Mediation Analysis in the Two Condition Pretest–Posttest Design: Treatment as Moderator of Time Effects

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Manuscript undergoing editorial review. DRAFT DATE: 30 July 2019. The version of MEMORE implementing the method discussed in this paper is not yet publicly available.

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Abstract

An intervention, such as a weight loss program or a form of psychotherapy, is perceived as effective by a person if he or she experiences some kind of change in thoughts, feelings, or behavior following the intervention. Intervention effects manifest themselves in people in the form of *changes over time*. In this paper, we provide an approach to mediation analysis in pretest–posttest designs that coincides with such within-person psychological experience of change. Our approach focuses on differences between conditions (i.e., between those who do versus do not receive the intervention) in the indirect and direct effects of the passage of time. We provide an example of the analysis and interpretation using data from a study examining the mediating role of abdominal adiposity (fat) in the effect of an exercise intervention on insulin sensitivity.

Keywords: Mediation Analysis, Pretest–Posttest Designs, Causal Mechanisms; Indirect Effects; Conditional Process Analysis

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In the day-to-day psychology of a person, the effect of an intervention, such as a weight loss program or a form of psychotherapy to treat a psychological ailment, is experienced in the form of a change over time in a behavior, thought, physical state, or psychological state. When a person experiences a change, such as a reduction in his or her social anxiety, that change is often attributed to something that happened between an earlier and a later observation, such as beginning psychotherapy. But scientists studying the effects of interventions recognize that change from a prior state following the implementation of an intervention is not sufficient to claim that the intervention had an effect. Perhaps the person's anxiety would have changed anyway, even if he or she didn't start therapy. For this reason, scientists studying the effects of interventions prefer to simultaneously observe a group of people who don't experience the intervention. Evidence that the intervention had an effect is obtained by showing that change over time was different in some manner for those who experienced the intervention compared to those who did not experience it.

Scientists thinking ahead will collect data relevant to possible mechanisms by which an intervention may work. For example, if a form of psychotherapy reduces social anxiety because the therapy reduces the perceived threat of social interactions, it would be important to measure not only people's social anxiety before and after starting psychotherapy, but also how threatening they construe certain social situations. With such data, a *mediation analysis* can be used to examine if those who do versus those who do not receive therapy show differences over time in their threat construal which in turn reduces social anxiety.

The reasoning above describes *treatment condition* (i.e., receiving psychotherapy or not) as a moderator of a mediation process. A *moderator* is a variable that influences or is in some way related to the size of the effect of one variable on another. The mediation process being examined is one where *time* influences the mediator (e.g., threat construals) and changes in the mediator then influence the outcome (e.g., social anxiety). If change in the mediator variable differs between those who do and do not receive the intervention and change in the outcome corresponds to change in the mediator, then we deem the intervention as responsible for differences between groups over time as a result of the change in the mediator which in turn causes differences in the outcome.

In this article, we present an approach to mediation analysis in two condition pretest–posttest designs that treats interventions as moderators of *time* effects. Relying on a difference-score approach to mediation analysis first described by Judd, Kenny, and McClelland (2001), later modernized by Montoya and Hayes (2017), we show how a difference between groups in change in an outcome variable over time breaks into differences between direct and indirect processes, and that a formal test of the difference in the size of the indirect effect of time in the two groups can be used as formal test of mediation. To facilitate adoption, we describe implementation of the method in the easy-to-use and freely-available MEMORE macro available for SPSS and SAS. We also provide comparable Mplus code that conducts the analysis in a structural equation modeling framework.

The Vocabulary and Mechanics of Mediation Analysis

Mediation analysis is used to test a hypothesis about the mechanism by which some causal agent X influences some outcome Y through a *mediator* variable M. A mediator is a variable causally located between X and Y, meaning that it is causally determined by X (at least in part) while also causally determining Y. Thus, X influences M and M in turn influences Y.

Ordinary least squares regression analysis is the most popular approach to mediation analysis when M and Y are continuous and measured only once and participants are observed on or randomly assigned to X. This approach is represented in the form of a path diagram in Figure 1. When using this approach, the *total effect* of X is estimated by regressing Y on X:

$$Y = i_Y + cX + e_Y \tag{1}$$

where i_Y is a regression constant and e_Y is an error in estimation of a person's Y from his or her X. The weight for X, c, is the total effect of X and quantifies the difference in Y between two cases that differ by one unit on X. If X is dichotomous and the groups are coded such that they differ by one unit (e.g., 0 and 1, or -0.5 and 0.5), then c is the difference between the group means on Y.

The total effect of X breaks up algebraically into a direct effect and indirect effect of X. These are estimated by regressing M on X and regressing Y on both M and X:

$$M = i_M + aX + e_M \tag{2}$$

$$Y = i_Y + c'X + bM + e_Y \tag{3}$$

The indirect effect of X on Y through M is the product of a and b and estimates the difference on Y between two cases that differ by one unit on X that is attributable to the joint effect of X on M and the effect of M on Y. The *direct effect* of X on Y is c'. It estimates the difference in Y between two cases that differ by one unit on X but who are equal on M. It represents the component of X's effect on Y that operates independently of the $X \rightarrow M \rightarrow Y$ causal sequence. When the indirect and direct effects are added together, they equal c, the total effect of X. That is $c = c' + ab$.

Historically, the causal steps approach popularized by Baron and Kenny (1986) or variants of it (e.g., Kraemer, Kiernan, Essex, & Kupfer, 2008) have been used to establish whether M is functioning as a mediator of the effect of X on Y. This approach requires establishing evidence of a nonzero total effect of X on Y (c in Figure 1) as well as statistically significant effects of X on M and M on Y (a and b in Figure 1). But since about the turn of the century, this approach has waned in popularity as a result of various criticisms that have gained traction in the literature. By 21st-century thinking, evidence of total effect of X is no longer seen as a prerequisite to empirically examining how a causal effect of X on Y may operate (Cerin & MacKinnon, 2009; Hayes, 2009; Hayes & Rockwood, 2017; O'Rourke & MacKinnon, 2018; Rucker, Preacher, Tormala, & Petty, 2011; Shrout & Bolger, 2002). Furthermore, an indirect effect can exist even if it can't be established that a and b are both significantly different from zero (Hayes, 2009, 2018).

Modern approaches to mediation analysis focus on the indirect effect of X on Y through M quantified as ab. An inference that ab is not zero combined with signs of a and b that are consistent with the proposed process statistically support a claim of mediation, even if a and/or b is not statistically significant. A vestige of 20th-century thought, some still use the Sobel test for inference about the indirect effect, which assumes the sampling distribution of the indirect effect is normal (Sobel, 1982). Modern thinking relies an inferential method that doesn't make assumptions about the shape of the sampling distribution of the indirect effect of X, as the Sobel test does. Of these methods, the bootstrap confidence interval has become most popular. For a discussion of bootstrap confidence intervals and other approaches to inference about an indirect effect, see Hayes (2018), MacKinnon, Lockwood, and Williams (2004), Preacher and Selig (2012), and Shrout and Bolger (2002).

