CHAPTER 25

STATISTICAL MODELS OF MEDIATION FOR DRUG PROGRAM EVALUATION

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Mediation analysis is the statistical method used to investigate how a prevention program changes mediating constructs that are hypothesized to influence designated outcomes. Mediation analysis contribute to program evaluation and improvement by identifying the causal intervening mechanism, determining effective and ineffective program components, checking manipulation, and refining the program accordingly. This chapter describes examples of mediation that form the backbone of drug prevention theory and quantitative mediation analysis in drug prevention research. The following areas are described: estimation of the mediated effect, assumptions and effect size measures, multiple mediator models, multilevel mediation, longitudinal mediation models, person-centered approaches, and categorical outcomes. Finally, recent promising quantitative methods and experimental design approaches to address causal inference in mediation models are described. Several of these approaches include estimation methods based on the potential outcomes approach, in which counterfactual data for each participant is estimated, to improve causal conclusions from mediation analysis. Also, sensitivity analyses that can test how robust the mediated effect is to violations of assumptions underlying causal inferences are presented. Future directions for mediation analysis are discussed.

Prevention programs are designed to target intervening variables (known as *mediators*) to prevent health problems. As many chapters in this volume reinforce, preventive interventions involve multiple "modalities" and as a result frequently target more than one social and cognitive process. The focus on multiple target risk mechanisms requires positing multiple mediators to maximize the intended effects of a program on consistent program outcomes. Mediation analysis is the statistical method used to investigate how a prevention program changes mediators (i.e., alters behaviors, skills, and cognitions) and the precise way mediators influence outcomes. A mediator differs from other third variables, such as confounders or moderators, in that the mediator is logically positioned as an "intervening" mechanism on the path from the program assignment measure to the designated outcome. In this respect, mediation analysis is also called *process analysis* because it is used to investigate the process through which an intervention exerts its effects (Judd & Kenny, 1981; MacKinnon, 2008). Moreover, mediation analysis is also known as *effect decomposition* in which the total effect of a program is separated into direct and indirect effects reflecting the different manner in which the program influences the outcome. This chapter describes examples of mediation that form the backbone of

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drug prevention theory and describe quantitative mediation analysis in drug prevention research.

The literature articulates three broad categories of reasons for using mediators in prevention studies (Judd & Kenny, 1981; MacKinnon, 1994; MacKinnon et al., 1991; McCaul & Glasgow, 1985). These reasons touch on theoretical, program improvement, and practical aspects of evaluating prevention programs.

One of the most important reasons for including mediators in prevention studies is their ability to confirm or refute prevention theory. Prevention programs are developed on the basis of theory articulating how components affect targeted outcomes (Sussman, 2001). Two critical aspects in developing prevention programs are conceptual theory and action theory (Chen, 1990). Figure 25.1 graphically illustrates the sequence used to assess mediation in a drug prevention program. The path designated by *a* informs action theory, or in other words, the effect of a prevention program on the targeted mediator; and the path indicated by *b* informs conceptual theory, that is, the effect of the mediator on the outcome. The action theory is based on the intervention theory relating the prevention program (the education strategies) to the targeted mediator, whereas the conceptual theory is based on the developmental or etiology theory relating the mediating variable to the outcome variable (Chen, 1990; Lipsey, 1993; MacKinnon, Taborga, & Morgan-Lopez, 2002). Conceptual theory justifies the mediators targeted by the prevention program.

Mediating variables in drug prevention research can be identified on the basis of a wide variety of information. Usually, this includes knowledge of epidemiology and etiology supported by empirical data, social learning theory, developmental theory, and even biological theories. After an in-depth study of action and conceptual theories, researchers decide which mediators will be measured based on research aims and practical considerations. Action theory guides the selection of program components to affect the targeted mediators. The success of drug prevention programs usually is measured with outcome variables assessing a wide range of behaviors, including alcohol misuse or marijuana use as well as intentions to use or quit using a particular drug. One advantage of mediation studies is that if the program has no effect on the designated outcome, researchers can identify which part of the program (action theory or conceptual theory) may have failed. Action and conceptual theories illustrate that mediation is linked closely with a developmental and theoretical framework connecting risk and behavior. Martino (2011) stated that "mediation analyses are not meaningful without theory, and theory cannot be tested without mediation analyses" (p. S2). Furthermore, according to the law of maximum expected potential effect, the magnitude of the relation between the mediator and the outcome influences the potential effect size of a program (Hansen & McNeal, 1996). This statistical limitation arises because axiomatically speaking the focus of a drug prevention program is to influence

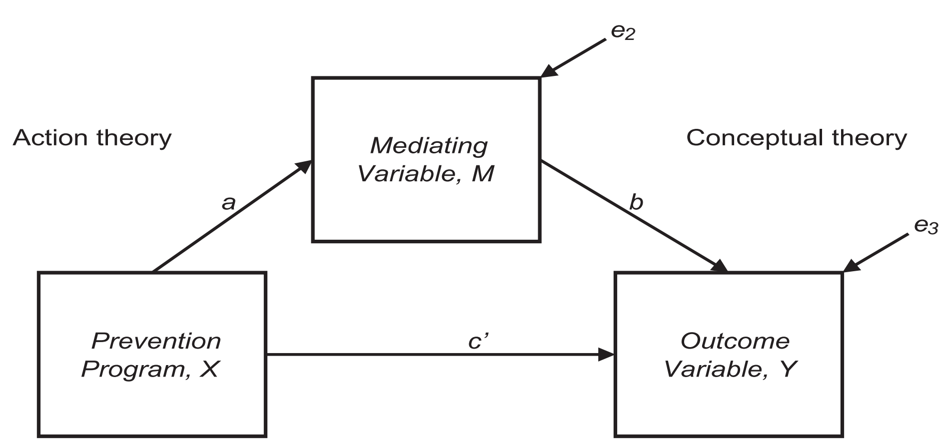

FIGURE 25.1. Single mediator model.

the mediator (i.e., reduce vulnerability by altering skills, beliefs, or attitudes), assuming that the relation between the mediator and the outcome has been established in prior research. Strictly speaking, the relation between the mediator and behavior is "unaffected" by the program. Because the relation between the mediator and the outcome already is expected based on theory and prior literature, the goal of the implemented program is to establish the link between the program and the mediator. Thus, the success of a program, from a mediation point of view, is primarily the degree to which the program changes the mediator, not the degree to which the mediator changes the behavior. The appeal of mediation analysis is evident in program improvement:

