The arrows with s_X , s_M , and s_Y are the stability of the measures; a_1 and a_2 represent the two longitudinal a paths in the X to M relation; b_1 and b_2 are the two longitudinal b paths in the M to Y relations; and c'_1 and c'_2 are the two longitudinal direct effects in the X to Y relations.

A second autoregressive model (Fig. 3) includes both longitudinal mediation and contemporaneous mediation (mediation within the same wave) for the last two time points. Because of issues concerning the timing of measurement versus the timing of the mediated effect, results of contemporaneous mediation may be more accurate than longitudinal mediation.

A third type of autoregressive mediation model allows the relations between X, M, and Y to vary freely, in which paths opposite to the traditional direction (i.e., Y to M and X or M to X) are estimated (Fig. 4). These relations (indicated in bold) violate the temporal precedence of the mediation model but may be more reasonable than assuming these relations are zero; there may be a theoretical reason that such a cross-lag relation could exist. One example is involvement in an online weight loss program (X), designed to increase social support (M), which reduces weight (Y). Weight loss at Time 1 could increase the likelihood both of remaining involved in the online program and obtaining social support at Time 2. Again, theory and prior empirical evidence should guide these modeling decisions.

Autoregressive mediation models provide one flexible way for examining the extent to which a sample shows similar rank ordering among individuals for X, M, and Y for both cross-sectional and longitudinal relations. The most notable limitations of these models are that small sample sizes tend to yield biased standard errors, and cross-lag coefficients may be inaccurate because of sampling error (49). It is also important to note that autoregressive models are intended to measure stability, or lack of a sample's movement in the levels of X, M, and Y. Thus, these models may be useful for data that are not expected to show large amounts of change over time. For research questions concerning the extent of individual change or "trajectories" of variables and the mediation relations among these trajectories, latent growth modeling may be an appropriate choice.

Latent Growth Models—Latent growth modeling (LGM), or parallel process modeling, has become an increasingly common method of analyzing longitudinal data (50). In the LGM framework, change in an observed continuous variable over time (i.e., slope) and the starting point (i.e., intercept) are treated as latent variables, which can either predict or be predicted by other latent variables. Average slopes within an LGM analysis can be either linear or nonlinear, adding further flexibility for more complex tests. Mediation LGMs in which X is continuous consist of three latent growth trajectories, one each for X, M, and Y (Fig. 5). The relations in mediation LGM are similar to those for a nonlatent mediation model, such that the relation between X and Y is explained by both the indirect effect through M and the direct effect. In the LGM case, the growth of M mediates the relation between the growth of X and the growth of Y.

Figure 5 shows a parallel process LGM of linear growth. The α path is the relation between the slope (change) of X and the slope of M. This path corresponds to the a path in the single mediator model. A significant α coefficient would indicate that a change in the trajectory of X predicted a change in the trajectory of the mediator. The β path is the relation between the slope of the mediator and the slope of the Y variable; this path corresponds to the b path in the single mediator model. The product of α and β represents the mediated effect. LGM can also be applied to models for which X is a categorical treatment condition. In this case, the α path is the mean difference in the growth rate of the mediator between the treatment and control group. A significant α coefficient in the expected direction would indicate that the prevention or treatment program was effective in changing the trajectory of the mediator. Significance testing of the mediated effect can be performed, using the bootstrap or distribution of the product methods described earlier.

To illustrate the parallel process LGM, we present findings from Adolescents Training and Learning to Avoid Steroids, a preventive intervention for male high school athletes (39). One of the goals of the program (X) was to improve athletes' dietary habits (Y) through the perceived importance of information from their peer team leaders (M). Participants received either a team-based intervention program (X = 1) or a pamphlet addressing health behaviors (X = 0) and were measured four times at 6-month intervals. Figure 6 shows the findings of the linear growth model. The $\alpha\beta$ mediated effect was $0.859 \times 0.891 = 0.765$ and the

standard error (σ_{ab}) of the mediated effect was 0.210. Significance testing, using first-order solution proposed by Sobel (51), indicates a significant mediation effect, ($z_{a\beta} = 3.643$; $p < .001$); the same is true for the test of asymmetric confidence intervals (95% confidence interval, 3.72, 1.20).