Mediation Analysis in the Two-Instance Repeated Measures Design

The mediation model just described assumes M and Y are measured only once and that X (i.e., intervention) is the causal agent of interest. When M and Y are measured twice, once at pretest and again at posttest, there are many approaches to testing whether M can be deemed as serving a mediating role in the effect of X on Y while using information about the repeated measurements over time (MacKinnon, 2008; Valente & MacKinnon, 2017). These approaches all treat the intervention manipulation as the focal causal agent X and the data analysis focuses on estimating the indirect effect of the intervention on change in Y through change in M. Our approach is different though mathematically related. With our approach, we conceptualize *time* as X, with time affecting Y through the effect of time on M. Mediation is established by showing that the indirect effect of time on Y through M differs between the two conditions. Thus, experimental condition is construed as a *moderator* of the indirect effect of time on Y through the effect of time on M. In this section, we describe our approach by showing how to quantify the total, direct, and indirect effects of the passage of time on Y. Later we note some of the similarities and differences between our approach and others.

In our notation, Y_t and M_t refer to measurements on a dependent variable Y and mediator variable M at time t, where $t = 1$ denotes the first measurement occasion (e.g., pretest) and $t = 2$ refers to the second measurement (e.g., posttest). In the pretest-posttest design, the result is four variables containing the measurements of M and Y for each participant, two that occur at pretest (Y_1, M_1) and two at posttest (Y_2, M_2). A fifth variable W codes group. The mathematics of our discussion below assumes groups are coded with values of 0 and 1. In our example, the control condition is group $w = 0$ and the exercise condition is $w = 1$.

Working Example

We rely on data from a study of older (60 to 80 years) obese adults reported in Ko, Davidson, Brennan, Lam, and Ross (2016) and based on a randomized clinical trial described in Davidson et al. (2009). The study sought to identify mediators of the effect of an exercise intervention on insulin sensitivity. The inverse of insulin sensitivity, *insulin resistance*, is a precursor to various serious diseases and conditions such as diabetes and cardivascular health problems as well as general morbidity. Our analysis focuses on *abdominal adiposity* or, more simply, abdominal fat, as a mediator of the effect of exercise on insulin sensitivity. Adbominal fat produces hormones and other chemicals that can enhance the likelihood of health problems such as diabetes.

Fifty nine participants were randomly assigned to an exercise condition and 21 were randomly assigned to a no exercise control condition. Insulin sensitivity and abdominal fat were measured at randomization as well as 6 months after the exercise intervention or a comparable delay for those assigned to control. The data are publicly available and can be obtained at the location provided in the "Supplementary materials" section. Descriptive statistics for each variable at each time as well as the difference over time can be found in Table 1.

Repeated-measures t-tests show that on average, those assigned to the exercise intervention experienced a reduction in abdominal fat, $7.448 - 8.236 = -0.788$, $t(58) = 8.993$, $p < .001$, as well as improved insulin sensitivity, $23.503 - 19.315 = 4.188$, $t(58) = 6.215$, $p < .001$ over time. Similar though smaller changes in the same direction also occurred among control participants ($8.406 - 8.453 = -0.047$ for abdominal fat, $21.922 - 21.678 = 0.244$ for insulin sensitivity), but neither of these changes is statistically significant, both $|t| < 1$, both $p > .60$. And individuals in the exercise condition experienced a $-0.788 - (-0.047) = -0.744$ kilogram larger reduction in abdominal fat over time compared to those in the control condition. This difference in change is statistically significant using a mixed ANOVA with time as a within factor and condition as a between factor, $F(1, 78) = 23.357, p < .001$, as is the difference in change in insulin sensitivity, $4.188 - 0.244 = 3.944$, $F(1, 78) = 9.112, p = .003$.

Although the analysis just described is not a mediation analysis, the pattern of results suggests that the effect of exercise on insulin sensitivity may operate in part by reducing abdominal fat. Among those who exercised, abdominal fat was reduced and insulin sensitivity improved over time. But among those who did not exercise, there was no corresponding change in insulin sensitivity or abdominal fat during the same time period.

Conditional Total, Direct, and Indirect Effects of Time

In a mediation analysis, an effect is decomposed into two components or "pathways of influence," indirect and direct. In a pretest-posttest design, the effect of interest is the change in Y over time, with something happening (or not) between the two measurements assumed to be responsible for any observed change. The average change in Y between measurements is the *total effect* of time. In a two-group intervention study with pretest and posttest measurements, there are two total effects of time, one for each group. Let c_w denote the average difference in Y over time using only the participants in group w:

$$c_w = \overline{\Delta Y} = \overline{Y}_2 - \overline{Y}_1 \tag{4}$$

where ΔY is the difference between a participant's Y at posttest relative to pretest (i.e, $Y_2 - Y_1$). We call these *conditional total effects* of time. They are conditional because they apply to one of the groups. In the language of mediation analysis, they are *total* effects because they represent the effect of the passage of time on Y, not accounting for any effect the mediator may have on Y.

In the insulin sensitivity study, from Table 1, the conditional total effects of time are

$$c_0 = 0.244 = 21.922 - 21.678 \tag{5}$$

in the control group ($w = 0$) and

$$c_1 = 4.188 = 23.503 - 19.315 \tag{6}$$

in the exercise group ($w = 1$). Because the measurement at time 1 is subtracted from the measurement at time 2, a positive value reflects an increase in insulin sensitivity over time. So in both conditions, insulin sensitivity increased over time. Increases in insulin sensitivity are ultimately the goal of the exercise intervention, as low insulin sensitivity is predictive of later negative health outcomes.

An alternative approach to estimating the conditional total effect of time is to regress the difference in Y over time among on a constant–a "constant only regression"–as in

$$\Delta Y = c_w + e_Y \tag{7}$$

This equation is depicted visually at the top of Figure 2 panels A and B.

Building on the mathematics outlined in Judd et al. (2001), Montoya and Hayes (2017) describe a path-analytic approach to mediation analysis in the repeated measures design that breaks these total effects into direct and indirect effects. This is accomplished by estimating two regression models, one for the difference in M over time and one for the difference in Y over time. We depict the mathematics of this approach in visual form in Figure 2, where the triangle is used to denote a regression constant, a square is used to denote a measured variable, and a circle denotes an error in estimation. Panel A is for group $w = 0$ (the control group) and Panel B is for group $w = 1$ (the exercise group).

These path diagrams depict two equations estimating the difference in Y and the difference in M using the data from participants in group w:

$$\Delta M = a_w + e_M \tag{8}$$

$$\Delta Y = c'_w + b_w \Delta M + d_w[(\Sigma M - \overline{\Sigma M})/2] + e_Y \tag{9}$$

where $\Delta M = M_2 - M_1$, the difference between a participant's measurements on M at pre- and posttest, ΣM is the sum of a participant's measurements of M over time, $M_1 + M_2$, and $\overline{\Sigma M}$ is mean of the sum of mediator measurements for participants in group w. Thus, $(\Sigma M - \overline{\Sigma M})/2$ is a participant's group mean-centered average mediator measurement.

In equation 8, a_w is the average change in M over time in group w. That is,

$$a_w = \overline{\Delta M} = \overline{M}_2 - \overline{M}_1$$

In equation 9, c'_w estimates the part of the effect of time on Y in group w not attributable to change in M in group w. In the lingo of mediation analysis, c'_w is the *direct effect* of time on Y in group w. But here it is a *conditional* direct effect, because it applies only to group w. And b_w in equation 9 estimates the effect of change in M on change in Y in group w.