> This kind of research is important because it can identify the "*active ingredients*" in existing prevention programs, guide future refinements to existing prevention approaches, and provide important information that may lead to the development of new prevention approaches. Examining the way in which effective prevention programs work can also lead to further refinements of the theories upon which current prevention approaches are based. (Botvin, 2000, p. 893)

Consider a drug prevention program that targets decision-making skills. If the program does little to change decision-making skills, program developers will need to reconsider whether their intervention strategies effectively boost skills. There are many reasons for program failure, foremost among them the intervention model may not be developmentally sound, the implementation design may be flawed, and the measures of active ingredients may not be sensitive to change. Corrective action for each of these problems requires reconsideration of the program delivery methods as well as construction of the hypothesized mediation chain. Also, if a program does not cross-validate well with other populations, this may indicate that the program component needs to be further refined for lack of external validity.

A practical reason to conduct mediation analysis is that process evaluation provides a manipulation check for the prevention program. In other words, mediation provides a means for program developer to assess whether their intervention strategies change skills, beliefs, and attitudes, which then produces behavioral change. McCaul and Glasgow (1985) also called this *treatment construct validity*, suggesting that mediation provides the necessary information to evaluate whether the program worked in the manner hypothesized. For example, a prevention program aimed at reducing intentions to use drugs by increasing knowledge about the negative effects of drug use should have a significant effect on measures of drug consequence knowledge. Furthermore, mediation analysis can reduce program costs by identifying ineffective program components, which can be discarded in the interest of a more cost-effective and streamlined program.

EXAMPLES OF MEDIATION IN DRUG USE PREVENTION RESEARCH

Many different types of possible mediators can be applied in prevention research. Drug prevention programs typically target psychological measures as mediators (e.g., future intentions to use or expectancies that take shape as beliefs about the perceived effects drugs will have when used) or behavioral indicators as mediators (e.g., drug refusal or resistance behaviors). Certain psychological characteristics referred to as risk or protective factors (Hansen, 2002) often are targeted by prevention programs to modify outcomes. Table 25.1 provides examples of studies that have used mediation analysis as well as the target mediators, outcomes, and corresponding statistical methods used to evaluate program efficacy.

Social influence components constitute an important set of mediators for drug prevention programs (Cuijpers, 2002). Social influence programs examine mediators such as social norms, perceived peer approval of drug use, and perceived acceptability of drug use (Donaldson et al., 1996). Other programs found that social norms among friends were a significant mediator for drug prevention programs in school settings, whereas refusal skills were

TABLE 25.1

Examples of Mediation Studies in Drug Prevention Research

Reference	Mediators	Outcomes	Analysis
Ellickson, McCaffrey, & Klein, 2009	Alcohol misuse Drug misuse	Unprotected sex because of drug use Sex with multiple partners Inconsistent condom use	Sobel test
Buhler, Schroder, & Silbereisen, 2008	Knowledge about life skills	Alcohol use Nicotine use	Sobel test
DeGarmo, Eddy, Reid, & Fetrow, 2009	Youth aggression Youth social and problem-solving skills Family problem solving	Tobacco use Alcohol use Illicit drug use	Latent growth curve analysis
Henry, 2008	Association with friends who use drugs	Alcohol use Marijuana use Tobacco use	Structural equation modeling
Longshore, Ellickson, McCaffrey, & St. Clair, 2007	Resistance self-efficacy Intentions to use Positive and negative beliefs about drinking and smoking consequences Perceived-peer influence	Marijuana use Alcohol use/Consequences High-risk alcohol use	Causal steps and also Sobel test
Orlando, Ellickson, McCaffrey, & Longshore, 2005	Resistance self-efficacy Positive and negative beliefs about drinking and Smoking consequences Perceived peer influence	Cigarette and alcohol use Alcohol misuse Intentions to use	Longitudinal structural equation modeling
Spoth, Trudeau, Guyll, Shin, & Redmond, 2009	Substance initiation in adolescence	Alcohol, cigarette, and illicit drug use Polysubstance use	Latent growth curve analysis
Stephens et al., 2009	Intention to use (alcohol) Intention to use (cigarettes) Intention to use (marijuana)	Alcohol use Cigarette use Marijuana use	Structural equation modeling with categorical outcomes, also adjusting for cluster effects
Wang, Simons-Morton, Farhart, & Luk, 2009	Maternal knowledge Paternal knowledge Peer substance use	Alcohol use Cigarette use Marijuana use	Structural equation modeling
Epstein & Botvin, 2008	Drug skill refusal techniques	Adolescent drinking	Longitudinal structural equation modeling
Wenzel, Weichold, & Silbereisen, 2009	School bonding	Alcohol use	Multiple regression with residual change scores
Woodford, Krentzman, & Gattis, 2012	Experiencing/witnessing incivility Experiencing/witnessing hostility	Alcohol use/abuse Substance use/abuse	Logistic regression Sobel test Bootstrapping

not (Donaldson, Graham, & Hansen, 1994; Hansen & Graham, 1991; MacKinnon et al., 1991; Wynn, Schulenberg, Maggs, & Zucker, 2000). Likewise, Project Northland (Komro et al., 2001) found that peer influence to use alcohol significantly mediated program effects on behavior, whereas reducing access to alcohol did not mediate program effects.

Programs targeting similar outcomes (i.e., drug use) may focus on different mediators and use different statistical methods to assess mediation. Following conventions proposed by Hansen (1992), MacKinnon, Taborga, and Morgan-Lopez (2002) suggested grouping mediators into categories, including attitudes toward drug use, prevalence estimation, perceived benefits of drug use, availability, social norms, and refusal skills. Researchers may target different mediators to achieve similar program outcomes. For example, Bühler, Schröder, and Silbereisen (2008) examined whether knowledge of life skills mediated program effects on nicotine and alcohol use. DeGarmo, Eddy, Reid, and Fetrow (2009) investigated the effects of the Linking the Interest of Families and Teachers (LIFT) on tobacco, alcohol, and drug use outcomes for students from fifth to 12th grade. The program was designed to influence aggressive behavior on the playground and affect family problem-solving skills. Project ALERT modeled resistance self-efficacy and positive beliefs about use as significant mediators of program effects on drug use (Orlando et al., 2005). The Midwestern Prevention Project found that perceived peer reactions and intentions to use significantly mediated program effects on drug use in sixth- and seventh-grade students (MacKinnon et al., 1991).