Thus, the program altered significantly the trajectory of importance of peers as an information source, which, in turn, altered the trajectory of nutrition behaviors.

In the difference score approach to longitudinal mediation, differences between the mediator and dependent variables scores are taken, as is the independent variable if it does not reflect assignment to treatment condition. These difference scores are then analyzed, using the same equations as for cross-sectional models. The latent difference score (LDS) model can also be applied to 3 or more waves, using a latent framework (52–54). In the LDS model, fixed parameters and latent variables are used to specify latent difference scores, such that the model represents differences between waves as dynamic change. The LDS model can be especially useful in situations where it is expected there will be different predictors at different measurement occasions. For example, treatment effects may be significant for the first two waves of a study but not the final wave.

Timing Considerations—A central task for any longitudinal study is to minimize the discrepancy between the timing of measurements and the timing of observable changes in the variables under study. Measurement timing decisions are not easily made and are even more complicated for longitudinal mediation models because there are at least two sequences ($X \rightarrow M$ and $M \rightarrow Y$) to consider. It has been suggested that longitudinal mediation analyses require a minimum of three time points to measure longitudinal relations for both the a and b paths (48). Consider a case, however, in which a mediated effect does not exist for a three-wave autoregressive model with a randomized X variable (Fig. 7a). This finding may actually reflect a measurement timing failure in which a mediated effect has been “missed.” For example, X -linked changes in the mediator may not be observable until a later time point (Fig. 7b). In this case, a two-wave model is favored because it represents more accurately the theoretical model for change.

Categorical Data

Categorical outcomes, such as the presence versus absence of a given disease or substance abuse diagnostic category, are common in psychosomatic medicine research. Logistic regression is the method of choice for categorical outcomes because it transforms the expected values of the outcome so that these values can be interpreted in the same manner as ordinary least squares (55). This transformation is necessary to prevent the prediction of impossible values, such as numbers <0 or >1 in the binary case.

If logistic regression is used to analyze data for mediation analysis in Equations 1 to 3, the ab and $c - c'$ estimates are not equivalent because of the fixing of logistic regression error terms across equations (24). As a result, c will differ from c' because of the mediated effect but also because the error term is fixed across equations, unlike ordinary least squares regression where the error term is allowed to differ across equations. Specifically, the ab mediated effect increases appropriately as the value of b increases, whereas the $c - c'$ method increases initially and then levels off and begins to decline, even though the true mediated effect continues to increase (56). Therefore, the $c - c'$ method of assessing mediation is not accurate for logistic regression or any method that fixes error variance to a certain value. One solution to this issue is to use a computer program that simultaneously estimates all regression equations so that the standardization is equivalent across regression equations (57). The Mplus computer program, for example, can be used to accomplish this goal (45). Similarly, variables can be specified as Poisson and other types of distributions.

Person-Centered Approaches

Each of the methods described thus far can be characterized as “variable-driven”; they measure the extent to which the relations between X, M, and Y (and consequently the mediated effect) are different from zero. Person-centered approaches provide a way of summarizing the data according to similarities in levels of or relations between variables. For the purpose of this article, we present approaches that have the common goal of identifying groups of people who are similar with regard to the type or intensity of mediation. We also discuss a hybrid mediation model, which combines variable-and person-centered analysis in a single model.