The *conditional indirect effect* of time on Y in group w operating through change in M over time is $a_w b_w$. It estimates the change in Y over time attributable to change in M over time for people in group w. When $a_w b_w$ is added to c'_w, the result is c_w, the conditional total effect of time on Y in group w from equation 4. That is, $c_w = c'_w + a_w b_w$.

Most any decent data analysis program can be used to estimate the effects in equations 7, 8, and 9. For example, assuming the mediators, outcome, and variable coding group are named `y1`, `y2`, `m1`, `m2`, and `group`, the SPSS code below conducts the analysis and produces the results described below and depicted in Figure 2 panels A and B.

```
/* construct difference scores */.
compute deltam=m2-m1.
compute deltay=y2-y1.
/* construct mean-centered means of mediators */.
if (group=0) summ=((m1+m2)-16.8602)/2.
if (group=1) summ=((m1+m2)-15.6851)/2.
/* generates c_w and a_w */.
sort cases by group.
split file by group.
descriptives variables=deltay deltam.
/* generates c'_w and b_w */.
regression/dep=deltay/method=enter deltam summ.
split file off.
```

Alternatively, the MEMORE macro for SPSS and SAS can be used (Montoya & Hayes, 2017). MEMORE automatically constructs differences scores and mean centers the mean of mediators with no additional input from the user, thereby minimizing the code the analyst has to write. The SPSS MEMORE code

```
memore y=y2 y1/m=m2 m1.
```

would be executed twice, once for cases in group $w = 0$ and once for cases in group $w = 1$.

Regardless of method used, as can be seen in Figure 2 panels A and B, among those in the exercise condition ($w = 1$), there was an average reduction in abdominal fat of slightly more than 3/4 kg ($a_1 = -0.788$), and those who saw greater losses of abdominal fat saw greater increases in insulin sensitivity over time ($b_1 = -2.508$). So in the exercise group, the conditional indirect effect of time on insulin sensitivity through change in abdominal fat is $a_1 b_1 = -0.788(-2.508) = 1.975$. The conditional direct effect of time on insulin sensitivity, which is the component of change in insulin sensitivity over time not attributable to changes in abdominal fat, is $c'_1 = 2.213$. The sum of the conditional direct and conditional indirect effects of time in the exercise group is c_1, the conditional total effect of time from equations 4 and 6. That is, $c_1 = c'_1 + a_1 b_1 = 2.213 + 1.975 = 4.188$

A comparable analysis using the data from the control group reveals that $a_0 = -0.047$, meaning an average descrease in abdominal fat, and the greater the reduction in abdominal fat over time, the greater the increases in insulin sensitivity over time, $b_0 = -2.873$. So among those in the control group, the indirect effect of time on insulin sensitivity through abdominal fat is positive, $a_0b_0 = -0.047(-2.873) = 0.133$. The direct effect of time in the control group is $c'_0 = 0.111$. When added to the indirect effect, the result is the total effect of time in the control group: $c_0 = c'_0 + a_0b_0 = 0.111 + 0.133 = 0.244$, from equations 4 and 5.

Comparing Conditional Effects Between Conditions and a Formal Test of Mediation

By estimating the total, direct, and indirect effect of time among those in the exercise condition, we see a pattern of results which are consistent with change in abdominal fat as the mechanism by which exercise can influence insulin sensitivity. Among those who exercised, insulin increased by $c_1 = 4.188$ units over time, and this change can be partitioned into a positive indirect effect of $a_1b_1 = 1.975$ units through change in abdominal fat over time and a positive direct effect of $c'_1 = 2.217$ units. However, at this point, we have merely described the pattern in the data. We have not yet discussed statistical inference. Furthermore, we have not addressed the issue that a similar pattern of total, direct and indirect effects of time occurred among those who did not exercise, albeit to a much lesser degree. This may cast doubt on whether we can attribute the pattern of results observed among those who exercised to anything about the exercise itself.

In this section, we develop a formal test of mediation in a two condition pretest-postest design. We do so by first showing how the direct, indirect, and total conditional effects estimated in the two sets of regression analyses just described can be estimated with one set of regression analyses using all of the data simultaneously. We then show how the difference between the conditional total effects, which is of much substantive interest, breaks into the difference between the conditional indirect and the difference between conditional direct effects. We next show that mediation is supported if the conditional indirect effects of time *differ* between the two groups. We conclude this section by discussing implementation and inference using the MEMORE macro for SPSS and SAS. We also provide Mplus code that implements our approach using structural equation modeling.

Estimation using Moderated Regression Analysis

It is not necessary to conduct two separate analyses, one in each group, to generate the conditional direct, indirect, and total effects of time. All of the regression coefficients estimated separately in each group in the prior analysis can be generated from one set of two regression models estimating the change in M over time and the change in Y over time, using all of the data simultaneously. The models are

$$\Delta M = a_0 + aW + e_M \tag{10}$$

$$\begin{aligned} \Delta Y &= c_0' + c'W + b_0\Delta M + d_0[(\Sigma M - \overline{\Sigma M})/2] + b(\Delta M)W \\ &\quad + d[(\Sigma M - \overline{\Sigma M})/2]W + e_Y \end{aligned} \tag{11}$$

where ΔY, ΔM and ΣM are defined as earlier and W is still coded $w = 0$ and $w = 1$. In equation 11, $(\Sigma M - \overline{\Sigma M})/2$ is a participant's within-group mean-centered sum of mediators. That is, the centering is done around the mean of the mediators calculated across all participants in his or her group.

Equations 10 and 11 can be estimated using any regression analysis program. Assuming ΔM, ΔY, and $(\Sigma M - \overline{\Sigma M})/2$ are construced as in the earlier code and stored in variables named `deltam`, `deltay`, and `summ`, the SPSS code below does the work.

```
compute deltamw=deltam*group.
compute summw=summ*group.
regression/dep=deltam/method=enter group.
regression/dep=deltay/method=enter group deltam summ deltamw summw.
```

The resulting regression coefficients are found in Table 2 and Figure 2, panel C. However, additional computations, a structural equation modeling program, or the assistance of

MEMORE (described later) is needed for some inferences and to formally test a mediation hypothesis.