The Single Mediator Model

To describe the quantitative methods used to estimate mediated effects, we use a school-based prevention program (i.e., indicated by the convention *X*) targeting the use of gateway drugs (e.g., alcohol, cigarettes, and marijuana, or outcome variables represented by *Y*) as an example throughout the remainder of the chapter. To continue with this example, discussion of mediation entails the role of social norms (indicated by the convention *M*). Social norms, for argument sake, entail the perception of how many peers or adults are using drugs (i.e., whether drug use is socially normative or acceptable). A potential covariate (i.e., using *W*) that possibly can affect the mediation paths is gender of the students (e.g., the program may have a stronger effect for girls than boys). Additional mediators and design elements will be added to the example in the following sections. In our example, individual students are assigned randomly to treatment and control groups, although mediation analysis also can be performed with nonrandomized *X* variables with corresponding analyses to address potential confounders of an observed effect in a nonrandomized intervention.

The following regression equations are used to assess mediation in a single mediator model:

$$Y = i_1 + cX + dW + e_1 \tag{25.1}$$

$$Y = i_2 + c'X + bM + eW + e_2 \tag{25.2}$$

$$M = i_3 + aX + fW + e_3 \tag{25.3}$$

where *Y* is the dependent (outcome) variable; *X* is the independent variable; *M* is the mediator; *W* is the covariate i_1, i_2, and i_3 are intercepts (i.e., the value of the dependent variable when the independent variables are set to zero); and e_1, e_2, and e_3 are residuals (i.e., unexplained variability). Using the example outlined earlier emphasizing social norms as the mediator and drug use as the outcome variable, the coefficient *c* in Equation 25.1 represents the total effect of the prevention program on drug use adjusted for the effect of participants' gender. The coefficient c' in Equation 25.2 is the effect of the prevention program adjusted for the effects of social norms and participants' gender (i.e., this notation indicates the *direct* effect). The coefficient *b* in this same equation is the effect of social norms on drug use adjusted for the program effect and the effect of participants' gender. The coefficient *a* in Equation 25.3 represents the relation between the prevention program and social norms adjusted for the effect of participants' gender.

Estimating the Mediated Effect

Mediation traditionally has been evaluated using three different approaches: the causal steps approach, the difference in coefficients approach, and the product of coefficients approach (MacKinnon, Lockwood, Hoffman, West, & Sheets, 2002). The causal steps approach also is known as the Baron and Kenny method (Baron & Kenny, 1986; Hyman, 1955; Judd & Kenny, 1981). This approach requires the following four steps are conducted in sequence: (a) The effect of *X* on *Y* in the first equation must be significant (i.e., the *c* path); (b) the effect of *X* on *M* in Equation 25.3 must be significant (i.e., the *a* path); (c) the effect of *M* on *Y* adjusted for *X* must be significant (i.e., the *b* path); and (d) the relation between *X* and *Y* should be weaker (or even approach zero) when the mediator is added to the model. In other words, $c\text{-}c'$ should be greater than zero. Although the causal steps approach commonly has been used by researchers, it has important limitations. First, the magnitude and significance of the mediated effect is not estimated. Second, the method requires a significant total effect, whereas a prevention program's effect on the outcome variable may be mediated even when the total effect is not statistically significant. Third, the requirement of a significant total effect means that the method also requires larger sample sizes compared with other methods (Fritz & MacKinnon, 2007).

A second approach to estimating the mediated effect is the difference in coefficients method. This method quantifies the mediated effect as c-c' and allows for the computation of the standard error of the mediated effect, confidence intervals, and significance testing. An important limitation of this method, however, is that it does not allow computing individual mediated effects in a multiple mediator model.

A third approach, termed the product of coefficients method, computes the mediated effect as the product of the path coefficients a and b. The standard z method for testing significance of the mediated effect uses the point estimate of the effect, ab, divided by its standard error and compares it with the normal distribution. The standard error of the product of coefficients is based on the multivariate delta method (Sobel, 1982).

$$SE(ab) = \sqrt{a^2 SE(b)^2 + b^2 SE(a)^2}$$

$$CI(ab) = ab \pm SE(ab) * z_{Type\ I\ error}$$

This method constructs confidence intervals for the mediated effect assuming that the product term ab is distributed normally. The product of two normally distributed coefficients, however, may not follow a normal distribution (Aroian, 1947). This results in low statistical power for the test of the mediated effect, especially for small to moderate sample sizes (MacKinnon, Fritz, Williams, & Lockwood, 2007; MacKinnon, Lockwood, & Williams, 2004) Currently, the program PRODCLIN (MacKinnon et al., 2007), also available in the R software package RMediation (Tofighi & MacKinnon, 2011), computes the confidence limits for the mediated effect using the distribution of the product term.

An alternative method to adjust for the nonnormality of the product of coefficients is the resampling approach. Resampling methods, such as bootstrapping, obtain repeated samples from the data set (with replacement or without replacement depending on the method used). The mediated effects for each sample then are calculated to form an empirical distribution of the mediated effect to be used in confidence interval construction (Bollen & Stine, 1990; MacKinnon et al., 2004). A main advantage of the resampling approach to mediation is that it is not limited to two-path mediated effect (as PRODCLIN is) and so it can be used in multiple path models. Also, studies on resampling methods in mediation showed that the bias-corrected bootstrap had more statistical power than the percentile bootstrap or PRODCLIN methods, but the methods may have high Type I error rates in small sample sizes (Fritz & MacKinnon, 2007; Fritz, Taylor, & MacKinnon, 2012). Several bootstrapping software options are now available in Mplus (L. K. Muthén & Muthén, 1998–2010), Amos (Arbuckle & Wothke, 1999), EQS (Bentler, 1997), and in SAS and SPSS (Lockwood & MacKinnon, 1998; Preacher & Hayes, 2004).