Collins and others (58) have proposed a method for identifying people with mediation “patterns” in treatment studies with three waves and binary X, M, and Y. To qualify for mediation with this method, individuals in the treatment group must have higher likelihoods of acquiring the expected level of the mediator (e.g., performing vigorous exercise for 20 minutes each day) and, subsequently, the expected level of the outcome (e.g., absence of major depressive disorder) than individuals in the control group. Specifically, three conditions must be met in order for individuals to meet requirements for mediation. First, assuming that individuals begin at a state that is absent of the mediator (i.e., they are not exercising for 20 minutes each day) and absent of the outcome (i.e., they have a diagnosis of major depressive disorder), the probability of being in both the mediator and outcome stage is greater in the treatment group than in the control group. Second, the probability of transitioning into the mediator stage from the no mediator stage is greater in the treatment group than in the control group. Using the example above, individuals who transition begin the study by exercising less than 20 minutes per day but, after exposure to treatment, exercise 20 minutes or more per day. This condition is congruent to a significant *a* path in Equation 3. Finally, for individuals not already in the outcome stage, being in the mediator stage increases the probability of transitioning into the outcome stage for both the treatment in control groups. Thus, membership in the state of exercising at least 20 minutes per day increases the probability that depressed individuals will transition into the “nondepressed” state. This condition applies regardless of treatment condition because the M→Y relation is not manipulated by the researcher.

The person-centered approach proposed by Collins et al. (58) can be useful in determining the extent to which a program is relatively effective for certain types of people, but the model assumes that individuals have neither the mediator nor the outcome at baseline measurement, which may be unrealistic for psychosomatic medicine researchers. As a result, this strategy may have more use in studies of very specific populations (e.g., depressed individuals who do not exercise). A second challenge with this approach is that it is only applicable to binary independent variables, mediators, and outcomes, resulting in reduced power to detect real effects (59).

MacKinnon (10) suggested that a person-oriented approach may be applied to continuous data by classifying individuals according to an underlying mediation process. Recently, von Eye et al. (60) proposed an application of configural frequency analysis to mediation. This method tests whether there are subgroups who differ from one another with regard to no, partial, or full mediation and can be applied to continuous X, M, and Y variables. The categories of mediation were constructed according to the conventions of Baron and Kenny (13), which may present considerable power issues because the sample is split into groups (23). The statistical properties of the configural frequency approach to mediation have not been tested in simulation studies.

A third application of person-oriented methods of mediation analysis identifies classes of individuals on the basis of shared, unobserved distributions, or mixtures, within a sample

(61,62). Mixtures can represent latent (i.e., unobserved) classes at one point in time, latent growth classes, or regression classes. This framework also accommodates either categorical or continuous indicator variables. Although there is no established method for integrating mediation analysis into a mixture modeling framework, hybrid models testing the relation between class membership and an outcome can be used to determine indirect effects. Consider the latent growth example described earlier of the longitudinal effects of a preventive intervention on high school male athletes' dietary habits. If there were a theoretical or empirical reason to believe that the sample contains unobserved groups with different growth shapes of the mediator (importance of peer leaders' information), a growth mixture model (GMM) can be tested to determine the number of growth classes. Specifically, it may be reasonable to expect that some individuals show an increase in importance of peer leaders' information, whereas others show no change. Yet, another group may show an increase but not until a later wave. Figure 8 shows a hypothetical model in which growth mixture class, denoted as CM, mediates the relation between treatment condition and athletes' dietary habits. CM is a categorical latent trajectory class variable. In this example, the latent trajectory class of the mediator predicts the outcome dietary behaviors. Interpreting the full model, treatment condition predicts individuals' membership in a given trajectory class, which, in turn, predicts levels of dietary behaviors. The indirect effect from X to Y and the bootstrapped standard errors can be obtained in the Mplus software program (45).

Because there are very few well-developed guidelines for assessing mixture models, it is important to use a systematic model-building procedure in addition to incorporating substantive theory. The statistical procedure for testing hybrid models should follow three general steps. First, determine the number of latent classes for the latent class variable. To begin, test the quality of a one-class model versus a two-class model and continue to increase the number of classes until the optimum number of classes is reached. A variety of fit indices and information criteria are available for determining the number of classes. For latent class analysis, the Bayesian information criterion (smaller numbers indicate more accurate models) and the Bootstrap Likelihood Ratio Test identify the correct model most consistently (63). Additionally, Tofighi and Enders (64) found that the sample size-adjusted Bayesian information criterion (65) and the Lo-Mendell-Rubin likelihood ratio test (66) provide the most consistent results for GMMs. The second step in testing hybrid models is to test the effect of covariates on class membership. In the mediation GMM example described above, treatment condition (X) is considered a covariate. Thus, a logistic regression analysis of the growth mixture class of the mediator (CM) on treatment condition (X) is the second step in this particular model. The final step is to test whether latent class membership predicts distal outcomes. This CM to Y relation is congruent to the *b* path in the simple mediation model described earlier. The significance of the indirect effect can then be calculated once this model-building procedure is complete. It is important to note that these models have strong assumptions concerning normally distributed repeated measures and that the introduction of covariates into a mixture model can affect the number of latent classes (67,68).

