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Mediation Analysis With Longitudinal Data

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Mediation analysis provides a multivariate framework for testing hypotheses about chains of causal relationships among multiple variables (MacKinnon, 2008). The most straightforward mediation model is one where a primary causal variable *X* leads to changes on an observed mediating variable *M*, which in turn causes changes on an outcome variable *Y*. This relatively simple model is remarkably useful in many research contexts. It can be used, for example, to evaluate the hypothesized causal mechanisms that account for intervention effects on outcomes or to examine the fit of purely observational data to theoretically derived causal models. Suppose that a randomized controlled trial (RCT) has demonstrated that a physical exercise training program (*X*) improves cognitive functioning (*Y*) in a relevant population. A subsequent mediation analysis question might involve a test of whether a proportion of the cognitive benefits of this training program can be explained by changes on a certain mechanistic variable, such as a measure of regional cerebral blood flow (*M*). In purely observational research, the primary causal variable is not manipulated, but naturally occurring variability in exercise participation might still be linked to cerebral blood flow and, indirectly, with cognitive performance along the same causal pathways. Mediation analysis, therefore, provides a flexible analytic framework for examining conceptual models that consist of chains of causal relationships and requires, at a minimum, at least one primary causal or exogenous variable, one mediator or proximal effect of that causal variable, and one outcome or more distal effect of that causal variable.

The conceptual models can quickly become more complex and interesting when multiple exogenous *X* variables, multiple mediating *M* variables, and multiple outcome Y variables are measured. Numerous options and complexities are also introduced when multiple waves of data are collected over time. It is this dimension, the longitudinal aspects of mediation modeling, that is the primary focus of the examples and the discussion provided in this chapter.

Another area of complexity, and potential confusion, is that some variables can take other roles besides that of a mediator in multivariate causal models (Kraemer, Stice, Kazdin, Offord, & Kupfer, 2001). For example, some variables might be hypothesized to serve as effect modifiers or moderating variables. A moderator is an independent or predictor variable that has a statistical interaction effect with another predictor, and therefore, has a conceptual interpretation that is distinct from that of a mediating variable (Baron & Kenny, 1986). Using the example discussed above, if exercise improves cognitive functioning more for those with low cerebral blood flow than for those with high cerebral blood flow, then cerebral blood flow moderates the effect of exercise on cognition, whereas if exercise improves cognitive function *because* it increases cerebral blood flow, then cerebral blood flow mediates the effect of exercise on cognition. Furthermore, models with both moderation and mediation effects are conceivable, and it is possible, for example, to construct models that test for the mediators of moderation effects (e.g., Edwards & Lambert, 2007; Fairchild & MacKinnon, 2009). In this chapter, our goal is to provide an overview of the general concepts of mediation analysis only and to discuss the issues involved in applying mediation analyses to longitudinal (multiple wave) data. Many of the concepts and options discussed here surely extend to more complex multivariate models with both mediation and moderation effects.

In addition to a conceptual overview of mediation in the longitudinal analysis context, we also illustrate the execution of example longitudinal mediation analyses using data from an RCT of an intervention to improve the health and well-being of spousal caregivers of dementia patients. As we demonstrate, there are many analytic alternatives to testing mediation hypotheses in longitudinal models. Many alternatives involve either (a) deriving indirect or mediated effects, and their standard errors, from the estimates obtained in separate linear regression equations (or other generalized linear models) or (b) estimating these same effects and their standard errors from a single structural equation model (SEM). We provide examples of both of these approaches. All of our examples are based on directly observed variables, but much of the logic and the steps illustrated can be generalized to more comprehensive structural models that have latent variables as identified in embedded measurement models. In analyses with latent variables, the concepts and procedures illustrated here typically apply to the structural portions of the model, which are usually addressed after the measurement modeling and latent variable confirmation process has occurred (Anderson & Gerbing, 1988; Kline, 2005).

Elementary Concepts in Mediation Analysis

The basic three-variable mediation model with one primary causal variable (X), one mediator (M), and one outcome (Y) is illustrated in Figure 6.1. In many applications, the effects in Figure 6.1 are estimated with ordinary least squares linear regression equations. First, an initial regression equation estimates the unadjusted effect of X on Y:

$$Y = i + cX + e \tag{6.1}$$

The regression coefficient c is referred to as the *total* or *unadjusted effect* (of X on Y).

Next, two additional regression equations are fit to the data:

$$M = i + aX + e \tag{6.2}$$

$$Y = i + bM + c'X + e \tag{6.3}$$

In all three equations, i refers to an equation-specific intercept or the predicted value of the dependent variable when all predictor variables are zero, and e refers to a residual or error term that is specific to each individual subject in each equation. Typically, it is assumed that the error terms are normally distributed and that their magnitude is not systematically related to the predictor variable(s) in the model.

The effects represented by the regression coefficients a and b from Equations 6.2 and 6.3, respectively, account for the *mediated* or *indirect* effect of X on Y, whereas the regression coefficient c' from Equation 6.3 represents the *unmediated* or *direct* effect of X on Y. This unmediated or direct effect is also sometimes referred to as the *adjusted* effect (of X on Y) after controlling for the mediating (or confounding) effect of M. In the case of total or complete mediation, all of the observed impact of X on Y can be explained or accounted by the combination of the $X \rightarrow M$ and $M \rightarrow Y$ relationships, and in that case, the c' effect is equal to 0. In the case of partial mediation, some, but not all, of the $X \rightarrow Y$ relationship can be explained by the intervening $X \rightarrow M$ and $M \rightarrow Y$ relationships, leaving a nonzero c' unmediated effect.

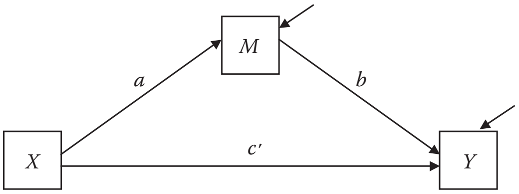

FIGURE 6.1
Basic three-variable mediation model.

There are two general methods for estimating the size of the mediated effect from a simple mediation analysis: $a \times b$ and $c - c'$. In an ordinary least squares linear regression with a single causal variable X and a single mediator M, it has been shown that $a \times b$ is algebraically equivalent to $c - c'$ (MacKinnon, Warsi, & Dwyer, 1995). However, this potentially reassuring equality does not usually hold in most other mediation models, including those with multiple mediators, categorical outcome variables, or categorical mediators (MacKinnon & Dwyer, 1993). As we demonstrate shortly, this equivalence is also usually not evident in longitudinal models because of the many ways in which these models may be specified. Fortunately, multiple methods are available for estimating the standard errors and confidence intervals (CIs) for either $a \times b$ or $c - c'$ (MacKinnon, Lockwood, Hoffman, West, & Sheets, 2002). By becoming more informed about these choices and options, investigators should be empowered to select methods that are optimal for the particular research questions under investigation.

The single mediator model illustrated in Figure 6.1 has been influential for testing the independence of observed relationships between predictors and outcomes. Mediation models are often used with cross-sectional data collected from either observational or experimental research designs. The inferences that can be drawn from this type of model are based on some important assumptions, both statistical and theoretical, and incorrect or misleading inferences can be made when some of the assumptions are not satisfied (Gollob & Reichardt, 1991; Maxwell & Cole, 2007). For example, the simple three-variable mediation model of Figure 6.1 is statistically equivalent to a simple confounding model as illustrated in Figure 6.2 (MacKinnon, Krull, & Lockwood, 2000). Notice that in Figure 6.2, the causal direction of the $X \rightarrow M$ relationship has been reversed, and X is now the mediator of M's effect on Y. In both models, the direct effect of X on Y is c' and is determined statistically after accounting for the $M \rightarrow Y$ relationship. If X is years of education, M is annual salary, and Y is a health care adherence variable, for example, then c' represents the impact of education on the health care variable after controlling for income regardless of whether income is seen as an effect of education (a mediation effect) or as just a correlated socioeconomic indicator (a potential confounding effect). In this uncontrolled cross-sectional analysis, the unmediated and unconfounded effects of education on health care are equivalent—both

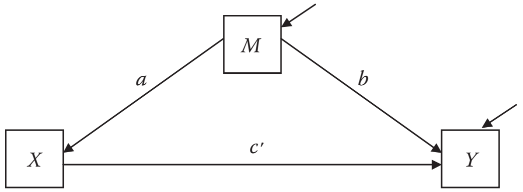

FIGURE 6.2
Simple confounding model.

are simply the covariate-adjusted effect of X on Y after statistically controlling for the effect of M.

Some researchers consider the terms "mediator" and "confounder" to be interchangeable due to the equivalence of their estimated effects in simple cross-sectional analyses. However, the more theoretical approach considers a mediating variable to be an *effect* of the primary causal variable and implies that a causal interpretation is plausible for the $X \rightarrow M$ relationship. Furthermore, the theoretical assertion that M also transmits a causal effect on Y places another causal assumption on the b effect of the model. These assumptions are useful for positing that a specific type of relationship exists among the variables and for elucidating the mechanisms of change in the context of a causal sequence of potentially controllable effects. The degree of confidence that investigators can claim regarding these causal assumptions largely depends on the type of research design that is used. Fortunately, the design elements that can strengthen cause-and-effect interpretations (e.g., randomization, longitudinal relationships) can also easily be incorporated into analytic models that test mediation relationships.