Assumptions

To accurately estimate the mediated effect in single mediator models, several statistical assumptions need to be met. First, it is assumed that the variables in the model are reliable and valid measures of the study variables. The second assumption, the additivity assumption, holds that X and M do not interact (Collins, Graham, & Flaherty, 1998; Judd & Kenny, 1981). An interaction between X and M in the single mediator model means that the effect of M on Y differs across levels of X. In other words, the effect of social norms on drug use would differ for the treatment and control group before the intervention. This interaction can be tested and added to the model to control for any pretest differences between experimental conditions. It also is assumed that the variables are continuous and normally distributed; however, models with nonnormally distributed variables may be estimated accurately using transformations (Cohen, Cohen, West, & Aiken, 2003; MacKinnon, 2008).

There are several assumptions regarding the causal nature of the mediation model to identify the mediated effect. It is assumed that the causal paths between X, M, and Y are correctly specified without bidirectional effects. Additionally, there are no omitted variables affecting the causal paths in the model, an assumption that will be discussed in more detail in the section on causal inference (Holland, 1988; Pearl, 2001, 2012; Robins & Greenland, 1992).

Effect Size Measures

In addition to testing the significance of the mediated effect, researchers usually want to know the magnitude of the mediated effect to practically evaluate the achievements of a prevention program (see previous discussion about statistical limitations to this effect). Although the standardized regression coefficients are also measures of effect size, several ratio measures can be used to determine the effect size of the mediated effect. A common method is the *proportion mediated*, which is the ratio of the mediated effect to the total effect [$ab/(ab+c')$]. For example, a proportion-mediated measure of 0.20 would mean that 20% of the total effect of the drug prevention program may be due to the mediated effect through social norms. Another measure is the *ratio mediated*, which is the ratio of the mediated effect to the direct effect (ab/c'). According to prior research, large sample sizes are required to have stable measures of these effect size measures (Freedman, 2001; MacKinnon, Warsi, & Dwyer, 1995). The *standardized effect* is also a ratio measure, which yields the size of the mediated effect in terms of the standard deviation of the outcome variable for a one unit change in X such as program versus control (ab/s_y; MacKinnon, 2008). Additionally, researchers may use R^2 effect size measures to determine the observed variance in the outcome variable that is attributable to the mediated effect or direct effect. R^2 effect size measures are shown to perform well for smaller sample sizes (Fairchild, MacKinnon, Taborga, & Taylor, 2009).

Multiple Mediator Models

Up until this point, discussion of mediation has focused on a single mediator. This is a simplified view of drug prevention, which normally entails multiple mediators corresponding to multiple program modalities. To illustrate, in the example used throughout this chapter, a multimodal drug prevention program may target additional mediators, such as knowledge about the consequences of drug use and attitudes about drugs (in addition to social norms). Given this is the current Zeitgeist for most prevention programs, it is important for the researchers to investigate the potential multiple causal mechanisms of the prevention program. Multiple mediators can be added easily to Equations 25.2 and 25.3. For instance, the equations for a two mediator model can be as follows:

$$Y = i_1 + cX + dW + e_1 \tag{25.4}$$

$$Y = i_2 + c'X + b_1M_1 + b_2M_2 + eW + e_2 \tag{25.5}$$

$$M_1 = i_3 + a_1X + fW + e_3 \tag{25.6}$$

$$M_2 = i_4 + a_2X + gW + e_4 \tag{25.7}$$

where M_1 and M_2 are the two mediators (i.e., social norms and attitudes toward drugs), X is the independent variable (program assignment), W is the covariate (i.e., gender of the participant), and Y is the outcome variable (drug use). The specific mediated effects for the two mediators M_1 and M_2 are then equal to the product of coefficients a_1b_1 and a_2b_2, respectively. The standard errors for the mediated effects to compute the confidence intervals are given in MacKinnon (2008). Also, the equality of multiple mediated effects can be tested (formulas provided in MacKinnon, 2000). The sum of the two mediated effects is called the *total mediated effect* of X on Y.

When all the mediated and direct effects in a mediation model have the same sign, then it is termed a *consistent mediation model*. If one of the mediated effects has a different sign, however, it is an *inconsistent mediation model* (Blalock, 1969; Davis, 1985; MacKinnon, Krull, & Lockwood, 2000). For example, participants in the treatment group may report an increased interest in marijuana use, which leads to an increase in marijuana use, at the same time that the program reduces intentions to use marijuana, which reduces marijuana use. In such a case, researchers may not detect the program effect if they do not investigate pathways corresponding to multiple mediators.

Multiple mediator models also may specify mediators in a sequential "chain." For instance, a model specifying three mediation paths could hypothesize the following sequence: $X \rightarrow$ Mediator $1 \rightarrow$ Mediator $2 \rightarrow$ Outcome. Taylor, MacKinnon, and Tein (2008) found that joint significance tests or resampling methods produced more accurate results for testing three path models. For models with multiple *X*, *M*, and *Y* variables, structural equation modeling is needed to correctly estimate the individual paths and indirect effects (Bollen, 1987).

Multilevel Mediation

Multilevel mediation models take into account the clustering effects determined by sampling such characteristics as school, family, or hospital. Individuals in the same group (i.e., cluster) have correlated observations because they have shared characteristics. These shared characteristics often occur with intact social groups that share unique environmental contexts (neighborhoods or workplace units). Failure to acknowledge the magnitude of clustering violates the independence of observations assumption and leads to elevated Type I error rates (i.e., false positives). Multilevel analysis corrects for the standard errors of clustered data and achieves better Type I error rates and statistical power (Raudenbush & Sampson, 1999). Clustering also can occur when multiple observations are obtained from the same individual. Multilevel mediation analysis provides a framework to incorporate longitudinal measures in which the individual is the second level and repeated observations within each individual constitute the first level. Also, programs that incorporate treatment for dyads (e.g., husband and wife, parent and child) may require multilevel analysis. Methods for multilevel mediation models have been developed and studied in simulation studies (Dagne, Brown, & Howe, 2007; Krull & MacKinnon, 1999, 2001; Pituch, Stapleton, & Kang, 2006).

An important feature of multilevel mediation analysis is that this approach estimates program effects at more than one level. Clustering of individuals in contexts means that contextual-level factors may influence the results. Failure to take contextual effects into consideration may lead to asserting stronger effects for individual-level variables than are appropriate. For example, continuing with the drug prevention example outlined earlier, a school-based program may influence the school environment (creating more conservative social norms schoolwide) as well as the individuals (altering resistance skills; MacKinnon, Kisbu-Sakarya, & Gottschall, 2013). In addition, in modeling mediation, path coefficients can be modeled as fixed (i.e., constant across clusters) or random (i.e., varying across clusters). For instance, in the case of repeated observations within each individual, program effects can be tested for each individual (i.e., do individuals change across time) and also across the mean of individuals aggregated by school membership, the latter representing program effects for which school is the unit of observation.