When W is coded 0 and 1 for the two groups, equations 10 and 11 produce the conditional direct, indirect, and total effects of time in each group. In equation 11, the regression constant $c'_0 = 0.244$ is the conditional direct effect in the control group ($w = 0$), and $c'_0 + c' = 0.111 + 2.102 = 2.213 = c'_1$, the conditional direct effect in the exercise group ($w = 1$). It follows that the difference between the conditional direct effects is c' in equation 11:

$$c' = c'_1 - c'_0 = 2.213 - 0.111 = 2.102$$

Both conditional indirect effects as well as the difference between them are likewise generated by the regression coefficients in equations 10 and 11. In equation 10, $a_0 = -0.047$ is the average change in M over time in the control group. The average change in M for those in the exercise group, a_1, is $a_0 + a = -0.047 + (-0.741) = -0.788$ from equation 10. Therefore, a is the difference between the groups in change over time in M:

$$a = a_1 - a_0 = -0.788 - (-0.047) = -0.741$$

Likewise, b_0 and b_1, the effect of change in M on change in Y, are generated from equation 11: $b_0 = -2.873$ is the regression coefficient for ΔM in equation 11 and $b_1 = b_0 + b = -2.873 + 0.365 = -2.508$. So b in equation 11 is the difference between the groups in the effect of change in M over time on the change in Y over time:

$$b = b_1 - b_0 = -2.508 - (-2.873) = 0.365$$

From earlier, the conditional indirect effect of time on change in Y through change in M in group $w = 0$ is a_0b_0, which can be computed from equations 10 and 11. The indirect effect in group $w = 1$ is a_1b_1, or $(a_0 + a)(b_0 + b)$ in terms of equations 10 and 11. So the difference between the two conditional indirect effects using only the regression coefficients in equations 10 and 11 is

$$\begin{aligned} a_1b_1 - a_0b_0 &= (a_0 + a)(b_0 + b) - a_0b_0 \\ &= a_0b + a(b_0 + b) \end{aligned}$$

Indeed, observe from the insulin sensitivity study,

$$\begin{aligned} a_1b_1 - a_0b_0 &= a_0b + a(b_0 + b) \\ 1.975 - 0.133 &= -0.047(0.365) + (-0.741)(-2.873 + 0.365) \\ 1.842 &= 1.842 \end{aligned}$$

The difference between the conditional total effects, $c_1 - c_0$, typically tested through a mixed ANOVA, is of much substantive interest because this difference quantifies differential change between groups on dependent variable Y over time on average. The difference between the conditional total effects could be more directly estimated by regressing the difference in Y over time on W, the variable coding experimental condition:

$$\Delta Y = c_0 + cW + e_Y \tag{12}$$

In this model, the regression constant c_0 is average change in Y over time for participants in group $w = 0$ (the control group) and the difference in Y over time for those in group $w = 1$ (the exercise group) is $c_1 = c_0 + c$. So c is the mean difference in change over time in Y between the two conditions—the difference between the conditional total effects of time

$$c = c_1 - c_0 = 4.188 - 0.244 = 3.944$$

Estimation of equation 12 is not necessary, however, as this difference can be computed from the regression coefficients in equations 10 and 11 because it is equivalent to the sum of the difference between the conditional direct effects and the difference between the conditional indirect effects. That is,

$$\begin{aligned} c &= (c'_1 - c'_0) + (a_1b_1 - a_0b_0) \\ &= c' + [a_0b + a(b_0 + b)] \end{aligned}$$

Indeed, from the insulin sensitivity study,

$$\begin{aligned} 3.944 &= (2.213 - 0.111) + [-0.788(-2.508) - (-0.047)(-2.873)] \\ 3.944 &= 2.102 + 1.842 \\ 3.944 &= 3.944 \end{aligned}$$

Thus, we have now established both that the total effect of time within each group the sum of the direct and indirect effect of time within each group and also that the *difference* between the groups in the total effect of time is the sum of the difference between the groups in the direct effect of time and the difference between the groups in the indirect effect of time.

A Formal Statistical Test of Mediation

As previously discussed, 21st-century thinking about mediation analysis stipulates that mediation is supported by the statistical evidence if the indirect effect of X is different from zero with the pattern of signs of a and b consistent with the logical or theoretical argument being made about the process at work. We now apply this modern logic to the two-group pretest-posttest design. An intervention is deemed effective if those who receive the intervention change over time on Y in some desirable way and in a manner different than those who don't experience the intervention. This is manifested statistically in the difference between conditional total effects of time, $c_1 - c_0$. We showed that this difference breaks into indirect and direct components or, more precisely, the difference between the conditional indirect effect of time on Y through changes in M over time $(a_1b_1 - a_0b_0)$, and the difference between the conditional direct effects of time, $c'_1 - c'_0$. We propose that change in M over time as the mechanism by which an intervention operates on change in Y occurs when conditional indirect effects of time are *different* between the two groups. That is, does the magnitude of the change in Y over time attributable to change in M over time differ across those who receive the intervention relative to those who do not?

Of course, mere difference between groups in the indirect effects of time would not be sufficient to support a specific mediation hypothesis. The observed difference must be larger than can plausibly attributed to chance by a hypothesis testing standard or a confidence interval that does not include zero. Although several approaches to comparing two conditional indirect effects exist, we recommend the use of a bootstrap confidence interval, as the difference between conditional indirect effects involves the product of regression coefficients so its sampling distribution isn't likely to be normal or symmetrical in form. Bootstrapping also does not require an estimate of the standard error of the difference, the derivation of which would require certain assumptions being met. In addition, bootstrapping is already a well-accepted inferential approach in mediation analysis when the goal is to determine whether an indirect effect differs as a function of a moderator (Hayes, 2015).

But it is still not sufficient to merely establish by an inferential standard that two conditional indirect effects of time are different. Also important is that the pattern of change in M and Y in the two groups (e.g., the signs of change, and the relationship between change in M and change in Y) be logically consistent with the theory or hypothesis about how the intervention is presumed to operate in the presence of the intervention but not in its absence. Two conditional indirect effects could be different, but the pattern of change may be inconsistent with expectations given the predictions about change made by the hypothesis or theory.

Our approach is a test of mediation, but analytically, mediation is established by showing a pattern of results that can be interpreted instead as *moderation*—moderation of an indirect effect of time by condition. Affirmative evidence of moderation is often "probed" in order to be able to articulate under which conditions, situations, or for what types of people an effect exists or does not, or when the effect is large versus small. An analogous probing exercise after establishing that two conditional indirect effects differ would involve examining which of the causal paths differ between the two conditions (e.g., the effect of X on M; the effect of M on Y; both?) as well as conducting an inference about the conditional indirect effect of time in each group. Is the conditional indirect effect statistically different from zero in one group but not another?[1]

An important consequence of our approach is that even though it is often the difference between the conditional total effects of time that leads one to ask questions about how differential change operates, one does not need to find a statistically significant difference between conditional total effects to test for mediation in a pretest-posttest design such as this. The difference between the conditional total effects carries no information about the difference between the conditional indirect effects. That is, $c_1 - c_0$ does not determine or in any way influence the size of $a_1b_1 - a_0b_0$. It is the difference between conditional indirect effects that ultimately matters, not the difference between the conditional total effects. So one can proceed with a mediation analysis even if one cannot definitively establish differential change between groups in Y over time. Groups may differ in indirect effects of time even if they don't appear to differ in the total effects of time.

Implementation and Inference in Computing Software

As already discussed, any regression analysis program can estimate equations 10 and 11, but inference for conditional indirect effects and the difference between them requires the integration of information across the two equations, something not available from canned regression analysis programs. A structural equation modeling program such as Mplus could be used, and we provide Mplus code in Appendix B that conducts this analysis. But most will find the MEMORE macro for SPSS and SAS much easier to use so we restrict our discussion to the interpretation of MEMORE output. Through originally designed for repeated-measures mediation analysis in two-instance single group designs (see Montoya & Hayes, 2017), features have recently been added to MEMORE to conduct tests

[1]Note that differences in significance of the conditional indirect effects is not a requirement of mediation. What matters is whether the conditional indirect effects are statistically different from *each other*. Nevertheless, establishing evidence of mediation in one group but not another when combined with evidence that the two indirect effects differ from each other is a more elegant and potentially more convincing pattern of results.

of moderation (Montoya, 2019) and, now, the moderation of conditional indirect effects estimated in two groups. In one line of code, MEMORE constructs the needed difference scores, group mean centers sums of mediators, estimates equations 10, 11, and 12, and provides point estimates as well as ordinary least squares standard errors and confidence intervals for most of the effects we have discussed, both within and between groups. For inference about indirect effects, it conducts our test of mediation by generating a bootstrap confidence interval for the difference between the conditional indirect effects, as well bootstrap confidence intervals for each of the conditional indirect effects.