Strengthening Causal Interpretations

At the most fundamental level, when an investigator wishes to determine whether an observed association between two variables represents a causal relationship, there are a few critical methodological strategies that can be used either to reduce the likelihood that simple confounding is being observed or to increase the likelihood that a true causal relationship is being observed. For the simplest two-variable relationship, the most straightforward and unequivocal demonstration of a cause-and-effect relationship is provided by the randomized controlled experiment. In this design, the investigator manipulates the independent variable X by randomly assigning subjects to one of two or more possible conditions that comprise that independent variable. Effects of that manipulation are then observed on one or more dependent variables. Because the variability of the independent variable in an RCT is only randomly associated with all other measured (and unmeasured) factors at that moment of randomization, all other variables, such as M and Y in the mediation model, that are measured after the randomization event and are statistically associated with the randomized X variable (beyond what would be expected on the basis of random chance alone) can be more clearly interpreted as causal effects of that independent variable.

The RCT, therefore, is a powerful and relatively straightforward methodology for strengthening cause-and-effect inferences for simple bivariate relationships. However, in many situations, the RCT it is not the optimal research strategy for investigating hypothesized causal mechanisms. For some hypothesized causal variables, randomization is not possible, feasible, or ethically defensible. Another potential weakness of the RCT concerns its more limited usefulness for testing causal relationships that exist as part of multivariate causal systems. In the aging, health, and social sciences, most outcome variables are affected, at least in theory, by multiple causal agents, but the simultaneous randomization of multiple causal agents is usually not feasible in a single study, and isolated manipulations of a single causal variable using an RCT can sometimes lead to misleading findings or effects that have little applicability in the real world. In cases where multiple simultaneous randomizations are attempted, it is often questionable whether such experimental control accurately reflects the naturally covarying influences of the multiple causal agents. Consequently, investigators must often utilize other research strategies to identify the causal effects of predictor variables that cannot be randomized and to study more complex multivariate causal systems.

The philosophy that randomization is necessary to confirm cause-and-effect relationships appears to place some limitations on the inferences that can be made from mediation modeling. The primary difficulty is that the proposed mediator M cannot be simultaneously randomized to confirm the causal significance of the $M \to Y$ effect and allowed to vary naturally as a consequence of the $X \to M$ relationship. In other words, if an investigator wishes to confirm the causal nature of the b effect for the $M \to Y$ relationship in Figure 6.1, then an RCT can be designed to accomplish that objective, but this method will also eliminate, by design, the possibility of observing the a effect for the $X \to M$ relationship (beyond what would occur only by chance). Thus, for the $a \times b$ mediation effect, experimental verification of the causal nature of the b portion eliminates the possibility of observing a. Similarly, randomization of X can be used to provide experimental verification of the a effect, but this does not, by itself, confirm the causal nature of the b effect. Multiple sequential randomized studies are sometimes recommended to verify the multiple causal relationships in a chain of causal effects, but these approaches do not allow examining M as both a naturally varying effect and an experimentally manipulated causal variable in the same analytic model.

Another strategy that is often used to strengthen cause-and-effect interpretations for observed associations among variables is alluded to above in our discussion of the RCT, namely, whether the association involves a temporal sequence whereby the hypothesized causal influence precedes the emergence of the hypothesized effect over some relevant period of time. This temporal dimension of causation is directly targeted by most longitudinal research designs. Because causal influences are presumed to precede their effects in time, these lagged sequential relationships should be detectable, at least in theory, from properly timed, repeated waves of data collected over some carefully selected temporal intervals. By incorporating longitudinal, multiple-wave designs that depend on the temporal dimension of causality, important advances are possible for testing causal models that involve hypothesized mediation effects.

The randomized trial, therefore, has an important place in the evidence hierarchy, but the sole reliance on randomization for supporting cause-and-effect interpretations is a limited approach that artificially isolates causal variables and often falls short of testing the relevance of more complex, multi-determined causal models. The mediation model is a good example of a model where an outcome is assumed to be multi-determined through a sequence of separate causal relationships. In applied clinical work, where the control of complex problems over time is desired, multivariate longitudinal mediation models offer much promise for advancing the evidence base for clinical practice (Tucker & Roth, 2006).

It is important to clarify that mediation analyses can be conducted in the context of either an RCT or a purely observational study (MacKinnon, 1994; Shrout & Bolger, 2002). Mediation effects can also be specified in longitudinal analyses or in purely cross-sectional models. The investigator's confidence that the observed effects represent causal relationships should be determined largely by the research design and not by the type of statistical analysis used. It is also important to acknowledge that the RCT and the multiple-wave longitudinal design are not mutually exclusive methods for strengthening cause-and-effect interpretations. In fact, the dementia caregiver intervention study that serves as our primary applied example in this chapter was a study that implemented both of these methodological strategies. Experimental manipulation, therefore, still has an important role to play in many multivariate longitudinal research applications, and designs that integrate randomization and longitudinal analysis methods might be especially useful for combining conventional evidence of intervention efficacy, for example, with longitudinal evidence of the pathways by which interventions achieve their ultimate effects. Although mediation analyses are becoming much more common in many research areas in the aging, health, and social sciences, more substantive and methodologic work is needed to further refine our use of these methods with longitudinal data and to advance our understanding of the strengths and limitations of specific modeling choices.

Key Features of Longitudinal Mediation Models

Longitudinal studies, by definition, involve repeated measurement occasions for at least some of the variables under investigation. Measured variables then detect changes across two different dimensions in a longitudinal study: (a) across time within each subject and (b) across different subjects. Variables that are measured only once are often referred to as *time-invariant* variables, and the observed variability for these measures is restricted to that observed across different subjects only. Some time-invariant measures may truly be fixed over time, such as gender or genotype, whereas others may simply be single snapshots of variables that could potentially change over time but were measured only once in the study. Stable demographic characteristics such as socioeconomic status or education level are often measured only once in a longitudinal study, and assumed to be time-invariant, although change is certainly possible over time for some participants. Variables that are measured repeatedly are referred to as *time-varying* measures, and the repeated observations of the same variables over time allow investigators to measure changes across time within individual subjects. This facilitates important options for testing mediation hypotheses under more restrictive conditions because differences on potential mediating variables can now be examined both across time within the same individuals and across different individuals (Judd & Kenny, 1981; Judd, Kenny, & McClelland, 2001; MacKinnon, 2008). Conceptually, both mediators and outcome variables must be amenable to change over time within individual participants, and a major advantage of the longitudinal design is that it allows investigators to examine these within-person or time-varying changes in ways that are more consistent with the causal hypotheses being evaluated.

The timing and number of repeated measurements in a longitudinal study are usually determined with the goal of measuring these time-varying, within-person changes with sufficient precision and sensitivity. Primary causal variables, on the other hand, can be either time-varying or time-invariant. Likewise, confounding variables can be either time-varying or time-invariant. A key distinction between a mediator and a confounding variable that can be accomplished in a longitudinal study is the assertion that a mediator is a time-varying effect of a primary causal variable in a way that is consistent with a causal relationship, whereas a confounder can simply be a time-invariant correlate of the primary causal variable. A person's gender, for example, could be a confounder of an observed association between health care utilization and an outcome variable, but gender will never be a mediator of that relationship because health care utilization does not cause changes to the person's gender.

The number of options for analyzing multivariate longitudinal mediation models tends to expand greatly as the specific elements of the model are considered and cross-tabulated with other elements. Some key questions related to the nature of the analytic model include the following: (a) Does the longitudinal design include two, three, or four or more waves of data? (b) Is one mediating variable being examined, or multiple mediators? (c) Are the primary causal variable(s) time-varying or time-invariant? (d) Are the primary causal variable(s) experimentally manipulated at some point, or naturally varying? (e) Are raw scores using different time points analyzed or are within-person difference scores using a common baseline analyzed? (f) Are preceding observations on the same time-varying variables used as covariates, as in what is commonly known as an *autoregressive model*? (g) Are trajectories of change over time considered, as in what is commonly known as a *latent growth curve model*? (h) Are the time-varying mediator effects on outcomes time-lagged in such a way to take full advantage of the presumed temporal sequence of true causal effects? (i) Are latent variables extracted from multiple indicator variables for any aspect of three components of the $X \rightarrow M \rightarrow Y$ mediation chain? (j) Are mediators and outcomes continuous variables with typical normal distribution assumptions, or are some variables categorical or time-to-event measures?

Answers to each of these questions are ideally considered before the study. Theory and previous research provide guidance regarding when changes over time are likely to occur and the best timing of the data collection to measure those changes (Collins & Graham, 2002). Similarly, inclusion of the mediators is guided by theory and includes both the important variables related to the process under study and variables omitted from previous research that may influence observed results. Generally, methods that focus on the product of coefficients approach for assessing mediation using the $a \times b$ estimator of indirect effects is preferred over the $c - c'$ method because specific mediation relations are most easily estimated in this framework, that is, estimates of specific mediation relations in a complex model can be obtained. However, there are situations where the $c - c'$ approach is suitable, such as when a single estimate of the total mediated effect is needed when many mediators are included in the model.