Longitudinal Mediation Models

Temporal precedence is an essential assumption in mediation analysis (Gollob & Reichardt, 1991; Judd & Kenny, 1981). The general framework for mediation suggests that *X* should precede *M*, and *M* should precede *Y* to provide an appropriate amount of time for program effects to occur. Cross-sectional data typically do not contain sufficient information to address longitudinal relations (Cheong, MacKinnon, & Khoo, 2003; Cole & Maxwell, 2003; MacKinnon, 2008). Importantly, longitudinal designs allow researchers to detect potential delayed effects, increase the statistical power to find an effect through reduction in error variance, and investigate developmental phenomena across time (Fritz & MacKinnon, 2012; Venter & Maxwell, 1999). This framework requires the mediator and outcome to be measured on at least two measurement occasions separated by sufficient time to allow program effects to surface. Adding more measurement waves provides additional information that can reveal the underlying developmental process linking the prevention program with change in the target outcomes. The need for temporal sequencing, however, also introduces a challenge in determining the measurement timing of each variable, which needs to rely on theory and prior research. Furthermore, the tendency to measure follow-up at 1-year intervals may lead to missing effects among measurements, especially processes occurring soon after program delivery and bursts of activity that occur during the onset of drug use, for example. Additionally, researchers need to be careful not to omit potential variables or paths to avoid misspecification error. In the following sections, several common methods for two- and three-wave (or more) models are outlined.

Two-Wave Models

Many longitudinal studies have two waves of data, including a baseline pre- and single posttest or follow-up assessment. There are three commonly used approaches to the analysis of two-wave data: analysis of covariance (ANCOVA), difference score analysis, and residualized change score analysis (Bonate, 2000; Kisbu-Sakarya, MacKinnon, & Aiken, 2013). The ANCOVA approach treats the baseline measures of the variables as covariates in mediation equations to adjust for baseline differences. Following the drug prevention example used thus far, a program developer can assess social norms and self-reported drug use at baseline. These variables can be assessed again at follow-up staged a few months after delivery of the program. The difference score approach computes the difference between the change in social norms from baseline to posttest, and likewise it computes the same score for self-reported drug use as the change from baseline to posttest. These difference scores then are used to test mediation.

Residualized change scores first regress a posttest score on its corresponding pretest score. Then the residualized change scores are computed by subtracting the predicted posttest scores from the observed posttest scores. The residualized change scores then are modeled in the mediation equations. If a researcher wants to reduce the two waves of measurement into single scores in modeling mediation, then residualized change scores can be used as an alternative to difference score analysis because difference score analysis may encounter reliability problems with floor and ceiling effects (Cronbach & Furby, 1970). Theoretically, the residualized change score approach is similar to ANCOVA because both analyses adjust for baseline measurement. The statistical adjustments used in both methods, however, differ (Bonate, 2000).

Autoregressive Models

Autoregressive mediation models for the analysis of three or more wave models specify adjacent longitudinal relations consistent with longitudinal mediation. Figure 25.2 shows the basic autoregressive model consistent with two follow-up waves of data collection following program implementation. The autoregressive model shown in Figure 25.2 tests a lagged measurement configuration separating the program (*X*) from the mediator (*M*) and the outcome (*Y*) by temporally spacing the assessment waves ($X_{T1} \rightarrow M_{T2} \rightarrow Y_{T3}$). Furthermore, contemporary mediation relations (e.g., $X_{T1} \rightarrow M_{T2}$, $M_{T2} \rightarrow Y_{T2}$) can be added to the longitudinal autoregressive mediation model to estimate the cross-sectional mediated effect within each wave, except for the first wave, in which the relations among *X, M*, and *Y* usually are specified as correlated (or fixed at zero owing to randomization of *X*, which should lead to nonsignificant correlations between X_{T1} and M_{T1} and X_{T1} and Y_{T1}).

Autoregressive models allow researchers to test for specific mediated effects and to compare them with other specific mediated effects within the same model, especially for many repeated measurements. The significance of specific mediated effects then can be tested by using the point estimate of the mediated effect and its standard error. The sum of all specific mediated effects between the prevention program and drug use is equal to the total mediated effect that also can be tested for significance. The total mediated effect represents the effect of the prevention program measured at Time 1 on the drug use outcome measured at the last wave of measurement, as mediated by social norms (specified as an intervening mechanism). A possible limitation of autoregressive models is that the model is fixed for

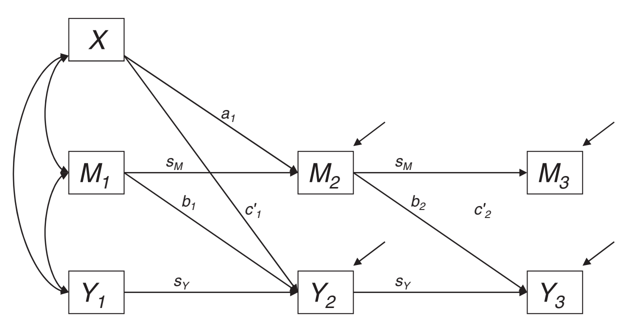

FIGURE 25.2. An autoregressive mediation model.

each individual in the study rather than allowing change to differ across individuals (Rogosa, 1988). As a different longitudinal approach, latent growth models (described in the next section as well as in Chapter 26, this handbook) may be preferred over autoregressive models if researchers are interested in the mediation of change across time, such as the relation between change in social norms and change in drug use.

Latent Growth Curve Models

Latent growth curve modeling (LGM) incorporates growth (change) in measures over time and individual differences in growth (B. O. Muthén & Curran, 1997). LGM computes continuous variable change (i.e., slopes) and intercepts as latent variables. Three growth trajectories are estimated for *X*, *M*, and *Y* to investigate whether the change in *X* is related to the change in *M* and if the change in *M* is related to the change in *Y*. Other model configurations also can be estimated, including positing a relation between an intervention and change in social norms and a change in drug use, or the effect of change in social norms on change in drug use at some later point in time. Cheong et al. (2003) used a piecewise parallel process model to estimate program effects on mediators at one point in time and then estimated effects of the mediator on growth of drug use at a later point in time. Piecewise modeling allows the investigator to dissect the curve into segments that may correspond to program effects at one point in time (junior high school) from effects that may surface at later points in time (high school).