Experimental Approaches to Assessing Mediation

Because mediation entails causal relationships between variables, randomization of the predictor variables is necessary to establish causality. Many experiments within psychosomatic medicine have randomized the treatment or intervention (X), which allows the differences in means of groups on the mediator (M) and outcome (Y) variables to be attributed to the experimental manipulation. Because the mediator often cannot be directly manipulated, however, the M→Y (*b*) path is correlational. Experimental designs can help address this issue by manipulating the hypothesized mediator as directly as possible. For

example, a blockage design uses an experimental manipulation to block the mediation process. If the resulting relation is removed, then there is evidence for mediation. Consider a study in which social support mediates the relationship between a cognitive behavioral stress management intervention (CBSM) and immunoglobulin G antibody titers to herpes simplex virus Type 2 (69). A theoretical blockage design would assign randomly those receiving the CBSM treatment to either a group which limits associations with friends or a group where no specification about social interaction is given (control). If social support mediates the relation between CBSM and immunoglobulin antibody titers, then herpes simplex virus Type 2 immunoglobulin G titers should be reduced in the control group but not in the group for which social support was limited.

A second experimental design is an enhancement design. This design is similar to a blockage study, but elevated levels of the mediator are used to enhance the mediation process. Miller, Cohen, and Herbert (116) described a mediation relation where depression reduced lymphocyte proliferation through physical activity. An enhancement design of this process would assign randomly those with depression to groups with varying levels of physical activity or a group that is given no instruction (control). If depression reduced lymphocyte proliferation through physical activity, then reduced lymphocyte proliferation should be seen in all physical activity groups, with elevated results for the groups with the highest levels of physical activity. For both the blockage and enhancement designs, the effect of assignment to the treatment (blocked versus not or enhanced versus not) group can be found by testing the equality of the a and b paths across the groups (10,71).

Limitations of the Mediation Model

Several limitations of the mediation model warrant discussion. Holland (33) first outlined how the usual structural equation modeling defined by Equations 2 and 3 does not clearly lend itself to causal effects even when X represents a randomized intervention. When X represents a randomized intervention, the a and c relations represent causal effects but the b relation does not, as it is a self-selected treatment. Several methods have been proposed to improve the interpretation of this relation as a causal effect. In principal stratification (72), independent strata of individuals' mediator to outcome relation are hypothesized to obtain more accurate estimates. In marginal structural modeling, the influence of covariates is used to create propensity score approaches toward improving inference for this relation (17,73). Although these models attempt to address the complex task of identifying mediating variables, it remains unclear whether these more complicated models improve causal inference for real data (74).

A second issue related to causal inference is the problem of collider bias, which results from omitting one or more relevant covariates. Failure to incorporate covariates leads to inaccurate estimations of the $M \rightarrow Y$ relation. It is not possible to know definitively whether all relevant variables are included in the model, but theory and previous literature can guide these decisions.

Finally, because the mediation model is longitudinal by design, it may be of limited use in cross-sectional studies. Cole and Maxwell (48) and Maxwell and Cole (75) emphasized criticisms by Gollob and Reichardt (47) of cross-sectional mediation models, which do not account for the temporal ordering among the three variables. Two-wave mediation models allow for a longitudinal relation of the a path, but three-wave designs may provide a more convincing result in some cases, given that the variables are measured in concert with the true change process.

