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Improved methods to investigate mediation effects: an independent application to an instance of mediated moderation

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Abstract

Recently, simulation studies have investigated different methods to detect indirect effects. Among others, resampling methods showed to be superior to the traditional asymptotic *z*-test based on large-sample approximations. This paper is aimed at showing the advantage of using such improved methods over the asymptotic test by providing an independent application of different methods on a small set of valuable longitudinal data. Small data sets are particularly vulnerable for tests that are only asymptotically valid. The effect under study concerns an instance of mediated moderation. The results show the advantage of using the bias-corrected bootstrap method that appeared superior in simulation studies. Moreover, our application shows the straightforward extension of these methods to more complex mediational models such as mediated moderation.

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Keywords

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Introduction

Traditional and/or well-known statistical tests, even if widely used, may not always be the optimal approach to deal with a specific problem. For example, the non-parametric Mann-Whitney test may often be preferred over the widely used *t*-test. Likewise, the asymptotic Wald method to construct confidence intervals for a proportion are shown to be inferior to other methods such as exact tests or the modified Wald test [1]. This is also the case for the detection of mediation effects (also termed indirect effects). These are typically investigated using the classical approach [2] or using an asymptotic *z*-test, commonly known as the Sobel test [3]. Simulation studies have shown that more powerful methods exist [4-5]. This paper independently demonstrates that the use of methods that are superior for example with respect to power, may help researchers in getting out of their data what is in it. More specifically, our example deals with mediated moderation, an extension of basic mediation. In this way, the present work also shows the straightforward use of improved methods for more complicated mediation situations.

An indirect effect (or mediation effect) occurs when the effect of one variable (X_I, the independent) on another variable (Y, the dependent) occurs at least in part through a third variable (X_m, the mediator): X_I has an effect on X_m which in turn affects Y (see Figure 1, panels A and B). Mediation effects are frequently investigated in the medical literature (for a few recent examples see [6-15]). Three model equations are important for investigating indirect effects:

$$Y = \gamma_1 + \tau X_1 + \varepsilon_1 \quad (1)$$

$$Y = \gamma_2 + \tau' X_1 + \beta X_m + \varepsilon_2 \quad (2)$$

$$X_m = \gamma_3 + \alpha X_1 + \varepsilon_3. \quad (3)$$

According to the seminal paper by Baron and Kenny [2], an indirect effect entails three conditions: X_I must affect both X_m (i.e., $\alpha \neq 0$) and Y (i.e., $\tau \neq 0$), and the effect between X_I and Y should at least partly be taken over by X_m once the mediator is entered into the

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model (i.e., $\beta \neq 0$). If these conditions are met, it should follow that the effect of X_1 on Y should be smaller in equation 2 than in equation 1 (i.e., $\tau' < \tau$). A drawback of this method is that the hypothesis under scrutiny is not directly addressed. It does not inform us on the indirect effect itself, for example by giving the magnitude of or variability in the indirect effect. Therefore, we will focus ourselves to methods relying on a point estimate of the indirect effect. Notice also that MacKinnon and colleagues [4] found that Baron and Kenny's method to test for an indirect effect is suboptimal due to very low Type-I error rate and power. It turned out that the test for the joint significance of α and β [16] emerged as a method with good balance of Type-I error and power over various situations. There is also discussion about the necessity for testing whether τ is significant [17].

A single estimate of the indirect effect can be computed as $\hat{\alpha}\hat{\beta}$, thus by multiplying the estimated effect of X_1 on X_m, $\hat{\alpha}$, with the estimated effect of X_m on Y, $\hat{\beta}$. Another, algebraically equivalent [18], method entails subtracting the effect of X_1 when controlling for the mediator from the zero-order effect: $\tau - \tau'$. The traditional method to test for significance of $\hat{\alpha}\hat{\beta}$ estimates the variance using the multivariate delta method [3]. The variance $\hat{\sigma}^2_{\hat{\alpha}\hat{\beta}}$ is estimated as

$$\hat{\sigma}^2_{\hat{\alpha}\hat{\beta}} = \hat{\alpha}^2\hat{\sigma}^2_{\hat{\beta}} + \hat{\beta}^2\hat{\sigma}^2_{\hat{\alpha}}. \qquad (4)$$