General models for estimating the parameters of longitudinal models with categorical and continuous variables that accommodate the unique aspects of assessing mediation are now available (Muthén & Muthén, 1998–2010). An important aspect of programs developed from this approach is the calculation of the many different mediated effects and confidence limits for complex longitudinal models. For example, it is possible to obtain specific mediated effects at each follow-up wave of an intervention study. Such different mediated effects at different follow-up measurements are often expected because intervention process effects may be expected to occur at early follow-up measurements but not at later measurements. Many of these models include the possibility of identifying unique trajectories of change over time that may more accurately model theoretical predictions of nonlinear change. Other modeling approaches focus on person-oriented trajectories that are either consistent or inconsistent with mediation (von Eye, Mun, & Mair, 2009). In these person-oriented models, patterns of change in X, M, and Y responses across time are used to classify individuals in terms of whether their individual results are consistent or not with the pattern predicted by mediation theory.

NYU Intervention Study

We illustrate here a small sample of possible mediation analyses using data from the New York University (NYU) dementia caregiver intervention study (Mittelman, Haley, Clay, & Roth, 2006; Mittelman, Roth, Coon, & Haley, 2004; Roth, Mittelman, Clay, Madan, & Haley, 2005). All models will have just one primary causal variable, a time-invariant, randomized comparison of an active intervention condition compared to a usual care control condition. All models will also examine just one potential mediating variable, a continuous measure of the participant's reported satisfaction with his or her social support network. Following a brief description of the randomized trial that evaluated the NYU dementia caregiver intervention, multiple longitudinal mediation models will be constructed and analyzed to illustrate key concepts in longitudinal mediation modeling.

A psychosocial intervention aimed at enhancing the social support resources of spouse–caregivers of persons with Alzheimer's disease was designed, implemented, and evaluated over nearly two decades of research at the Silberstein Aging and Dementia Research Center of the NYU School of Medicine. The enhanced support intervention included four components: individual counseling sessions for the spouse–caregiver, family counseling sessions for the spouse–caregiver and at least one other family member, monthly support group sessions, and ad hoc telephone counseling as needed. A primary goal of the individual and family counseling sessions was to involve other family members besides the spouse in the care of the person with dementia and, more broadly, to mobilize the social support resources of the spouse caregiver. Through regular participation in support group sessions and ad hoc telephone counseling, caregivers were expected to gain additional support resources and to utilize available support from other family members.

Participants were recruited in two cohorts over a 10-year period beginning in 1987. A total of 406 spouse caregivers qualified for the investigation, and they were randomly assigned to either the enhanced support intervention condition (n = 203) or a usual care control condition (n = 203). Follow-up structured interviews, which repeated many of the same instruments from the baseline assessment, were then administered at approximately 4 months post randomization, 8 months post randomization, 12 months post randomization, and every 6 months thereafter. Comparisons of the intervention condition to the usual care condition have been previously conducted on key outcome variables including caregiver depressive symptoms (Mittelman et al., 2004), caregiver physical health (Mittelman, Roth, Clay, & Haley, 2007), and whether a nursing home placement occurred for the spouse with dementia (Mittelman et al., 2006). Using multilevel growth curve analyses, significant benefits for the enhanced support intervention were found, which first emerged around the 8-month assessment and were maximized at approximately 1 year after the onset of the intervention (Mittelman et al., 2004). A subsequent analysis was conducted on only the baseline and 12-month waves of data for the 312 caregivers who provided care in their homes at both waves to determine how much of the intervention effect on depressive symptoms could be explained by the mediating effects of multiple social support variables (Roth et al., 2005). Those results indicated that most of the antidepressant benefits of the intervention could be attributed to improvements in the caregivers' social support resources, with the strongest mediation effects for the caregivers' reported level of satisfaction with the support being received.

A related set of analytic models is presented for illustrative purposes to further examine this most impactful social support mediating variable. The enhanced support intervention has also been shown to delay or avoid nursing home placements for the persons with dementia, an effect that also appears to be mediated by the time-varying social support measures and other variables (Mittelman et al., 2006). The mediating effect of the caregiver's satisfaction with social support in the context of this time-to-event analysis is also examined in further detail in this chapter.

Outcome Variables

Two different outcome variables are examined in the mediation models illustrated in this chapter. First, the caregiver's *depression* score, as measured by the 30-item geriatric depression inventory (GDS: Yesavage, Brink, Rose, & Adey, 1983), is analyzed as a continuous time-varying outcome variable. Second, the *time to nursing home placement* of the spouse with dementia is analyzed with proportional hazards models that revisit the intervention's effect on nursing home placement rates.

Mediating Variable

The mediating variable that is analyzed in these examples is the spouse–caregiver's *satisfaction* with their social support networks. Based on the methods developed by Stokes (1983), at each assessment caregivers were asked many questions about their social support networks and the degree of assistance they were receiving from family members and friends. This included three summary questions about "how satisfied" they were with their social support network, the amount of tangible assistance they were receiving, and the level of emotional support available. Each summary question was answered on a 6-point scale ranging from 1 (very dissatisfied) to 6 (very satisfied). The average rating across these three summary questions was used as the measure of the caregiver's satisfaction with his or her social support network.

Two-Wave Models

Perhaps the most straightforward longitudinal mediation model is one that includes only two waves of data, has one continuous mediating variable, and has one continuous outcome variable. As we will see, however, there are several analytic options even with this relatively limited and simple example. To illustrate these options, we will use the same data from the NYU caregiver intervention study, which were analyzed by Roth et al. (2005), namely, the baseline and 12-month post-randomization waves of data for the 312 caregivers who provided care in their homes to their spouses with dementia throughout this initial year in the study.

One option for analyzing two-wave data is to simply calculate change scores for the mediating and outcome variables and to use these change scores in the standard three-variable mediation model equations. That is, referring back to Equations 6.1 through 6.3, Y now represents change in depression (12-month depression score minus baseline depression score), M represents a similar change score for the caregiver's satisfaction with social support, and X is an indicator variable for intervention condition (1 for those assigned to the enhanced intervention condition, 0 for those assigned to the usual care condition). Using this approach with the NYU data, the total effect c from Equation 6.1 was found to be –1.322 (SE = .600, p = .028). This raw or unstandardized effect indicates that the 1-year decrease in depressive symptoms for the intervention participants was observed to 1.322 points greater, on average, than the decrease observed for the usual care participants. The results when Equations 6.2

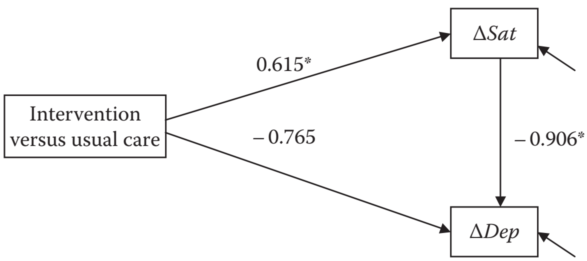

FIGURE 6.3
Basic three-variable mediation model using raw difference scores from two waves of data.

and 6.3 were estimated are displayed in Figure 6.3. Here the intervention had a significant impact on change in satisfaction (a = 0.615, SE = .128, p < .0001), and change in satisfaction had a significant effect on change in depression (b = −0.906, SE = .261, p = .0006). Thus, both legs of the mediated effect are highly significant, with the mediated effect of $a \times b$ equal to −0.557. The standard error of this mediated effect, as calculated with the delta method (Sobel, 1982), is 0.198 and $a \times b/SE$ = −2.81, indicating that the mediated effect is highly significant using this common method. However, the distribution of a product is not normally distributed, and the asymmetric CI should be computed using methods that account for this distribution (MacKinnon, Lockwood, & Williams, 2004). The 95% lower confidence limit (LCL) was −0.987 and 95% upper confidence limit (UCL) was −0.215, and as this 95% CI does not include zero, the mediated effect is confirmed as being statistically significant at the p < .05 level. Interestingly, the direct or unmediated intervention effect from this model was not statistically significant (c' = −0.765, SE = .611, p = .212). Thus, although the mediated effect was smaller in magnitude than the unmediated or direct effect, the mediated effect was actually found to be significantly different from zero, whereas the direct effect was not, due to the different distributional properties of each estimated effect.

Notice that in Figure 6.3 we introduced another change in comparison to Figure 6.1 such that the mediating variable has been shifted from the middle to the right side of the figure. This was done to emphasize the important dimension of time. In this example, only two waves of data are analyzed, and the observed changes on the dependent variable are not lagged in time relative to the observed changes on the hypothesized mediator. While a mediator is hypothesized to be an intervening variable, it is not possible with only two waves of data to subject both paths of the mediated effect ($X \rightarrow M$ and $M \rightarrow Y$) to distinct time delays that represent the sequential temporal relationships presumably underlying the causal chain of effects. For this, a minimum of three waves of data would be needed.