Summary and Recommendations

The purpose of this article was to outline the major approaches to testing mediation relations and provide an introduction to recently developed methods. Mediation models are natural tools for assessing causal processes in psychosomatic medicine because they help explain the often complex relations between the mental and physical domains of human functioning. The increase in the number of mediation studies has given rise to a wide variety of options for testing mediating processes, each with its own strengths and limitations. Baron and Kenny's (13) causal steps approach has been the most widely used method in this journal over the past 10 years, but now newer more accurate methods are available. One challenge with this method is its reduced power due to the requirement that the relation between *X* and *Y* is significant (23). Additionally, other commonly used methods that use the standard normal distribution to test mediated effects are underpowered (22). Bootstrapping and confidence limits based on an asymmetric distribution produce more accurate results (22). Effect size measures, such as the proportion mediated (for samples with at least 500 cases) and *R*² measures, can provide additional information on the size and meaning of the mediated effect (14,43,44). None of these methods, however, can replace theory and prior research-driven decisions of model testing.

Because the mediation model assumes specific temporal ordering of links among variables, more studies testing mediated effects over time are encouraged. Tests of longitudinal mediation, although complex, provide a more convincing case for temporal precedence than cross-sectional designs (10,48,75). Autoregressive models can estimate longitudinal mediated effects of 2 or more waves, but the interpretability of paths can sometimes be difficult (49,76). Rogosa (49) suggested addressing this issue with latent growth models. Parallel process latent growth models are useful in explaining mediated relations of growth among variables (39). LDS tests can be applied to models in which *X* does not represent a randomized treatment condition. Each of these and other tests of longitudinal mediation require careful attention to capturing the mediated effect as it actually occurs and to measuring variables as accurately as possible.

New approaches to mediation analysis, including experimental approaches, longitudinal mediation models, person-centered methods, and causal inference strategies may provide additional information about the links between bodily and psychological processes. Causal inference and experimental mediation designs may strengthen the evidence for causality because they introduce further manipulation into the *M*→*Y* relationship. Person-centered approaches provide a way of identifying groups that have similar mediational process patterns. Longitudinal models directly address temporal precedence among variables in the mediation process. These methods, still under development, represent promising tools for the difficult task of identifying mediating mechanisms in psychosocial and physiological processes.

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Glossary

ATHENA	Athletes Targeting Healthy Exercise and Nutrition Alternatives
CBSM	cognitive behavioral stress management intervention

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Figure 1.
Basic mediation model.

Figure 2.
Basic autoregressive mediation model.

Figure 3. Autoregressive mediation model with longitudinal and contemporaneous mediation.

Figure 4. Autoregressive model with all paths free to vary (bold paths violate the temporal precedence of $X \rightarrow M \rightarrow Y$).

Figure 5.
Latent growth curve mediation model. I = intercept; S = slope.

Figure 6.

Results from parallel process growth model. Only values relevant to the final mediation analysis are shown. For more details, see Cheong et al (39). Program = prevention program condition (X); Nutrit = nutrition behaviors (Y); Perleader = team leaders as an information source (M); IM = initial status factor of PerLeader; SM = growth rate factor of Perleader; IY = initial status factor of Nutrit; SY = growth rate factor of Nutrit.

Figure 7.
Importance of the match between theoretical model for change and measurement in a longitudinal mediation model.

Figure 8.
Hypothetical growth mixture model in which peer leader's information growth mixture class (*CM*) is a mediator between treatment condition and outcome (dietary habits).