Assuming that the variable coding group (exercise intervention or control), W in our notation above, is named `group` in the data, the SPSS version of the MEMORE command

```
memore y=y2 y1/m=m2 m1/w=group/model=4.
```

estimates the model. The resulting MEMORE output can be found in Appendix A. In the right margins of the output we provide the symbols for various effects we have discussed and that appear in Figure 2, with arrows pointing to the relevant row in the MEMORE output to ease following our discussion. But these symbols do not appear in the output itself.

The top section of the output provides information about the variables being used in the analysis and the names of difference scores and (mean centered) mediator sums as they appear in the output. Below this can be found the model of the difference in Y over time from equation 12 that produces the total effect of time on insulin sensitivity in the control group c_0 as well as the difference between the total conditional effects of time, c, which as discussed is equal to $c_1 - c_0$. The conditional total effects of time differ between the groups, $c = 3.944, p < .001$. These two conditional total effects can be found just below in the section labeled "Conditional effect of X on Y at values of the moderator(s)." As can be seen, in the control group (group=0), there is no statistically significant change in insulin sensitivity, $c_0 = 0.244, p = 0.829$, but insulin sensitivity is significantly higher at posttest among those who exercised (group=1), $c_1 = 4.188, p < .001$. But recall that as noted above, a statistically significant difference between the total conditional effects of time is not a requirement of mediation.

The next section of output contains the results of equation 10 that estimates change in the mediator from condition. The two regression coefficients here are the conditional effect of time on change in abdominal fat in the control condition (a_0) and the difference in change in abdominal fat between the groups (a). As can be seen, there was a significant difference in change in abdominal fat between those who exercise and those who did not, $a = -0.741, p < .001$. Below the regression model, in the section that reads "Conditional effect of X on M at values of moderator(s)" are the two conditional effects of time on change in abdominal fat. Among those who exercised (group=1), abdominal fat was significantly lower at posttest compared to at pretest, $a_1 = -0.788, p < .001$. There was no statistically significant difference over time in abdominal fat among those who did not exercise (group=0), $a_0 = -0.047, p = .731$.

The next section of output is the model of the difference in Y corresponding to equation 11. This model generates the conditional direct effect of time in the control group c'_0 as well as the difference between the conditional direct effects in the two groups (c'), but we save a discussion of these until later, when and where they appear in the summary section of the MEMORE output. Also found here are b_0, b_1, and b the conditional effect of the change in abdominal fat on change in insulin sensitivity in each group as well as the difference between the groups in this effect. As can be seen in the section labeled "Conditional effect of Mdiff on Ydiff at values of the moderator," among those who exercised, a reduction in abdominal fat was associated with a significant increase in insulin sensitivity, $b_1 = -2.508, p = .011$. Not so among those who did not exercise, $b_0 = -2.873, p = .286$. However, the regression coefficient for the product of the difference in M over time and group W is $b = 0.364$ and not statistically significant, $p = .898$. So we cannot conclude that these conditional effects are different from each other.

The last section of output is a summary of the conditional direct, indirect, and total effects of time in the two groups as well as differences between them. Everything here is derived from the earlier model equations, and some of this output is redundant with sections of output that appear earlier, such as the conditional total and direct effects. New information includes the conditional indirect effects and the test of mediation we developed based on the difference between the conditional indirect effects.

As can be seen in the section labeled "Conditional indirect effect of X on Y through M," the conditional indirect effect of time on change in insulin sensitivity through change in abdominal fat among those who did not exercise (group=0) is $a_0 b_0 = 0.133$. This positive indirect effect is the result of the reduction (though nonsignificant) in abdominal fat among those who did not exercise, which translates to an increase (though nonsignificant) in insulin sensitivity. But among those who exercised (group=1), the indirect effect is $a_1 b_1 = 1.976$, resulting from the reduction (and statistically significant) in abdominal fat that translates into an increase (that is statistically significant) in insulin sensitivity. Importantly, these two conditional indirect effects are different from each other, as revealed in the section labeled "Test of moderation of the indirect effect." The difference between these conditional indirect effects is 1.842, and we can rule zero out as a plausible value of the difference, as a 95% bootstrap confidence interval based on 5,000 bootstrap samples (the default in MEMORE) does not include zero (0.129 to 3.554). This is evidence of mediation of the effect of exercise on change (an increase) in insulin sensitivity resulting from a change (a reduction) in abdominal fat that, in turn, influences (by causal assumption) insulin sensitivity.

With evidence of mediation, manifested in the moderation of the indirect effect of time by condition, we can probe this result by noticing that the conditional indirect effect of time on insulin sensitivity through abdominal fat is not definitively different from zero among those who did not exercise, as a bootstrap confidence interval for the indirect effect of 0.133 includes zero (−0.497 to 1.087). However, among those who exercised, the increase in insulin sensitivity over time due to the decrease in abdominal fat during this same period (1.986) is definitively different from zero, with a bootstrap confidence interval that is entirely above zero (0.498 to 3.578).

Causal effects can operate through mechanisms or other processes that are not part of the statistical model being used. These other processes at work manifest themselves in the form of direct effects. The conditional direct effects of time in each condition as well as a test of the difference between them can be found in the final summary section of the MEMORE output. As can be seen in the section titled “Conditional direct effect of X on Y” and “Tests of moderation of direct effect”, the conditional direct effect of time among those who exercised is $c_1' = 2.213, p = .029$, meaning an increase in insulin sensitivity over time not attributable to change in abdominal fat. No statistically significant direct effect is observed among those in the control condition $c_0' = 0.111, p = .919$. However, difference in significance does not mean statistically different. But a formal test of the difference between these conditional direct effects reveals that we cannot say they differ from each other, $c' = 2.102, p = .158$.

Extensions and Alternatives

In this paper, we have described an approach to mediation analysis in the two-condition pretest-posttest design that conceptualizes an experimental intervention as a moderator of the total, direct, and indirect effects of time. We showed that evidence of mediation of the effect of an experimental intervention can be found in differences between groups (intervention versus control) in the indirect effects of time on an outcome Y through a mediator M. This approach corresponds statistically with the psychology of intervention effects, as changes experienced in people over time, while providing information the scientist needs about how an intervention influences this change. We conclude by discussing some extensions of this method as well as some alternative analytical approaches.

More Than One Mediator

Throughout this article we have focused on a single mediator representing the sole mechanism by which an effect operates. But our method is easily extended to models with more than one mediator (see e.g., Hayes, 2018; Preacher & Hayes, 2008). Equations 10 and 11 can be generalized to multiple mediators in parallel or in serial. A thorough exposition of this generalization is beyond the scope of this article. Suffice it to say that MEMORE allows the user to specify more than one mediator. More information about multiple mediator models in pretest–posttest designs can be found in Montoya and Hayes (2017) and the MEMORE documentation at *akmontoya.com*.