In this simple two-wave change score model, the proportion of the total intervention effect on change in depression that can be accounted for by the mediating mechanism of change in satisfaction with social support is 0.421. In the case for this simple, single-mediator, two-wave change score model with a continuous mediator and a continuous outcome variable, this proportion can be determined using either $(a \times b)/((a \times b) + c')$ or $(c - c')/c$. However, these two equations are typically not equivalent in more elaborate models with autoregressive effects, multiple mediators, categorical mediators, or categorical outcome variables.

The simple change score method is one straightforward option for two waves of longitudinal data, but raw or unadjusted change scores can be vulnerable to problems such as poor reliability and floor or ceiling effects. A caregiver who was quite satisfied with his or her social support network at baseline, for example, has little room to show an improvement in satisfaction but much room to report a decrease in satisfaction. More generally, ceiling and floor effects commonly restrict the size and direction of observed changes over time, often resulting in significant negative correlations between baseline scores and post minus baseline change scores. For this reason, many investigators avoid analyzing raw change scores and prefer to conduct an analysis of covariance instead, with the baseline observation serving as a covariate. In many cases, this analysis of covariance method provides at least a partial adjustment for the psychometric problems associated with raw change scores.

Figure 6.4 illustrates an analysis of the same changes over two waves of data, but in this case all observed changes are adjusted by including the baseline values of each variable as a covariate. Extending Equation 6.1 to now include a baseline covariate predictor, the covariate-adjusted total effect is given by c in the following equation:

$$\Delta Dep = i + c(intervention\,condition) + d(baseline\,Dep) + e \tag{6.4}$$

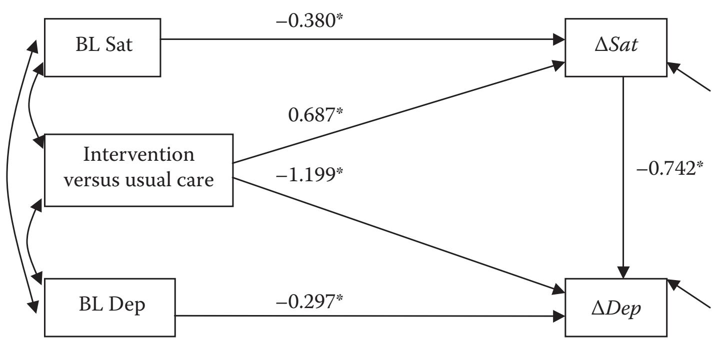

FIGURE 6.4
Basic three-variable mediation model using difference scores that are adjusted for baseline values.

This baseline-adjusted total effect was found to be –1.669 (SE = .558, p = .003). Similar extensions to Equations 6.2 and 6.3, respectively, follow:

$$\Delta M = i + a(\mathit{intervention\ condition}) + d(\mathit{baseline\ M}) + e \tag{6.5}$$

$$\Delta \mathit{Dep} = i + c'(\mathit{intervention\ condition}) + b(\Delta M) + d(\mathit{baseline\ Dep}) + e \tag{6.6}$$

The results from these analyses are displayed in Figure 6.4. Using this method, the intervention continues to have a significant impact on change in satisfaction even after adjusting for baseline satisfaction (a = 0.687, SE = .115, p < .0001), and change in satisfaction still has a significant effect on baseline-adjusted change in depression (b = −0.742, SE = .244, p = .003). Thus, both legs of the mediated effect remain highly significant, and the mediated effect of $a \times b$ is now equal to −0.510 (SE = .188, LCL = −0.910, UCL = −0.173). Highly significant (ps < .0001) negative baseline covariate effects are also evident for both change in satisfaction with social support and change in depression due to strong ceiling and floor effects, respectively.

One important difference between this model and the previous model of unadjusted change scores is that the direct or unmediated intervention effect from the baseline-adjusted change score model is now statistically significant (c' = –1.199, SE = .572, p = .037). Consequently, for these data, equating groups on baseline depression and controlling the baseline–change score relationships in the analysis resulted in a stronger effect size estimate and a smaller standard error for the unmediated effect, resulting in a more powerful test of this effect. Statistical control for baseline will not always improve power, however, because the baseline-adjusted direct effect can be either stronger or weaker than the unadjusted direct effect depending on the relationships present among the variables being analyzed.

Another important difference between the model in Figure 6.4 and that in Figure 6.3 is that the equivalence of $a \times b$ and $c - c'$ is no longer observed once covariate adjustments are made to the mediator and outcome variable. In this example, $a \times b$ = −0.510 whereas $c - c'$ = −0.470. Likewise, the proportion of the total effect that is mediated is different depending on which formula is used for that calculation: $(a \times b)/((a \times b) + c')$ = 0.298, whereas using $(c - c')/c$, the proportion is 0.282. In both cases, the proportions are smaller than the 0.421 estimated in the raw change score analysis. This decrease in the proportion due to the indirect effect is because the baseline covariate adjustments tended to strengthen both the total effect and the unmediated effect, while slightly weakening the size of the mediated effect.

A third distinct alternative for two-wave models besides the raw change score analysis and the baseline-adjusted change score analysis is the option in which the raw scores are analyzed with the baseline scores on each variable serving as that variable's covariate. A model in which the previous measurement occasion for each variable is included as a covariate for that variable is often referred to as an *autoregressive* model (Cole & Maxwell, 2003). In a two-wave analysis, this means that each wave 1 variable serves as a covariate of its wave 2 observation. In cases where there is just one independent variable X, one dependent variable Y, and the time 1 observation of that dependent variable Y is included as a covariate in the model, then the effect of the independent variable X on the dependent variable Y is identical regardless of whether the time 2 observation of Y is analyzed as the dependent variable or the time 2 minus time 1 change score on Y is analyzed as the dependent variable (Laird, 1983). In both models, the investigator is simply testing whether the independent variable X led to a baseline-adjusted change on the dependent variable Y.

In the context of our spouse–caregiver example, the baseline-adjusted change score model and the autoregressive model are identical for testing the total effect of the intervention on subsequent caregiver depression (as long as baseline depression is a covariate in the model). However, this equivalence across baseline-adjusted change score and autoregressive models does not extend to the estimates of the mediation effects. The results when the autoregressive model is applied to the two-wave data from the NYU caregiver intervention study are summarized in Figure 6.5.

As with the analyses displayed in Figure 6.4, the baseline-adjusted total effect is −1.669 (SE = .558, p = .003). Also, the a effect is the same in both analyses (a = 0.687, SE = .115, p < .0001), indicating again that the intervention has a significant impact on the caregiver's satisfaction with his or her social support network after adjusting for baseline satisfaction. All other effects in the analyses summarized in Figure 6.5 are different from their counterparts in Figure 6.4 and require reexamination. Satisfaction with social support at 12-month post-randomization is significantly related to

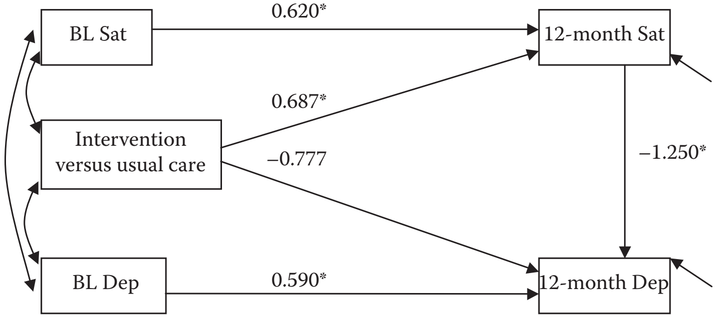

FIGURE 6.5
Mediation in a two-wave autoregressive model.

baseline-adjusted depression at 12 months ($b = -1.250$, $SE = .220$, $p < .0001$), and once again, both legs of the mediated effect are highly significant. The mediated effect of $a \times b$ is now equal to -0.775 ($SE = .209$, $LCL = -1.301$, $UCL = -0.487$). The increased strength of the b effect in Figure 6.5 relative to Figure 6.4 is because 12-month satisfaction with social support is more negatively correlated with 12-month depression than the corresponding 12-month minus baseline change scores. As the a effect is constant across both models, the increased strength of the b effect in Figure 6.5 leads to an increased $a \times b$ mediation effect from the autoregressive model.

Highly significant ($ps < .0001$) baseline covariate effects are also evident in Figure 6.5. In this case, these adjustments are positive and simply reflect the within-group correlations between baseline and 12-month scores on both variables. Of considerable interest is the unmediated direct effect for the intervention on baseline-adjusted 12-month depression scores, which is not statistically significant in this autoregressive model ($c' = -0.777$, $SE = .555$, $p = .162$). The proportion of the total effect that can be explained by the mediating mechanism of satisfaction with social support is 0.499 using the $(a \times b)/((a \times b) + c')$ method and 0.534 using the $(c - c')/c$ method. Both proportions are markedly higher than their counterparts using the baseline-adjusted change score analysis. Therefore, with these data, the autoregressive model yields higher estimates of the mediated effect and lower estimates of the unmediated or direct effect than the corresponding effects from the baseline-adjusted change score analysis.