Appendix

Mediation Articles, 1999–Present: *Psychosomatic Medicine*

Article	Model	Method
(77) Bosch et al., 2005	emotionality→catecholamines→NK mobilization	Baron & Kenny
(78) Brummett et al., 2005	social support→health bx→mortality	% reduction in IV coefficient
(79) Carney et al., 2007	depression→heart rate turbulence→time of death (survival)	Kraemer
(80) Chen et al., 2003	SES→stress/beliefs→cytokine	Stone
(18) Chesney et al., 2003	treatment→self-efficacy→psychological distress/well being	Baron & Kenny
(81) Christensen et al., 2004	SES→health behavior→BMI	% reduction
(82) Ciechanowski et al., 2004	attachment style→patient-provider relationship→diabetes adherence	Baron & Kenny
(83) Cohen et al., 1999	stress→IL-6→disease expression	Baron & Kenny
(84) Cohen et al., 2001	stress→health practices→antibody responses	Baron & Kenny, Stone
(85) Cohen et al., 2005	large structural equation model with multiple mediators	path analysis; unspecified
(3) Cohen et al., 2006	ed/income→psychosocial mediators→cortisol	Percent reduction in IV coefficient
(86) Creed et al., 2005	sex abuse→somatization→pain	Baron & Kenny
(87) D. Cruess et al., 2000	group assignment→change in BFS scores→Time2 cortisol	Baron & Kenny
(69) S. Cruess et al., 2000	CBSM →social support → HSV-2 IgG levels	Baron & Kenny
(88) Devriese et al., 2000	1 intervention→negative affectivity→selective conditioning 2 intervention→negative affectivity→generalization effect	unspecified
(89) Deykin et al., 2001	PTSD→depression symptoms/medical conditions→health services utilization	Path analyses
(90) Ditzen et al., 2008	intimacy→affect quality→cortisol	Sobel; MacKinnon's critical values
(91) DuHamel et al., 2004	large structural equation model with multiple mediators	Holmbeck; SEM
(92) Favaro et al., 2008	obstetric complications→harm avoidance→eating disorder	Baron & Kenny; Sobel; nonparametric bootstrapping procedure
(4) Frasure-Smith et al., 2002	treatment→anxiety→survival	Baron & Kenny
(93) Friedberg et al., 2007	alexithymia→anxiety→fatigue	Baron & Kenny
(5) Gale et al., 2008	childhood IQ→locus of control→health outcomes	% reduction in direct effect
(94) Gallo et al., 2001	education → HDL-C/smoking/waist-to-hip ratio → coronary calcification	Baron & Kenny, Reduction of unstandardized regression coefficient between IV and DV
(95) Gallo et al., 2003	marital grouping→pulse pressure→atherosclerosis	Baron & Kenny
(96) Garcia-Linares, 2004	abuse→psychological distress→immunity	Baron & Kenny
(97) Germain et al., 2003	stress exposure→psychophysiological reactivity→REM sleep parameters	Baron & Kenny
(98) Gleib et al., 2007	chronic stressors→perceived stress→physiological dysregulation	Baron & Kenny
(99) Grewen et al., 2004	depression→norepinephrine→blood pressure	Baron & Kenny
(100) Gump et al., 2001	social interaction→talking→DBP	Baron & Kenny
(101) Hall et al., 1998	intrusive thoughts/avoidance behaviors → sleep → natural killer cell # and function	Baron & Kenny
(102) Janicki-Deverts et al., 2007	SES→psychosocial factors→urinary catecholamines	% reduction in effect