Higher order cubic or quadratic trends can be estimated in addition to linear growth, positing that drug use reduces rapidly immediately after program delivery, but it then remains stable after a certain time period or starts to increase again. The LGM approach has been used in prevention program evaluation many times (Cheong, MacKinnon, & Khoo, 2001, 2003; Cheong, MacKinnon, & Pentz, 2002; Trim et al., 2007). When conducting LGM analysis, researchers should apply measurement invariance constraints over time because the change in measurement properties for developmental constructs may lead to confounded estimates. Furthermore, large sample sizes are needed to obtain adequate statistical power and a correctly hypothesized growth trajectory is required to obtain accurate estimates of program effects (Cheong, 2011).

Latent Change Score Models

In a latent change score (LCS) model, change scores are latent variables with error-free difference between the scores measured at two different time points (Ferrer & McArdle, 2010; MacKinnon, 2008; McArdle, 2001). LCS models allow researchers to estimate dynamic change in terms of the difference between assessment waves. The LCS model can be especially beneficial when testing a model in which the program affects the change in the outcome variable at earlier times but not at later times. For example, a smoking prevention program can have a favorable influence on cigarette use between Time 1 and Time 2, but it may have little effect on the same behavior between Time 3 and Time 4. LCS models also can estimate the rate of acceleration or deceleration between waves (i.e., second derivatives; Malone, Lansford, Castellino, Berlin, & Dodge, 2004). MacKinnon (2008) has provided additional information on estimation of LCS models with mediation.

Person-Centered Approaches

Up until this point in the discussion, the focus has been on variable-centered methods. Variable-centered methods estimate the influence of one set of variables on another set of variables using primarily correlation-based techniques. This methodology uses rank ordering and distributional overlap to discern statistical relations. Person-centered analyses, on the other hand, emphasize individuals' response patterns and statistical profiles based on their marginal distributions. That is, in person-centered analyses, whether individuals aggregate into discrete or homogeneous subgroups based on their response profiles is of greater interest than how one variable influences another. Tests of person-centered models can be used to examine whether a model is consistent or inconsistent with hypothesized mediation. The person-centered approaches include finite mixture models estimating trajectory classes (B. O. Muthén & Muthén, 2000), staged response across trials (Collins, Graham, & Flaherty, 1998), and configural frequency analysis (von Eye, Mun, & Mair, 2009).

All of these different approaches provide researchers a means to understand the mediational mechanisms at the individual level as well as at the group level. In the trajectory classes and staged response across trials methods, categorical latent variables usually are created to identify whether the individuals' responses are consistent with the mediation pattern. Configural frequency analysis, on the other hand, specifies the frequencies of responses to independent, mediating, and dependent variables that are consistent with the mediation pattern (von Eye et al., 2009).

Collins et al. (1998) also proposed a person-centered approach for categorical measures of *X*, *M*, and *Y* (where responses are coded as yes or no). The latent transition analysis (LTA) approach identifies mediation using an individual's probability of attaining the expected level of the mediator (e.g., negative attitudes toward cigarette use) and likewise estimates the probability of membership in a binary outcome variable (e.g., cigarette use or not). To illustrate the LTA approach, there should be a greater probability of transitioning from higher to lower status of risk (i.e., attitudes toward cigarette use) in the treatment group than the comparison control group. Also, individuals who transition into a lower level of risk also should have lower risk for the outcome variable (e.g., cigarette smoking). The transitional probabilities corresponding to the risk and consumption status groups are used to indicate program efficacy. Mediation is determined by estimating program effects on movement from a higher to lower risk status and movement from a higher to lower consumption status (or even from use to nonuse).

There are several assumptions to using the LTA approach. For one thing, classification methods like LTA assume there is a homogeneous group of individuals that belong within a discrete status group, for instance, a cluster of youth who report very strong antitobacco attitudes at baseline. This may not be realistic given that a very heterogeneous mixture of youth usually have both favorable and unfavorable attitudes toward tobacco use. This prevents there from being a clear demarcation of individuals based on their respective attitudes (or beliefs) toward tobacco use and its consequences. LTA, however, assigns youth based on a posteriori probabilities to membership in discrete status groups (those who responded favorably to anti-drug attitudes versus those who endorsed prodrug attitudes), an approach that may overlook making finer distinctions (Lockhart, MacKinnon, & Olrich, 2011). Additionally, the method is applicable only to categorical measures of *X*, *M*, and *Y*, which reduces statistical power to detect an effect. A test of significance for mediation using a person-centered approach has been proposed by Fairchild and MacKinnon (2009).

Categorical Outcomes

Categorical outcomes that capture discrete consumption patterns (e.g., tobacco use or no use) or drug use diagnostic categories (abuse/dependence) are fairly common in drug prevention research. In the case of categorical outcomes, Equations 25.1 and 25.2 can be estimated using logistic regression. Researchers, however, need to be careful when computing the mediated effect. The coefficient c' depends on both the mediated effect and the scaling of *Y* in Equation 25.2, and so the c-c' estimate of the mediated effect can be inaccurate (MacKinnon & Dwyer, 1993). The c-c' estimate is also no longer equivalent to the *ab* estimate, although researchers can convert the c-c' estimate into the *ab* estimate metric by simultaneously standardizing the regression coefficients to be used in estimating the mediated effect (MacKinnon & Dwyer, 1993; MacKinnon, Taylor, Yoon, & Lockwood, 2010; Winship & Mare, 1983). Pearl (2012) proposed a new formulation of the mediated effect that accommodates the nonlinear relations involved in categorical outcomes.

Causal Inference in Mediation

New methods have been proposed recently to improve causal inference in mediation analysis (Frangakis & Rubin, 2002; Holland, 1988; Jo, 2008; Pearl, 2009, 2010; Robins & Greenland, 1992; Rubin, 2004; Sobel, 2008). Several of these approaches include estimation methods to improve causal conclusions from mediation analysis, and they also offer sensitivity analyses that can test how robust the mediated effect is to violations of assumptions underlying causal inferences. Most of the approaches to causal inference in the mediation literature use the counterfactual approach, in which counterfactual data for each participant is estimated (Rubin, 1974). To understand the counterfactual method, consider a drug prevention program in which participants are assigned randomly to treatment and control conditions. Counterfactual scores for participants in the treatment condition would be the participants' potential responses if they had been assigned to the control condition, as is described in more detail in the later sections.