The analyses previously published by Roth et al. (2005) are conceptually similar to the baseline-adjusted change score results reported in Figure 6.4. However, there are some important differences between the two analyses. Roth et al. used a measurement model to identify multiple latent social support mediating variables, included the caregiver's reaction to care recipient behavior problems as an additional mediating variable, and did not estimate a direct or unmediated c' effect in their final analytic model. Although the same baseline-adjusted total effect of $c = -1.669$ was decomposed in the Roth et al.'s analyses, the proportion of the effect that could be explained by the mediating effects of change in satisfaction with social support was estimated to be 0.75. This proportion is much larger than observed here for the adjusted change score model shown in Figure 6.4, and this illustrates how sensitive these results and quantities can be to the specific analytic method being used. Sensitivity analyses (not shown here) indicate that most of the differences between the present analyses with observed mediating variables only and the 2005 analyses that used latent mediators can be explained by the improved psychometric properties of the latent mediators in the previous analyses. This type of discrepancy was noted by Hoyle and Kenny (1999), who showed that even modest amounts of measurement error in a mediating variable can lead to markedly underestimated mediated effects and overestimated direct effects. The extraction of latent mediators holds great promise for further enhancing longitudinal mediation analyses, especially in situations where observed indicators are known to have significant measurement error and more than two waves of data have been collected.

With regard to two-wave models with observed variables only, we have demonstrated three distinct analytic options—a raw change score analysis, a baseline-adjusted change score analysis, and an autoregressive model analysis. Both the baseline-adjusted change score and autoregressive models adjust for baseline effects on observed changes over time, but the covariate adjustments of both models also eliminate the equivalence of the $a \times b$ and $c - c'$ methods for calculating the size of the mediated effect. Differences across all three models are observed in the estimation of the b leg of the mediation effect. The b effect appears to be stronger in the autoregressive model than in either change score model because the 12-month satisfaction → 12-month depression effect from the autoregressive model includes a mixture of time-varying (within-subject) and time-invariant (between-subjects) covariation, whereas the change score models are restricted to time-varying (within-subject) associations only. As at least some of the time-invariant covariation between the mediating and outcome variable is probably unrelated to changes being caused by the intervention, it is possible to argue, in the case of an intervention trial, that the baseline-adjusted change score model is the more appropriate model. However, a different recommendation might be advanced in purely observational research with no randomized causal variable, and even subtle aspects of the design and the nature of the mediation hypotheses being tested could easily alter the preferences among existing models.

Three-Wave Models

Longitudinal designs that provide three or more waves of data over time allow for even more modeling options and analysis complexities than were possible with two-wave models. There are some important advantages to adding a third wave of data collection. First, with at least three waves of data, the investigator has at least two time lags between waves, and this allows both the $X \rightarrow M$ and $M \rightarrow Y$ relationships to be examined in connection with temporal sequences that strengthen cause-and-effect interpretations. Second, if an individual growth curve modeling approach is used to examine longitudinal trajectories for key mediating or outcome variables, then the presence of three or more waves of data allow for the estimation of within-person measurement errors when a simple linear change model is used. That is, with only two longitudinal data points, a straight line will provide perfect fit to each individual's change trajectory, and it is not possible to disentangle real change and measurement error at the individual level. With three or more longitudinal data points, some dispersion around the straight line of best fit across time is usually observed at the individual level, and this provides more flexibility in specifying the error structure as part of a multilevel change model (Singer & Willett, 2003). Third, with three or more waves of data, investigators can evaluate the temporal stability of lagged relationships over time to determine if the model has the property of stationarity. That is, investigators can examine whether the size and valence of the coefficients relating variables across wave 1 and wave 2 are consistent with those relating the same variables across waves 2 and 3 and other adjacent data collection waves if available. If the coefficients for a mediation effect change significantly across adjacent pairs of waves, this could reflect a mediating process that is sensitive to the time of observation and not generally consistent across all data collection waves (Cole & Maxwell, 2003; MacKinnon, 2008).

An extension of the autoregressive model to include three or more waves of data provides one commonly used method for assessing longitudinal mediation effects (Cole & Maxwell, 2003). An "empty" autoregressive model for three time-varying variables and three waves of data is illustrated in Figure 6.6. In this model, each variable is regressed on the preceding observation of that variable. Variance that is not explained by these autoregressive effects is allowed to freely correlate at the same time points across the three measures. A number of potential mediation models or hypotheses can then be added to this autoregressive model. Figure 6.7 illustrates an important mediation model whereby the primary causal variable X at time 1 exerts a causal influence on M at time 2 (path *a*), and the mediating variable M at time 2 exerts a causal influence on the outcome

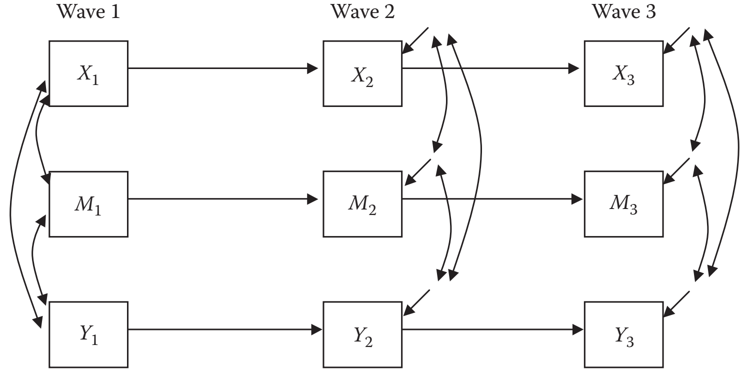

FIGURE 6.6
Basic three-wave autoregressive model with no mediated effects.

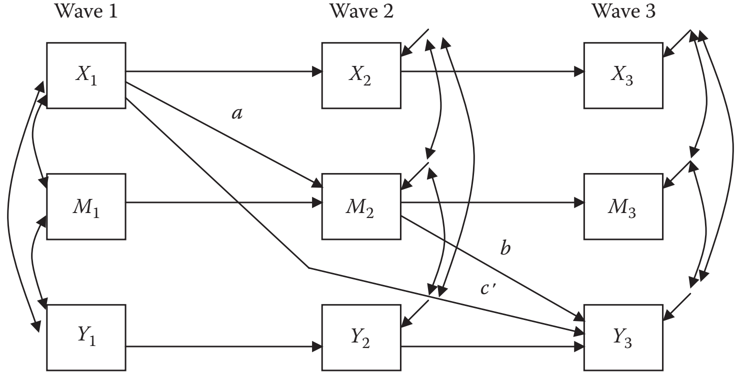

FIGURE 6.7
Three-wave autoregressive model with a longitudinal mediation effect.

variable Y at time 3 (path b). The direct or unmediated effect of X_1 on Y_3 is also depicted in Figure 6.7 (path c').

More complete autoregressive models are also possible with the addition of more paths. For example, an $X_2 \rightarrow M_3$ path could be added, and its effect could be compared to the a effect to examine the temporal stability (stationarity) of the $X \rightarrow M$ relationship over a single time lag. Likewise, an $M_1 \rightarrow Y_2$ path could be added to test the temporal stability of the b effect. Alternatively, time-lagged relationships in the opposing direction (e.g., $Y_1 \rightarrow M_2$ and $M_2 \rightarrow X_3$) could be added, which would subject the assumed temporal sequencing of these causal effects to more rigorous evaluation.

In cases in which the primary causal variable X is manipulated or is modeled as a time-invariant causal agent, repeated observations of that variable are not included in the model. If X_1 represents randomization to a treatment condition versus a control condition, then only X_1 is involved in this autoregressive model, with X_2 and X_3 and its associations being removed from the diagram.

In order to illustrate mediation analyses using three waves of longitudinal data, the NYU caregiver intervention data are again used. The same pretreatment baseline data serve as wave 1 and the 12-month outcome data analyzed in the two-wave models discussed previously are now analyzed as wave 3 data. For wave 2 data, the average of the 4-month and 8-month assessments for depression and satisfaction with social support are used and labeled as "6-month" data. The 12-month data continued to serve as the primary endpoint because this was the time point at which the effects of the intervention on caregiver depression were strongest (Mittelman et al., 2004). An alternative would have been to include both the 4-month and 8-month waves as separate waves of data and conduct a four-wave mediation analysis, but we thought it would be prudent to proceed systematically with a three-wave example. Straightforward extensions to

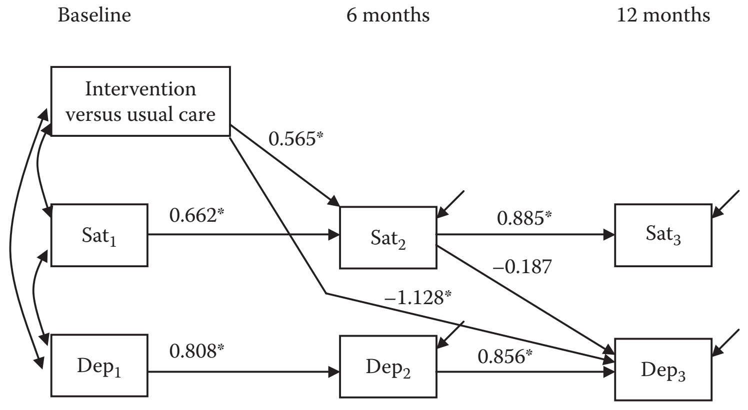

FIGURE 6.8
Three-wave autoregressive model with a mediation effect for the NYU caregiver intervention.

four and more waves are certainly possible, although complexities with more possible paths and larger amounts of missing data can increase as more and more waves of data are added to a longitudinal analysis.