Alternative Antecedents and Moderators

Our focus has been on the effect of the passage of time on an outcome through a mediator and how this effect is moderated by an experimental manipulation in a two-condition pretest-posttest design. But this is not the only design for which our approach is appropriate. The causal antecedent variable X need not be time. For example, in a related design, participants experience two versions of a stimulus that vary on some manipulated factor with the goal of examining how that manipulation affects a dependent variable. This is the very design that Judd et al. (2001) and Montoya and Hayes (2017) focused on in their treatment of mediation analysis that is the underpinning our method. In such repeated measures designs, order of stimulus is often randomized between participants to rule out order effects. Using our method, order could be used as the moderator to examine whether the indirect effect of the repeated measures manipulation on an outcome through a mediator depends on the order of stimulus presentation.

Indeed, our method can be used to examine any dichotomous variable as a moderator of the indirect effect of a variable manipulated within-person or measured over time. The moderator need not be an experimental manipulation. For example, a version of the insulin sensitivity study might seek to examine if the indirect effect of time on insulin sensitivity through abdominal fat among participants encouraged to exercise differs between Type I and Type II diabetics. In such a design, absent a no-exercise control condition, we would lose the ability to make claims about the effectiveness of exercise itself, but observing differences in the indirect effects of time consistent with predictions about how such groups should differ in the mechanisms at work can also be an approach to confirming whether that mechanism is indeed in operation.

A Simpler Difference Score Approach?

MacKinnon (2008) and Valente and MacKinnon (2017) describe an alternative difference score approach commonly used in the interventions literature. We call this alternative the treatment indirect effect (TIE) approach. In the TIE approach, the difference in M over time is first regressed on W, the variable coding condition, as in

$$\Delta M = a_0 + aW + e_M \tag{13}$$

When W is coded such that there is a one unit difference between the control and intervention condition (e.g., 0 and 1, or -0.5 and 0.5), a quantifies the difference in change in M between the control and intervention conditions, just as does a from our approach (equation 10, which is the same as equation 13).

Next, the TIE approach requires estimation of the difference in the outcome Y using experimental condition W and the difference in the mediator over time as predictors:

$$\Delta Y = i_Y + c'W + b\Delta M + e_Y \tag{14}$$

Using the TIE approach, mediation is established by showing that the indirect effect of the intervention on the change in Y through the change in M, ab, is different from zero.

Although simpler than our approach to be sure, the TIE approach makes two assumptions that our method does not. First, it assumes that the relationship between M and Y at pretest is the same as the relationship between M and Y at posttest. When met, this assumption warrants the interpretation of b as an estimate of the effect of change in M

on the change in Y. Second, it assumes, using our notation, that $b_0 = b_1$, meaning that the relationship between ΔM and ΔY is the same in the control and intervention conditions. When both of these assumptions are met, our approach and the TIE approach are equivalent. In that case, ab from the TIE approach corresponds to the difference between the two conditional indirect effects from our approach. But our approach is more flexible, in that it is works under these same assumptions the TIE approach makes but does not require them.

Do Groups Need To Be The Same at Pretest?

Randomization to experimental conditions in a pretest-posttest design largely ensures that groups are equal at pretest on observed and unobserved variables and so any differences observed at posttest can be attributed to the manipulation rather than preexisting group differences. However, sometimes random assignment to conditions is not possible or ethical. Our method does not require that the groups be randomized to condition or be the same at pretest in order to be valid, though differences at pretest introduce some potential complexities in inference.

Our method is based on observed difference scores on Y and M over time. Systematic differences between the two groups at pretest open up regression to the mean as a possible explanation for differences between groups over time. Regression to the mean is a common phenomenon where extreme measurements earlier tend toward the population mean over time. Successful randomization results in the expectation that regression to the mean will influence both groups equally, rendering it less of a threat to the validity of inferences about the effect of an intervention. If the moderator (experimental condition in our method) is not randomized and there are difference between the groups at pretest, differences between the groups may occur due to regression to the mean but incorrectly interpreted as evidence of mediation. For instance, in our example, if the exercise group was systematically lower on insulin sensitivity and higher in abdominal fat than the control group at pretest, then we might see an increase in insulin sensitivity and a decrease in abdominal fat over time due to regression to the mean in the treatment group but not in the control group.

Floor and ceiling effects in measurement can also produce difficulties in inference when groups are not equal at pretest. If those in one group tend to be closer to a measurement scale boundary on average than in the other group, opportunities for change may differ across conditions. This can manifest itself in the form of differential change between groups, in total, directly, or indirectly.

Because randomization is not always possible and such effects often cannot be ruled out, alternatives have been advanced, such as including both M_1 and Y_1 on the right sides of the equations that define the TIE approach. This ANCOVA approach, as Valente and MacKinnon (2017) call it, helps deal with regression to the mean and artifacts attributable to floor and ceiling effects, but it still makes the same assumptions the TIE method makes that our approach does not. Valente and MacKinnon (2017) have studied the relative strength and weaknesses of the TIE and ANCOVA approaches and favor the ANCOVA approach. Research comparing the performance of the TIE and ANCOVA approaches to our proposed approach would be worthwhile.

Author Contributions

A. F. Hayes and A. K. Montoya both worked on the derivations discussed in this paper. A. F. Hayes wrote the initial draft of the manuscript. Both authors revised and edited subsequent drafts prior to publication. A. F. Hayes wrote the Mplus code in Appendix B, and A. K. Montoya wrote MEMORE and implemented the procedure discussed in this paper in the version released with its publication. Both authors approved the final version of the manuscript prior to submission.

Conflict of Interest

The authors declare that there were no conflicts of interest with respect to the authorship or publication of this article.

Supplementary Material

The data for this example are publicly available at *https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0167734*. The variables used in the archived data are named `InsulinSensitivity1`, `InsulinSensitivity2`, `AbAT1`, `AbAT2`, and `Exercise`. In this paper, we refer to these variables as `y1`, `y2`, `m1`, `m2`, and `group`, respectively, in our analyses. The MEMORE macro for SPSS and SAS can be downloaded from *www.akmontoya.com*. The version of MEMORE used in this paper with the features we have described will be publicly released when this paper is published. Mplus output generated by the code in Appendix B can be downloaded as a supplementary file from this journal's web page.

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Table 1
Descriptive statistics from a randomized controlled trial examining the effect of a exercise treatment on change in abdominal adiposity (ΔM) and insulin sensitivity (ΔY).

		Abdominal Adiposity (M)			
		M_1	M_2	ΔM ($M_2 - M_1$)	
Control ($w = 0$)	Mean	8.453	8.406	−0.047	$\leftarrow a_0$
	SD	1.697	1.675	0.414	
Exercise ($w = 1$)	Mean	8.236	7.448	−0.788	$\leftarrow a_1$
	SD	2.223	2.252	0.673	
Difference between group means				−0.741	$\leftarrow a$
		Insulin Sensitivity (Y)			
		Y_1	Y_2	ΔY ($Y_2 - Y_1$)	
Control ($w = 0$)	Mean	21.678	21.922	0.244	$\leftarrow c_0$
	SD	8.038	7.452	5.041	
Exercise ($w = 1$)	Mean	19.315	23.503	4.188	$\leftarrow c_1$
	SD	9.179	9.669	5.176	
Difference between group means				3.944	$\leftarrow c$

Table 2
Regression coefficients (standard errors in parentheses) from a two-instance repeated measures mediation analysis with exercise intervention condition as moderator of all paths.