Article	Model	Method
(103) Johnston-Brooks et al., 1998	density→cardiovascular reactivity→number of Days Ill	Path analysis, significant indirect effect (unspecified) (Pedhazur quoted)
(104) Johnston-Brooks et al., 2002	self variables → self-care → HbA1c	Baron & Kenny
(105) Keogh et al., 2006	negative expectations→anxiety→fear	Baron & Kenny
(106) Kivimäki et al., 2002	stressful life events → increased psychological problems and behaviors involving risk →health	Path analysis
(107) Kivimäki et al., 2008	organizational justice→blood pressure→CHD	Kraemer
(108) Kullowatz et al., 2008	stress→airway inflammation→lung function	Baron & Kenny
(109) Labus et al., 2007	psych distress→gastrointestinal-specific anxiety→gastrointestinal symptom severity	Bias-corrected bootstrap
(110) Lackner et al., 2004	depression→catastrophizing→pain severity	Baron & Kenny
(111) Leucken et al., 2005	family relationships→self regulation→SBP reactivity/recovery	SEM; presence of nonsignificant direct paths
(112) Lustman et al., 2005	depression→diabetes care→hyperglycemia	Baron & Kenny; Kraemer; Babyak
(113) Lutgendorf et al., 1998	intervention→cognitive coping→total mood disturbance intervention→social support→total mood disturbance	Baron & Kenny
(114) Mancuso, et al., 2004	pregnancy-specific anxiety→CRH→gestational age	Baron & Kenny
(115) Manne et al., 2001	intrusions→avoidance→later distress (simplified description of complex structural equation model)	Path analysis
(116) Matthews et al., 2000	SES →reduced serotonergic function → health	Unspecified
(117) Miller et al., 1999	depression → physical activity → proliferative responses	% reduction in variance
(118) Miller et al., 2004	stress→cortisol/health practices→antibody response	Sobel; MacKinnon's critical values
(70) Miller et al., 2007	SES→stress disparities→respiratory problems	Unspecified
(119) Mohr et al., 2003	PTSD→sleep disturbance→somatic symptoms	Baron & Kenny
(120) Moore et al., 2002	Income → sleep quality → psychological distress education → income → health	Baron & Kenny
(121) Morin et al., 2003	stress→sleep arousal→sleep	Baron & Kenny
(122) Mykletun et al., 2007	depression→health behavior→mortality	% reduction of direct effect
(123) Niaura et al., 2000	Ho → BMI, WHR, and fasting insulin → TRG, HDL-C, SBP, and DBP	Path analysis
(124) Peters et al., 1999	(mental) effort effect → heart rate/SBP/DBP →CD8 ⁺ and CD16 ⁺ cells (percentage and absolute numbers) and NKCA	Baron & Kenny
(125) Raikonen et al., 2004	trait anger→metabolic syndrome→atherosclerosis	Path analysis; fit only
(126) Rodriguez et al., 2007	personal attributes→perceived harm→adult smoking	Model indirect (Mplus; delta method)
(127) Rojo et al., 2006	stress→comorbidity→eating disorder	AMOS indirect r-square
(128) Stansfeld et al., 1998	psychosocial factors→health-related behaviors/biochemical measures→decrements in functioning	Odds ratio adjustment
(129) Steffen et al., 2001	religious coping/ethnicity → satisfaction with support/BDI/alcohol Consumption → BP	Baron & Kenny
(130) Sullivan et al., 2001	depression→positive affect→physical health	Decrease in correlation b/n IV and DV by mediating variable
(131) Thomas et al., 2006	ethnicity→discrimination→diastolic pressor response	Baron & Kenny
(132) Thomsen et al., 2004	rumination→immunity→health care utilization	Baron & Kenny
(133) Thurston et al., 2006	educational attainment→depression/anxiety→CHD	Cox proportional hazards; 1-log(HRadjusted)/log(HRunadjusted).

Article	Model	Method
(134) Van Tilburg et al., 2001	BDI→SMBG frequency→HbA _{1c}	Baron & Kenny (weakened the effect of DV on IV)
(135) Vitaliano et al., 2005	caregiving→mental health→gingival symptoms	Baron & Kenny
(136) Waldinger et al., 2006	childhood trauma→fearful attachment→somatization	Baron & Kenny; Kraemer
(137) Whiteman et al., 2000	complicated SEM model	Path analysis
(138) Wilson et al., 2005	personality→behavior patterns→mortality	% reduction
(139) Wulsin et al., 1999	depression→chronic physical illness/smoking/alcohol abuse/suicide and related accidents→early death (4 mediators)	Various

NK = natural killer; bx = —; IV = independent variable; SES = socioeconomic status; BMI = body mass index; IL = interleukin; BFS = benefit finding scale; HSV-2 = herpes simplex virus Type 2; IgG = immunoglobulin G; PTSD = posttraumatic stress disorder; SEM = structural equation modeling; IQ = intelligence quotient; HDL-C = high-density lipoprotein cholesterol; DV = dependent variable; REM = rapid eye movement; DBP = diastolic blood pressure; HbA_{1c} = glycated hemoglobin; CHD = coronary heart disease; SBP = systolic blood pressure; CRH = corticotropin-releasing hormone; Ho = cook-medley hostility scalescore; WHR = waist/hip ratio; TRG = triglycerides; NKCA = natural killer cell activity; AMOS = statistical program; BDI = Beck Depression Inventory; SMBG = self-monitored blood glucose; HR = heart rate.