The results of one possible three-wave autoregressive model for the NYU data are summarized in Figure 6.8. Because separate regression equations are used for each dependent variable in Figures 6.8 and 6.9, unexplained residual associations between satisfaction with social support and depression are not modeled at the 6-month and 12-month assessments in these models. An examination of the findings in Figure 6.8 reveals that all four

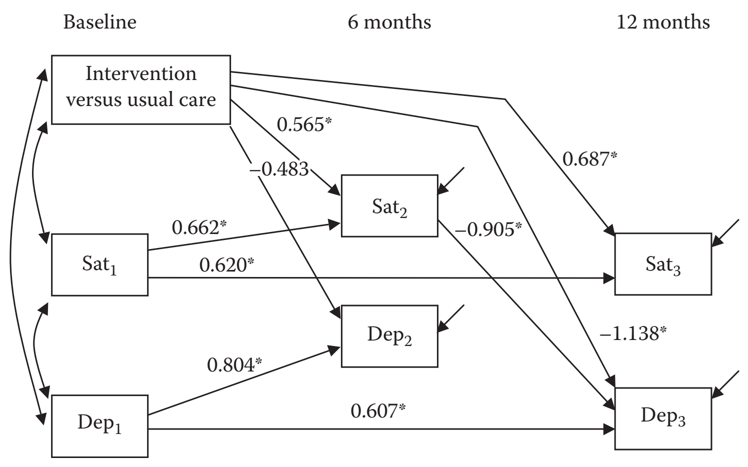

FIGURE 6.9
An alternative mediation model using three waves of data from the NYU caregiver intervention study.

of the autoregressive paths are highly statistically significant (*ps* < .0001). Second, path *a* regressing 6-month satisfaction with social support on the intervention condition after controlling for baseline satisfaction with social support is statistically significant (a = 0.565, *SE* = .093, p < .0001) with intervention caregivers reporting improved satisfaction relative to caregivers receiving usual care. However, path *b* of the mediation effect is not statistically significant in this model (b = −0.187, *SE* = .194, p = .34), whereas the direct or unmediated effect of the intervention on 12-month depression is statistically significant (c' = −1.128, *SE* = .420, p = .008). The $a \times b$ mediation effect is only −0.106 (*LCL* = −0.333, *UCL* = 0.107), and the proportion of the intervention effect on 12-month depression scores that is mediated by 6-month satisfaction with social support is only .083 using the $(a \times b)/((a \times b) + c')$ method.

It is informative to closely compare this three-wave autoregressive model with the two-wave autoregressive model presented earlier. Both the first and last waves of data are identical for the two models, but a major difference is that the mediator in the three-wave model is a preceding observation of satisfaction with social support and not a concurrent or simultaneous observation. By introducing a 6-month time lag for the mediator to outcome relationship, the size of the mediated effect was markedly reduced. Perhaps, 6 months is too much of a time delay to observe this particular causal relationship. The simultaneous relationship used in the two-wave model appears to partly reflect an association that does not stand up to subjecting the *b* effect to a 6-month time delay. It may also be possible that the intervention effect was only mediated at the third data collection wave, consistent with the design of the intervention where the largest effects were not expected until after the program was fully delivered.

Another fundamental difference between the two- and three-wave autoregressive models involves the nature of the autoregressive adjustments. For the 12-month depression outcome variable, the autoregressive adjustment in the two-wave model was provided by the baseline depression score observed before the caregivers received any intervention components. In the three-wave model, the 12-month depression score was adjusted for the 6-month depression score, and it is important to note that this 6-month depression score was observed after some of the intervention's effects may have began to accumulate. In other words, by statistically controlling for 6-month depression scores, a portion of the intervention's effect on the 12-month depression score could have been statistically removed from both the direct treatment effect and the mediated effect being evaluated. This can be a limitation of the conventional autoregressive model when it is applied to a randomized or time-invariant primary causal variable and three or more longitudinal waves of data are collected.

An alternative to the conventional autoregressive model displayed in Figure 6.8 is a model in which both waves of data collected after the onset of the intervention are adjusted for baseline observations only. In this model, the baseline level serves as a constant covariate of all subsequent waves of data over varying time delays. These covariate adjustments would control for observations before randomization only, and the *b* path of the mediation effect still involves a time delay that strengthens the cause-and-effect interpretation of that effect. This mediation model and the results obtained for the NYU caregiver intervention data are depicted in Figure 6.9. Additional direct effects are added from the intervention condition to 6-month depression and from the intervention to 12-month satisfaction with social support, although these paths do not affect the estimation of the intervention → 6-month satisfaction → 12-month depression mediation effect.

The results displayed in Figure 6.9 show the same relationship regressing 6-month satisfaction with social support on the intervention condition after controlling for baseline satisfaction with social support (a = 0.565, SE = .093, p < .0001). However, unlike the results in Figure 6.8, path b of the mediation chain is now statistically significant in the Figure 6.9 analysis (b = –.905, SE = .260, p = .0006). The direct or unmediated effect of the intervention on 12-month depression scores is similar to that observed in Figure 6.8 (c' = –1.138, SE = .569, p = .046). Other interesting effects in Figure 6.9 include a significant intervention effect on 12-month satisfaction with social support (estimate = 0.687, SE = .115, p < .0001) and a nonsignificant effect of the intervention on 6-month depression scores (estimate = −0.483, SE = .425, p = .26). In this case, even though the intervention did not have a statistically significant effect on 6-month depression scores, controlling for those 6-month depression scores in the original autoregressive model substantially reduced the observed mediation effect provided by 6-month satisfaction scores on 12-month depression outcomes in Figure 6.8. The $a \times b$ mediation effect from Figure 6.9 is −0.511 (SE = .169), and the proportion of the intervention effect on 12-month depression scores, which is mediated by 6-month satisfaction with social support, is .310 using the $(a \times b)/((a \times b) + c')$ on the displayed estimates. The mediation effect in Figure 6.9, therefore, is approximately four times larger than the same mediation effect in Figure 6.8, with the only important difference being whether the covariate adjustment for previous depression scores included measures that were obtained before (Figure 6.9) or after (Figure 6.8) the onset of the intervention.

Longitudinal Mediation Analyses Using an SEM Approach

All of the effects estimated up to this point could be easily obtained using ordinary least squares regression analysis. However, as multiple waves of data are added and as more variables are added to a multivariate analytic framework, investigators often wish to evaluate the overall fit of their statistical models. It should be noted that neither of the models corresponding to Figure 6.8 or Figure 6.9 provide acceptable overall fit to the observed data when estimated using an SEM approach. These piecemeal, regression-based, time-lagged models are not sufficient (a) for accounting for the simultaneous or same-wave correlations between satisfaction with social support and depression and (b) for accounting for the residual correlations between different observations of the same variable over time. The model in Figure 6.9, for example, was estimated using Mplus (Muthén & Muthén, 1998–2010) and was found to be insufficient for adequately reproducing the observed variances and covariances among the variables (χ^2 = 414.7, df = 9, p < .0001, root mean square error of approximation [RMSEA] = .380). Additional paths between variables must be added if acceptable overall model fit is desired along with targeted tests of theory-driven mediation hypotheses.

Some of the possible additions to the model in Figure 6.9 could be anticipated a priori, including correlated errors or "unanalyzed associations" that might be present after accounting for the causal paths in the model. These correlated residuals usually do not have a large impact on the causal paths or their interpretation, but adding correlated residuals can still be useful for improving overall model fit. Other additions to the model in Figure 6.9 might be suggested by empirical results, such as modification indices that suggest additional causal paths to be added to the model.

A modified model that provides excellent fit to the observed data is illustrated in Figure 6.10. In comparison with the model in Figure 6.9, this expanded model adds four correlated residual terms as indicated by the curved paths with arrows on both ends. In addition, two additional casual

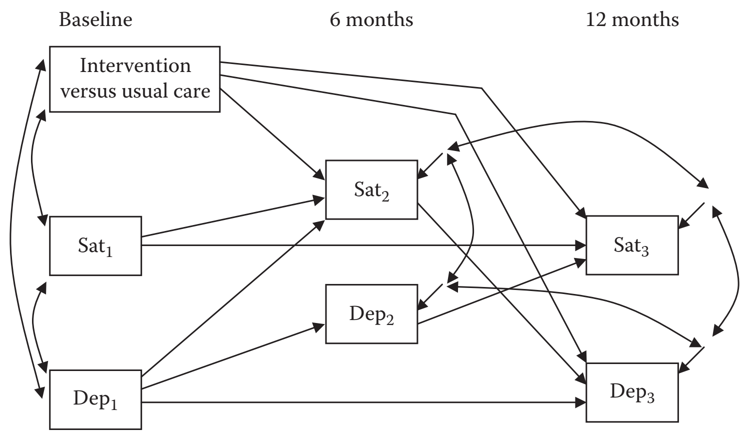

FIGURE 6.10
A better-fitting three-wave mediation model for the NYU data with correlated residual terms.

paths representing time-lagged relationships from depression to satisfaction (i.e., $Dep_1 \rightarrow Sat_2$, $Dep_2 \rightarrow Sat_3$) have been added. Finally, the nonsignificant path from the intervention to the 6-month depression score has been removed. This model, albeit partially exploratory because modification indices from the Figure 6.9 model were taken into account, was found to provide an excellent fit to the observed data ($\chi^2 = 3.77$, $df = 4$, $p = .44$, $RMSEA = 0.00$). All paths illustrated in Figure 6.10 are statistically different from zero ($ps < .05$).