		Equation 10		Equation 11		Equation 12
		Abdominal Adiposity (ΔM)		Insulin Sensitivity (ΔY)		Insulin Sensitivity (ΔY)
Constant	$a_0 \rightarrow$	-0.047 (0.135)	$c'_0 \rightarrow$	0.111 (1.086)	$c_0 \rightarrow$	0.244 (1.122)
W	$a \rightarrow$	-0.741 (0.157)	$c' \rightarrow$	2.102 (1.474)	$c \rightarrow$	3.944 (1.307)
ΔM			$b_0 \rightarrow$	-2.873 (2.673)		
$(M_2 + M_1)^+$			$d_0 \rightarrow$	-0.969 (0.662)		
$(\Delta M)W$			$b \rightarrow$	0.365 (2.842)		
$(M_2 + M_1)^+W$			$d \rightarrow$	0.795 (0.724)		
R^2		.223		.215		.105

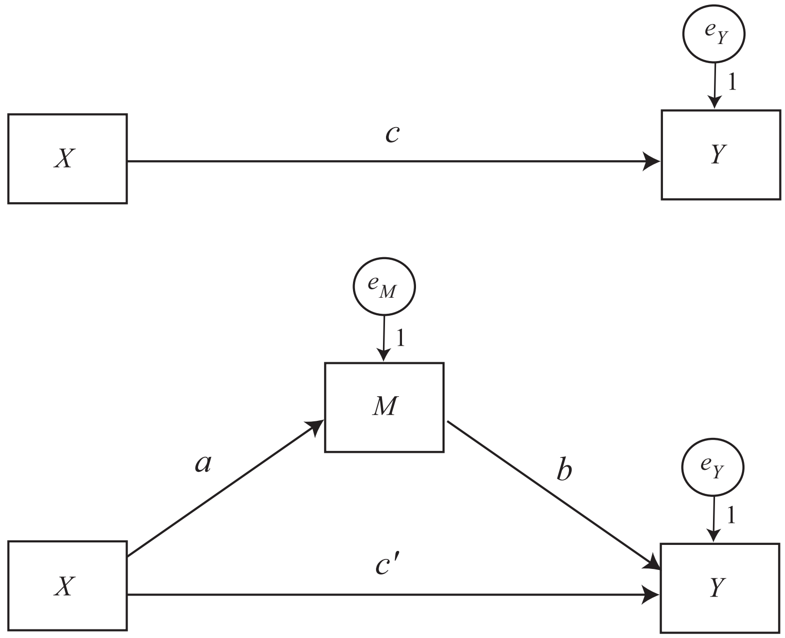

Figure 1. A simple mediation model in path diagram form.

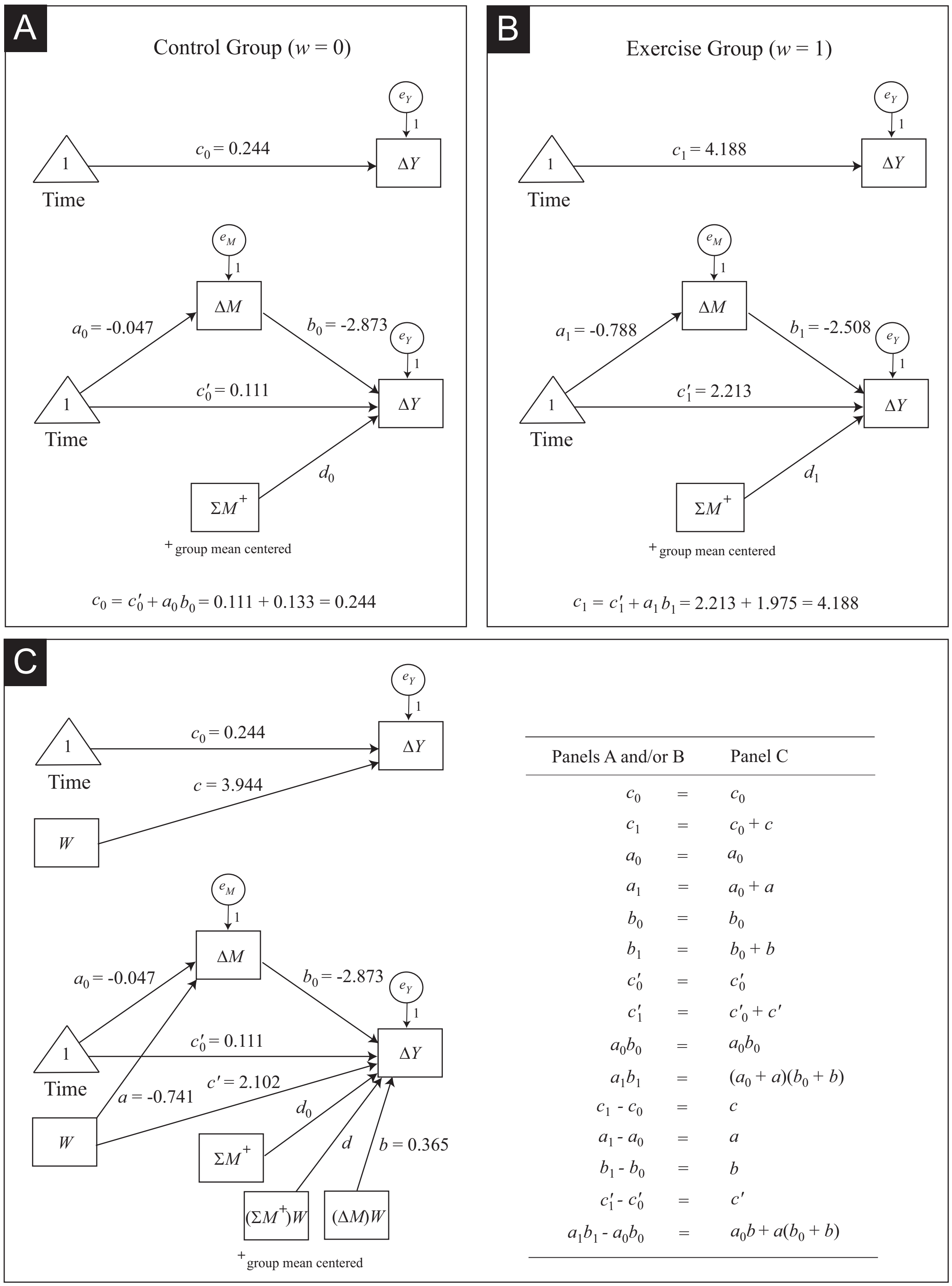

Figure 2. Path diagrams for estimating the total, direct, and indirect effect of time in the control group (A) and the experimental group (B). The path diagram in Panel C estimates all the effects in Panels A and B as well as moderation of these effects by group.