The main concern in causal inference for mediation is the effects of potential omitted variables (confounders) on the estimated paths. Omitted variables can introduce bias by reinforcing potential explanations for the relations estimated in the hypothesized mediation model (MacKinnon, 2008). For example, with randomization to experimental condition, the relation between program assignment (treatment vs. control) and the mediator (i.e., social norms) can be assumed to be causal because randomization balances the influence of omitted variables. In a single mediator model, randomization allows the path designating the "intervention effect" (a) to be interpreted as causal. Furthermore, randomization also allows the total effect (corresponding to the c path) of the drug prevention program on drug use outcomes to be causal. The effect, however, of social norms on drug use (the relation between the mediator and the outcome) cannot be interpreted as causal because social norms are not randomized; thus, omitted variables may contribute bias to the b path. Similarly, the direct effect of the program on drug use adjusted for the effect of social norms (the c' path) cannot be interpreted as causal.

The omitted variables (confounder) bias is described more formally by the *sequential ignorability* assumption (Imai, Keele, & Tingley, 2010; Lynch, Cary, Gallop, & Ten Have, 2008; Ten Have et al., 2007). The sequential ignorability assumption contains two parts. According to the *sequential ignorability I* assumption, there is no unmeasured confounder for the relation between X and M. Typically, this assumption is ensured by the randomization of participants to levels of X because randomization makes all other variables equivalent between the levels of X. According to the *sequential ignorability II* assumption, there is no unmeasured confounder for the relation between M and Y. In other words, there are no potential omitted variables that can lead to a potential explanation for the relation between the mediator and the outcome variable. Because the score on the mediator is not assigned randomly to participants but is self-selected by participants, this assumption is difficult to satisfy. Therefore, several methods have been proposed to address this important issue.

Sensitivity Analysis

Given the potential challenge to causal inference with studies that rely on mediation analysis, a researcher may want to assess how robust his or her results are to the effect of unmeasured third variables. The following discussion assumes randomization of X. Sensitivity analysis assesses how large a confounder effect (i.e., sequential ignorability II) corresponding to the M→Y relation must be to invalidate conclusions about mediation (Frank, 2000; Y. Li, Bienias, & Bennett, 2007; Rosenbaum, 2002). Current approaches that investigate sensitivity to confounder bias display the confounder values that would reduce the observed mediated effect to zero using plots (Imai, Keele, & Tingley, 2010; VanderWeele, 2010). The approach by Imai et al. (2010) presents confounder bias as correlated error terms between the error in the mediator model and the error in the outcome model (i.e., the error terms e_2 and e_3 in the single mediator model equations). If the sequential ignorability II assumption holds, then e_2 and e_3 must be uncorrelated. The plots by Imai et al. (2010) illustrate how much the mediated effect changes as a function of the magnitude of correlation between e_2 and e_3. Another sensitivity analysis approach by VanderWeele (2010) is based on the relation of the confounder to Y and the difference in the proportion of people with the confounder at the same value of mediator between groups. In addition to assessing the sensitivity of results to potential violations of the sequential ignorability assumption, several quantitative methods (described in the following sections) are proposed to improve causal interpretation of coefficients in mediation.

Inverse Probability Weighting

The potential outcomes framework (Holland, 1988; Rubin, 1974) makes a distinction between an individual's observed and counterfactual outcomes. Suppose an individual is assigned to the treatment group in a drug prevention program and as a result obtains an observed outcome value. Then the counterfactual outcome for that individual is the value she or he would have obtained on the outcome variable if she or he had been assigned to the control condition. According to Rubin (1974), the causal effect of the program on the outcome is then equal to the difference between the observed outcome for that individual and her counterfactual outcome. Because it is often not possible for the same person to appear in both groups (referred to as the "fundamental problem of causal inference" by Holland, 1988), the average causal effect then is computed as the mean difference between the observed outcomes of individuals under the treatment and control groups.

The potential outcomes framework allows for new definitions of direct and mediated effects using marginal structural models. Marginal structural models are different from linear regression models because they focus on potential outcomes, whereas linear regression models examine observed outcomes. Marginal structural models usually are estimated with inverse probability weighting (IPW), which creates a pseudo-population as a randomized cohort (Robins, Hernan, & Brumback, 2000). The IPW method creates weights that correspond to the inverse probability of receiving the treatment that the participant actually received, conditional on the measured confounder variables. IPW assumes that all confounders are measured and so allows for the estimation of causal effects. In a mediation context, the mediation equations are weighted using the derived weights. This procedure adjusts for possible confounders of the mediator-outcome relation. To illustrate, several potential confounder variables including gender and attitudes about drugs can be used to estimate a propensity score by regressing the mediator on a set of confounders. Then, the mediation Equation 25.2 can be weighted by using the IPW method based on those propensity scores. The IPW method has been used thus far in drug prevention research in a nonmediation context (Bray et al., 2006; L. Li, Evans, & Hser, 2010). Further details and data analysis syntax on conducting the IPW method in the presence of mediators and moderators can be found in Coffman and Zhong (2012).

Instrumental Variable Method

The instrumental variable (IV) method mimics randomization by introducing an instrument to the estimation process (Angrist, Imbens, & Rubin, 1996; Angrist & Krueger, 2001; Shadish, Cook, & Campbell, 2002). In the mediation context, for example, the random treatment assignment X can be used as an instrument to improve the causal interpretation of social norms on drug use. The instrumental variables approach uses the two-stage least squares method in which two equations are jointly modeled. In the first stage of estimation, the mediator M is predicted from the instrumental variable. In the second stage, the outcome variable Y is regressed on the predicted M scores. Then, the statistical significance of the coefficient relating predicted values of M to Y is the causal test of the b path for the mediated effect.