The estimates are not presented in Figure 6.10, but the key paths in the primary mediation chain remain statistically significant and similar to that observed previously ($a = 0.517$, $SE = .087$, $p < .0001$; $b = -0.710$, $SE = .219$, $p = .001$; $c' = -0.837$, $SE = .425$, $p = .049$). The $a \times b$ mediated effect of -0.367 ($SE = .128$, $LCL = -0.6417$, $UCL = -0.1370$) can be calculated either by hand or with the Mplus model indirect command, and in this case the mediated effect accounts for 34% of the intervention's effect on 12-month depression scores using the $(a \times b)/((a \times b) + c')$ method. The added lagged effects of depression preceding satisfaction with social support changes also suggest that depression may be a causal influence on subsequent satisfaction with social support, but depression does not serve as a mediator of the intervention effect because the effect of the intervention on depression is delayed until after the intervention exerts its effects on satisfaction with social support. Thus, our final three-wave model suggests some mutual causality between caregiver satisfaction with social support and caregiver depression, but only the satisfaction $\rightarrow$ depression pathway serves as a mediator of the intervention effect for these data.

Additional Models of Multiwave Data

All of the models discussed previously involve continuous mediators and continuous outcome variables. As discussed in detail elsewhere, mediation methods based on ordinary linear regression methods can be extended to generalized linear models that more broadly include categorical mediators or outcome variables (MacKinnon, 2008; MacKinnon, Lockwood, Brown, Wang, & Hoffman, 2007). For example, if a dichotomous indicator variable were used for the outcome variable of depression (1 = at or above a clinically relevant cutpoint, 0 = below the clinical cutpoint), then a logit link function would be applied to this variable and the b and c' effects would be estimated from binary logistic regression models. In this context, we recommend estimating the mediated effect with the $a \times b$ product method as opposed to the $c - c'$ difference in coefficients method unless c and c' are properly scaled or standardized to be comparable across their separate logistic regression equations. Similar modifications and recommendations are applicable to models in which the mediating variable is a dichotomous indicator.

Mediation effects can also be conceptualized in the context of other analysis approaches to multiwave longitudinal data. Latent growth curve models (LGMs), for example, can be specified to test mediation effects. More extensive information on LGM approaches is provided in Chapter 9, and only a limited discussion of an LGM approach to the NYU caregiver intervention data is provided here. In this example, an LGM model was constructed using Mplus to determine if the intervention was associated with linear changes in satisfaction with social support and linear changes in depressive symptoms across the three data waves depicted in Figures 6.8 through 6.10. This model also examined the extent to which the linear increase in satisfaction with social support mediated any intervention effect on the linear decrease in depressive symptoms. Parallel linear LGM trajectories with intercept and linear slope factors were specified for social support and for depression, and predictive paths were specified to test the direct and mediated intervention effects on linear changes in depression. This analysis revealed a significant effect (path *a*) from the intervention to the linear change variable for satisfaction with social support (standardized estimate = 0.434, SE = .107, $p < .001$) and a significant effect (path *b*) from the linear change in social support to the linear change in depressive symptoms (standardized estimate = −0.499, SE = .154, p = .001). The unmediated intervention effect (path c') was not statistically significant (standardized estimate = 0.036, SE = .119, p = .762). In this case, the $a \times b$ mediated effect of −0.217 (SE = .106, p = .04) was actually *larger* than the total effect (path *c*: standardized estimate = −0.181 [SE = .063, p = .004]), suggesting that essentially all of the beneficial linear reductions in depressive symptoms caused by the intervention could be explained by corresponding linear increases in satisfaction with social support.

Time-to-Event Models

In many longitudinal studies, the primary outcome variable being tracked is whether an individual experiences a discrete event over a certain observation period, and if so, the time until the occurrence of that discrete event. Biomedical research, for example, often wishes to examine the effects of treatment conditions for reducing the risk of mortality, and patient death serves as the discrete event under investigation in such an analysis. Time-to-event analyses are sometimes called *survival analyses* due to the common application of these methods, although the techniques can be easily applied to the prediction of other types of events besides patient death.

There are multiple methods for evaluating the occurrence and predictors of a discrete event (Allison, 2010; Hosmer & Lemeshow, 1999). One of the most flexible and commonly used methods is the proportional hazards model. Originally developed by Cox (1972), and sometimes referred to as a Cox regression model, this method is applicable regardless of the overall distribution of the event times. Further advantages include its conceptual similarity to standard logistic regression analysis for a binary outcome variable, its capability of simultaneously analyzing multiple predictors and determining covariate-adjusted predictive effects, and its capability of handling both time-invariant and time-varying predictor variables. These features also make the proportional hazards model a promising candidate for testing mediation hypotheses in the context of time-to-event hypotheses. If a treatment is shown to promote survival and delay patient death, for example, then a seemingly obvious follow-up question is what potential mechanisms might account for the survival benefits of the treatment. As straightforward as this question appears to be, there is surprisingly little methodological research on the use of mediation methods in the context of time-to-event analyses, with a few notable exceptions (e.g., Tein & MacKinnon, 2003).

The mediation modeling equations 6.1 through 6.3 can be extended to the proportional hazards model as follows. First, the total or unadjusted effect of X is specified as

$$\log h(t) = a(t) + cX \tag{6.7}$$

where

$h(t)$ refers to the hazard function at time t

$a(t)$ represents the log of the baseline hazard function at time t when X is 0

The hazard function represents the probability of experiencing the target event at time t, and the regression coefficient c represents the proportional change in this probability, or the change in log of the hazard at time t, for each unit increase in X.

Assuming that the mediator, M, is a continuous and time-invariant variable, Equation 6.2 is unchanged and is repeated here:

$$M = i + aX + e \tag{6.8}$$

When the mediator is then integrated into Equation 6.3 in the proportional hazards model, the equation becomes

$$\log h(t) = a(t) + bM + c'X \tag{6.9}$$

One important complicating factor in a time-to-event analysis is the presence of cases where the target event does not occur during the observation period. These cases are typically referred to as *censored cases*. In one of the few methodological studies to date of mediation tests in the context of survival analysis, Tein and MacKinnon (2003) conducted simulation studies of mediation hypothesis tests in proportional hazards models with one time-invariant mediator and no censored cases. They found that the conventional standard error formulas from ordinary linear regression analyses, such as the delta method (Sobel, 1982), tended to yield smaller standard errors than those obtained with empirical bootstrapping methods. This suggests that the extension of the standard linear regression methods to the proportional hazards model may result in elevated Type I error rates, and it is not presently known whether this potential bias is exacerbated or attenuated when the common situation of including many censored cases is encountered.

Another potential complicating factor in time-to-event analyses involves the inclusion of time-varying mediating variables. As we have discussed previously, mediators, by definition, are effects of primary causal variables, and in many cases it makes sense to examine changes on the mediator as predictors of the final outcome. Time-varying predictor variables can easily be incorporated into proportional hazards models. Typically, at each time point when any case experiences either a target event or becomes censored, the latest observed value of the time-varying predictor is analyzed as a predictor of that event occurrence (or taken into account in the reduced pool of cases being studied going forward because of the censoring). This results in straightforward recalculations of the b and c' effects in Equation 6.9 but raises considerable difficulty in estimating the a effect from Equation 6.8 because the outcome variable in Equation 6.8 is changing over time and in relation to each occurrence of a target event or a censoring occasion.

Methods to estimate and test mediation effects in the context of a proportional hazards model are now illustrated using the NYU caregiver intervention data. As before, the primary causal variable is the intervention condition and the mediating variable is change in satisfaction with social support. The outcome variable being analyzed in this model is the time to nursing home placement for the spouse with Alzheimer's disease. Censored cases included (a) patients who died before ever being placed in a nursing home, (b) caregivers who died or dropped out of the study before patient death or placement, and (c) caregivers who were still providing care in the home to the spouse with dementia at the time of the last observation considered in this analysis. Because the amount of change in satisfaction with social support is partly dependent on the baseline level of satisfaction in social support, that baseline observation was also included as a covariate in all analyses.