Appendix A

Output from the MEMORE Macro

The output in this appendix was generated by the SPSS version of the MEMORE macro when the command

```
MEMORE y=y2 y1/m=m2 m1/w=group/model=4.
```

was applied to the data from the insulin sensitivity study.

```
******************** MEMORE Procedure for SPSS Version 3.0 **********************

                          Written by Amanda Montoya

                   Documentation available at akmontoya.com

*********************************************************************************

Model:
  4

Variables:
Y = Y2 Y1
M = M2 M1
W = GROUP

Computed Variables:
Ydiff   =  Y2 - Y1
Mdiff   =  M2 - M1
Mavg    =  (M2 + M1)/2        Group-Mean Centered
Mdiff*W =  Mdiff*Group
Mavg*W  =  Mavg*Group


Sample Size:
  80

**********************************************************************************
Outcome: Ydiff =  Y2   -       Y1
```

Equation 12

```
Model Summary
          R       R-sq        MSE          F        df1        df2          p
      .3234      .1046    26.4391     9.1124     1.0000    78.0000      .0034

Model
             Effect         SE          t          p       LLCI       ULCI
constant      .2442     1.1221      .2177      .8282    -1.9896     2.4781
group        3.9441     1.3066     3.0187      .0034     1.3429     6.5453
```

← c_0

← c

```
Degrees of freedom for all regression coefficient estimates:
  78

Conditional effect of 'X' on Y at values of moderator(s)
      group     Effect         SE          t          p       LLCI       ULCI
      .0000      .2442     1.1221      .2177      .8287    -1.9896     2.4781    ←  c0
     1.0000     4.1883      .6694     6.2567      .0000     2.8556     5.5211    ←  c1

Degrees of freedom for all conditional effects:
  78

**************************************************************************************
Outcome: Mdiff =  m2        -       m1
                                                                          Equation 10

Model Summary
          R       R-sq        MSE          F        df1        df2          p
      .4720      .2228      .3805    22.3568     1.0000    78.0000      .0000

Model
             Effect         SE          t          p       LLCI       ULCI
constant     -.0465      .1346     -.3453      .7308     -.3145      .2215     ←  a0
group        -.7411      .1567    -4.7283      .0000    -1.0532     -.4291     ←  a

Degrees of freedom for all regression coefficient estimates:
  38

Conditional effect of 'X' on M at values of moderator(s)
      group     Effect         SE          t          p       LLCI       ULCI
      .0000     -.0465      .1346     -.3453      .7308     -.3145      .2215    ←  a0
     1.0000     -.7876      .0803    -9.8074      .0000     -.9475     -.6277    ←  a1

Degrees of freedom for all conditional effects:
  78

**************************************************************************************
Outcome: Ydiff =  y2        -       y1
                                                                          Equation 11

Model Summary
          R       R-sq        MSE          F        df1        df2          p
      .4636      .2149    24.4354     4.0511     5.0000    74.0000      .0026

Model
             Effect         SE          t          p       LLCI       ULCI
'X'           .1107     1.0858      .1020      .9191    -2.0529     2.2743     ←  c0'
Mdiff       -2.8727     2.6729    -1.0747      .2860    -8.1986     2.4533     ←  b0
MavgC        -.9694      .6615    -1.4654      .1470    -2.2875      .3487     ←  d0
W            2.1020     1.4737     1.4264      .1580     -.8343     5.0384     ←  c'
Mdiff*W       .3643     2.8420      .1282      .8983    -5.5286     6.0272     ←  b
MavgC*W       .7949      .7238     1.0982      .2757     -.6473     2.2370     ←  d
```

Degrees of freedom for all regression coefficient estimates:
74

Conditional effect of Mdiff on Ydiff at values of moderator(s)

group	Effect	SE	t	p	LLCI	ULCI	
.0000	-2.8727	2.6729	-1.0747	.2860	-8.1986	2.4533	$\leftarrow\ b_0$
1.0000	-2.5084	0.9657	-2.5974	.0113	-4.4321	-0.5841	$\leftarrow\ b_1$

************************* TOTAL, DIRECT, AND INDIRECT EFFECTS *************************

Conditional Total effect of X on Y

group	Effect	SE	t	p	LLCI	ULCI	
.0000	.2442	1.1221	.2177	.8282	1.9896	2.4781	$\leftarrow\ c_0$
1.0000	4.1883	.6694	6.2567	.0000	2.8556	5.5211	$\leftarrow\ c_1$

Test of moderation of total effect

	coeff	SE	t	p	LLCI	ULCI	
group	3.9441	1.3066	3.0187	.0034	1.3429	6.5453	$\leftarrow\ c$

Conditional direct effect of X on Y

group	Effect	SE	t	p	LLCI	ULCI	
.0000	.1107	1.0858	.1020	.9191	-2.0529	2.2743	$\leftarrow\ c'_0$
1.0000	2.2127	.9963	2.2108	.0294	.2275	4.1980	$\leftarrow\ c'_1$

Test of moderation of direct effect

	coeff	SE	t	p	LLCI	ULCI	
group	2.1020	1.4737	1.4264	.1580	-.8343	5.0384	$\leftarrow\ c'$

Conditional indirect effect of X on Y through M

group	Effect	LLCI	ULCI	
.0000	.1335	-.4966	1.0872	$\leftarrow\ a_0b_0$
1.0000	1.9756	.4984	3.5770	$\leftarrow\ a_1b_1$

Test of moderation of indirect effect

Index	LLCI	ULCI	
1.8421	.1292	3.5538	$\leftarrow\ a_1b_1 - a_0b_0$

***************************** ANALYSIS NOTES AND WARNINGS *****************************

Level of confidence for all confidence intervals in output:
95.00

Appendix B

Mplus Code Generating the Insulin Sensitivity Mediation Analysis

Execute twice, first as is, and then after removal of exclamation points in the ANALYSIS and OUTPUT sections to generate bootstrap confidence intervals for indirect effects. The output generated by this code can be found as a supplementary file on this journal's web page.

```
DATA:
 file is 'c:\mplus\insulin.csv';
VARIABLE:
 names are id group m1 m2 m1 m2;
 usevariables are exercise mdiff ydiff summ summg mdiffg;
DEFINE:
 ydiff=y2-y1;
 mdiff=m2-m1;
 if group==0 then summ=((m1+m2)-16.8602)/2;
 if group==1 then summ=((y1+y2)-15.6851)/2;
 summg=summ*group;
 mdiffg=mdiff*group;
ANALYSIS:
 !bootstrap=10000;
MODEL:
 mdiff on group (a);
 ydiff on group (cp)
          summ (d0)
          mdiff (b0)
          mdiffg (b)
          summg (d);
 [mdiff] (a0);
 [ydiff] (cp0);
MODEL CONSTRAINT:
 new a1 b1 a0b0 a1b1 cp1 c0 c1
     adiff bdiff cdiff cpdiff indiff;
 a1=a0+a;
 b1=b0+b;
 !indirect, direct, and total effects;
 a0b0=a0*b0;
 a1b1=(a0+a)*(b0+b);
 cp1=cp0+cp;
 c0=cp0+a0b0;
 c1=cp1+a1b1;
 !difference between effects;
 adiff=a1-a0;
 bdiff=b1-b0;
 cdiff=c1-c0;
 cpdiff=cp1-cp0;
 inddiff=a1b1-a0b0;
```

```
OUTPUT:
 !cinterval (bootstrap);
```