The IV approach has several required assumptions, four of which are described briefly here. First, the treatment assignment (i.e., instrumental variable) is random, implying that the treatment assignment is uncorrelated with unobserved pretreatment characteristics of the participants. A second assumption is that the random assignment affects the outcome only through the mediator (i.e., the exclusion restriction assumption). Third, the treatment assignment has a significant effect on the mediator (i.e., a significant a path). The instrument needs to be related strongly to the mediator to allow the predicted M to reflect randomization. Fourth, no participants act in the opposite direction of their treatment assignment. In the instrumental variables literature, this assumption is called *monotonicity*, suggesting that participants assigned to the intervention condition receive the treatment, and participants who are assigned to the control (untreated) condition do not receive any treatment (i.e., there is no "contamination" in the assignment procedure). These assumptions usually limit the applicability of the IV approach. Yet, more applications of IV mediation methods are needed to uncover the potential benefits of this approach.

Principal Stratification

The principal stratification method is based on the classification of different response patterns for the relations among *X*, *M*, and *Y*. Subgroups of study participants are identified based on how the relation between *M* and *Y* could change in response to the treatment, as will be described (Jo, 2008). For instance, in a drug prevention program with control and treatment groups, four subsets of people can be specified: (a) never-improvers, people whose mediator would not improve if they were in either treatment condition; (b) forward-improvers, people who would benefit from the intervention only if they received the treatment; (c) backward-improvers, people who would improve only if they were in the control group; and (d) always-improvers, people whose mediator would improve if they were in either treatment group. Covariates usually are used to determine stratification so that the classification is independent of individual treatment assignment (Jo, Stuart, MacKinnon, & Vinokur, 2011; Stuart, Perry, Le, & Ialongo, 2008). The mediated effect then is estimated within and between these stratifications (Angrist, Imbens, & Rubin, 1996; Frangakis & Rubin, 2002; Jo, 2008).

Experimental Design Approaches

Mediation analysis provides important information on a prevention program by exploring the underlying "psychological" processes affecting the outcome. The typical experimental design to test mediation involves an experimental manipulation hypothesized to change an outcome through the mediator, a process that is measured in each treatment group. Because the assignment to treatment conditions is usually random, the effect of the treatment *X* on the mediator *M* can be interpreted as causal. Because the mediator is not manipulated directly, the effect of the mediator *M* on the outcome *Y* does not represent a causal relation, nor does the mediated effect (as described in the earlier section discussing causal inference). This violation of the sequential ignorability assumption can be addressed by several research designs (MacKinnon, 2008) in addition to the quantitative methods described in the previous section.

The enhancement design is one experimental design that can strengthen causal inference with mediation. In this design, exposure to the mediator is manipulated by enhancing the dose of the mediator (e.g., Klesges, Vasey, & Glasgow, 1986). If *M* is a true mediator, then the $X \rightarrow Y$ relation will occur in greater magnitude in the enhanced mediator condition. Consider again the example of a prevention program that targets reducing intentions to use drugs by changing social norms. The program essentially teaches youth that drug use is not socially acceptable or normative (prevalence themes) and demonstrate to youth the anticipated effects of drugs are not beneficial. Participants in the treatment condition can be assigned randomly to enhanced social norm versus standard social norm conditions. The enhanced social norm condition then can manipulate normative education with the intention of deterring youth from using drugs based on altering perceived social acceptability of drug use. If social norms significantly mediate program effects, then the treatment group with the enhanced social norm condition should show a greater reduction in intentions to use drugs than the low social norm or control group. This type of stratification approach, which experimentally manipulates the mediator, is much needed to discern the relative importance of program dose.

A second approach involves strategies to "block" or stratify the mediator as a means of examining whether the mediated relation is observed in the usual treatment condition but not in the blocked condition (Robins & Greenland, 1992). Here, the mediator is blocked in one condition to provide evidence that the relation from $X \rightarrow Y$ depends on the mediator. For instance, using the social norm example provided previously, participants in the treatment condition would be assigned to a condition using the usual social activities (e.g., role-playing, small group consensus building) that change social norms, whereas a blocking condition would not have any of the social activities designed to change group norms. The idea is that blocking the activities that change social norms would not allow the social norm mediator to change, thereby blocking the program effect. If the $X \rightarrow Y$ relation no longer exists in the blocked mediator condition, then there is evidence that social norms mediate program effects.

Blocking and enhancement designs have several advantages and disadvantages. For one thing, these designs provide experimental evidence for causality, temporal precedence, and specificity (i.e., *Y* only occurs under certain conditions of *X* and *M*) of the mediated relation (MacKinnon & Pirlott, 2010; Spencer, Zanna, & Fong, 2005). Furthermore, the enhancement design reinforces the convergent validity of the mediating relation by testing its consistency across different representations of the same construct. On the other hand, these designs can strategically be difficult to employ. Although the use of experimental design to test for mediation is not new, only recently has this approach received more attention in the literature (Imai, Tingley, & Yamamoto, 2013; MacKinnon, 2008; Spencer et al., 2005). New developments in modern causal methods can be combined with experimental designs to achieve more evidence for mediated effects.

CONCLUSION

Mediation analysis is used widely across a range of areas, but it is of particular interest in drug prevention research where it can be used for design planning, analysis, and theory development. Taken as a whole, mediation analyses provide a means for investigators to test (and even contrast) multiple theories regarding how and for whom a drug prevention program works. Testing for mediation can extend to complex models with multiple mediators or can be applied (and help resolve) inconsistent models that contain opposing effect signs. More complex models also include nested mediation models and longitudinal mediation models, which can be tested using multilevel modeling, LGM, and LCS modeling. In addition to assessing mediation by looking at relations among variables, person-oriented approaches to mediation, which evaluate the patterns underlying individual response styles, can be used as well. Person-centered approaches to mediation are a new way to elucidate mediating mechanisms and provide a good contrast to the traditional variable-centered approaches that have formed the bulk of studies assessing mediation. A combination of person-centered and variable-centered approaches potentially could be beneficial as well.

Causal inference in mediation is an area of research that is now being studied in greater depth and continues to be an important area for advancements. Research in causal inference in mediation analysis has led to recent advancements in analyses designed to address causal assumptions of mediation models. Methods for handling causal inference assumptions in mediation, as well as tests of robustness to violations of those assumptions, are an important subject for future exploration. Enhancing mediation models through experimental designs is another new way to address causal inference issues in mediation and requires further examination as well. Developments in these areas will continue to broaden our knowledge of the mediation process and will increase our understanding of how prevention programs work.

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