Previous analyses of nursing home placement in this sample have shown that the intervention led to a statistically significant delay in nursing home placement compared to the usual care control condition (Mittelman et al., 2006). These significant intervention effects have been found regardless of whether patient death is considered a censoring event or a competing risk event (Szychowski, Roth, Clay, & Mittelman, 2010). Those analyses controlled for several baseline covariates (e.g., patient age, year of enrollment in the study, patient and caregiver health variables) and examined nursing home placement and censoring events as much as 15 years after enrollment in the study.

The present analyses were restricted to the 381 cases for whom the caregiver was providing care in the home at the 4-month post-enrollment assessment. In order to measure potential changes in social support as a mediator, the sample was restricted to those with at least one assessment of satisfaction with social support after baseline and before either patient nursing home placement or patient death occurred. A total of 25 of the original 406 cases (6.2%) were therefore excluded because either the patient died ($n = 11$) or was placed in a nursing home ($n = 14$) before the 4-month assessment was completed. We also chose to examine nursing home placement events up through 5 years after enrollment in the present analyses. A total of 161 nursing home placements occurred between the 4-month and 5-year assessments, and the remaining 220 cases were censored. Reasons for censoring included the caregiver still providing care in the home at 5 years ($n = 96$), patient death ($n = 92$), caregiver death ($n = 17$), and caregiver dropout ($n = 15$).

The initial proportional hazards model with only the intervention condition and baseline satisfaction with social support as predictors of time to nursing home placement revealed a significant total effect for the intervention ($c = -0.345$, $SE = .158$, $p = .029$). The hazard ratio of 0.708 (exp[c]) indicates that the rate of nursing home placement in the intervention group was about 71% of the rate of nursing home placement for patients in the usual care group. Following confirmation of this total effect, two different mediation models were estimated.

Table 6.1 contains the estimates, standard errors, and hazard ratios for the full models that predicted time to nursing home placement as a function of baseline satisfaction with social support, the intervention condition, and change in satisfaction with social support. The change in social support variable was analyzed both as a time-invariant mediator and as a time-varying mediator. For the time-invariant mediator analysis, the immediate

TABLE 6.1

Proportional Hazards Models Predicting Time to Nursing Home Placement

Effect	Estimate	*SE*	*HR*	*p*
Time-invariant mediator				
Intervention (c')	−0.272	.168	0.762	.105
BL Sat	−0.103	.060	0.902	.085
ΔSat (b)	−0.130	.094	0.878	.169
Time-varying mediator				
Intervention (c')	−0.218	.168	0.804	.193
BL Sat	−0.140	.062	0.869	.025
ΔSat (b)	−0.178	.074	0.837	.016

change in satisfaction with social support from baseline to 4-month post-enrollment was examined as an effect of the intervention condition using a standard linear regression analysis with 4-month change in social support as the dependent variable and baseline satisfaction with social support and the intervention condition as predictors. This analysis revealed significant effects for both predictors, including the finding that the intervention improves satisfaction with social support over the first 4 months of the study relative to the usual care condition ($a = 0.556$, $SE = .093$, $p < .0001$). However, none of the predictors in Table 6.1 corresponding to Equation 6.9 were found to be statistically significant predictors of time to nursing home placement. The effect of the proposed mediator yielded an estimate (b) of −0.130, resulting in a mediation effect ($a \times b$) of −0.072. Therefore, even though the a leg of the mediation effect was strong and highly significant, the b leg was much weaker and not statistically significant, and only 0.21 of the intervention effect on nursing home placement rates could be explained by this mediation mechanism using the $(a \times b)/((a \times b) + c')$ method.

A potential weakness of the time-invariant approach is that the intervention continued to unfold and exert its effects over time, certainly beyond the 4-month assessment point. Additional points, such as the 8-month or 12-month assessments, could have been selected as alternative time-invariant assessment points, but each later assessment point would have excluded more cases who had already placed their spouses in nursing homes prior to later assessment points. An alternative is to analyze change in satisfaction with social support as a time-varying predictor/mediator of the nursing home placement effect. This alternative method potentially avoids the limitations of the time-invariant approach and can be used to examine the effect of the most recently observed change score (from baseline) at each point before nursing home placements (or censoring events) are observed.

For the time-varying mediator analysis conducted here, the procedures for coding a time-varying predictor using SAS Proc PHREG were used as described in detail by Allison (2010). The most recent observation of change (from baseline) in satisfaction with social support was examined for the entire data set each time a case experienced either a nursing home placement or was censored. The estimates in Table 6.1 indicate that change in satisfaction with social support, when examined as a time-varying predictor, was significantly linked with the likelihood nursing home placement ($b = -.178$, $SE = .074$, $p = .016$). This provided a sensitive, time-varying estimate of the b path for the $a \times b$ mediation chain, but there is no straightforward linear regression analysis corresponding to the a effect from Equation 6.8 in this type of analysis. Consequently, the strength and significance of the mediation effect were not examined using the $a \times b$ method but were evaluated using the $c - c'$ method instead. With this difference in coefficients method, the mediation effect was estimated to be −0.127 and the proportion of the intervention effect that could be accounted for by its effect on the time-varying social support mediator was 0.37 (using the $(c - c')/c$ method). This proportion is very close to the 0.34 mediated proportion reported by Mittelman et al. (2006) from a model with as much as 15 years of follow-up data and many more baseline covariates.

A bootstrapping method was used to calculate an empirical standard error for this $c - c'$ mediation effect. The analysis sample of 381 cases was resampled with replacement a total of 1000 times, and the $c - c'$ estimate was calculated for each boostrapping sample. This resulted in an empirical standard error of 0.057. Taking the observed value of −0.127 divided by this empirical standard error yields a z statistic of −2.243, which corresponds to a p-value of .025. The 95% CI was −0.238 to −0.016, further confirming the statistical significance of the mediated effect. The time-varying mediator method, therefore, indicated that change in satisfaction with social support was a significant mediating mechanism by which the intervention delayed nursing home placement of the spouse with dementia.

Summary and Conclusions

The analyses reported in this chapter illustrate just some of the many options available to test mediation hypotheses with longitudinal data. The advantages of longitudinal data for assessing the temporal precedence relationships implied by the causal assumptions of mediation were discussed, and the importance of theoretical guidance was emphasized both for identifying the best timing of the measurements and for determining the specific form of the mediation model(s) to be tested. Data from an RCT were used to demonstrate that spousal caregivers' satisfaction with their social support resources mediated the impact of a caregiver intervention on caregiver depressive symptoms and on family decisions to place the spouse with dementia in a residential care facility. Significant mediation effects were typically found, but the size and significance of both the mediated effect and the unmediated or direct effect varied considerably across the specific models employed in these analyses. Additional methodological research and Monte Carlo simulation studies would be useful to better clarify the strengths and weaknesses of these multiple approaches. Space limited the number of different types of longitudinal models described in this chapter, and there are additional longitudinal models that can be adapted to test mediation hypotheses, including LGC models (e.g., Cheong, MacKinnon, & Khoo, 2003), latent change score models (e.g., Ferrer & McArdle, 2003), and models based on classifying individual patterns on mediators and outcomes (e.g., von Eye et al., 2009). As described in this chapter, there are many alternative approaches to longitudinal mediation model analysis, and the number of alternatives is growing, as is the software options for estimating these models. Theoretical guidance on the types of change expected and the ideal measurement strategies to capture those changes continues to be central issues in formulating responsive longitudinal mediation models.

Comments on Statistical Software

The major statistical packages such as SAS, SPSS, and STATA have ordinary linear regression and logistic regression procedures that can estimate the parameters and standard errors necessary for computing mediation quantities. All these packages have well-developed regression procedures and standard survival analysis programs that can be implemented to test mediation hypotheses as illustrated here. Asymmetric CIs based on the distribution of the mediated effect can be readily calculated from the estimates from these standard analyses (MacKinnon, Fritz, Williams, & Lockwood, 2007). More complicated multivariate models, including some of the longitudinal models described in this chapter, are more efficiently estimated using an SEM program such as Mplus, AMOS, EQS, or LISREL. SEM programs are often needed to simultaneously estimate the parameters of models with multiple outcome and mediator variable models. These programs are used to estimate the parameters of complex models simultaneously. Most SEM programs also estimate the mediated and direct effects and provide calculations of their standard errors.

A few SEM statistical packages also offer bootstrapping procedures for analyses of mediated effects. Default approaches found in some SEM packages (e.g., the Sobel delta method) are sometimes overly conservative, especially with small to moderate sample sizes, and bootstrapping alternatives are particularly useful in these situations (Shrout & Bolger, 2002). Mplus (Muthén & Muthén, 1998–2010), for example, will calculate specific and total mediated effects, their standard errors, and compute CIs using a variety of methods including the bootstrap. The Mplus program also has an option to calculate and bootstrap other quantities related to mediation, like the proportion mediated. More detailed information on mediation programs, including step-by-step examples, is available in MacKinnon (2008).

Recommended Readings

Cole, D. A., & Maxwell, S. E. (2003). Testing mediational models with longitudinal data: Questions and tips in the use of structural equation modeling. *Journal of Abnormal Psychology*, *112*, 558–577.

Ferrer, E., & McArdle, J. J. (2003). Alternative structural models for multivariate longitudinal data analysis. *Structural Equation Modeling*, *10*, 493–524.

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Example Articles

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