A test of significance is then constructed by computing $z = \hat{\alpha}\hat{\beta} \,/\, \hat{\sigma}_{\hat{\alpha}\hat{\beta}}$, assuming that the sampling distribution of the indirect effect is asymptotically normal [17,19]. The standard normal distribution can then be applied to obtain the p-value of the Sobel z test. Confidence intervals can be computed in a straightforward way as $\hat{\alpha}\hat{\beta} \pm z_{1-\omega/2}\hat{\sigma}_{\hat{\alpha}\hat{\beta}}$ for a (100 - ω)% confidence interval, with ω being the Type-I error rate of choice.

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The assumed large-sample approximation of a normal distribution does not hold, however [5]. On the contrary, the distribution of the indirect effect will often be skewed with high kurtosis. We are dealing with the product of two regression coefficients that are normally distributed asymptotically, and the product of two normal random variables is not normally distributed itself [20]. Deviations from normality are larger in small as compared to larger samples [19]. The traditional test will thus illegitimately produce symmetric confidence intervals that are too wide in the direction of the null hypothesis [21]. This results in lack of power to reject the null hypothesis that no indirect effect exists (H_0: $\alpha\beta = 0$).

Several authors [17,19] recommend the use of bootstrap methods to assess mediation, a fortiori when sample size is small. Bootstrapping is able to incorporate eventual skewness in its confidence intervals. MacKinnon, Lockwood, and Williams [5] present a simulation study showing the inadequate symmetric confidence limits of the traditional method as well as the superiority of two alternative types of methods. The first alternative is based on the distribution of the product of two normal random variables (called *M*-test and empirical *M*-test, cf. supra), leading to an improved alternative for the $z_{1-\omega/2}$-term in the CI formula given above. The empirical *M*-test tries to account for the fact that the product of two *t* rather than normal random variables should be considered due to unknown variances. The second alternative involves resampling methods such as the bootstrap, jackknife, and Monte Carlo methods. The bootstrap techniques under study were the percentile bootstrap, bias-corrected bootstrap, bootstrap *t*, bootstrap *Q*, accelerated bias-corrected bootstrap (BC_a), and *Q*-transform bootstrap. We refer to the original paper as well as to [22,23] for a detailed explanation of these methods. In general, one can conclude from MacKinnon and colleagues [5] that the bias-corrected and BC_a methods performed best with the highest power and the most accurate CIs. Both *M*-tests follow together with the bootstrap *Q* and *Q*-transform methods. These methods have lower power and rather low type-I error rates. The Monte Carlo, bootstrap *t* and percentile bootstrap methods performed inferior to the previous group. The worst methods are the traditional *z*-test and the jackknife with very low type-I and power rates.

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Further, it is noted that a clear advantage of resampling methods is mainly present when α/σ_α and β/σ_β are small.

The simulation study by MacKinnon and colleagues [5] deals with a straightforward mediation effect. However, real datasets often involve special cases of such an effect. In this paper we demonstrate that the methods outlined by MacKinnon and colleagues can easily be extended to suit the requirements of the analysis at hand. Extensions to the mediation effect are for example *mediated moderation* and *moderated mediation*. Even though discussion exist as to the definitions of these situations [2,24-26], these situations entail that the effect of X_1 on X_m or of X_m on Y depend on the value of a moderator variable X_2. What is clear in our opinion, is that the distinction between both situations is very thin. We will discuss here the definition of mediated moderation as given by Muller and colleagues [24] (Figure 1, panel C). This occurs when an effect of X_1 on Y is moderated by X_2 (e.g., when an effect is present for girls but not for boys) and the moderation or interaction can be explained by a mediating process (e.g., the $X_1 \rightarrow X_m \rightarrow Y$ mediating process is only present for girls). In this case, the $X_1 \rightarrow X_m$ link (case A) and/or the $X_m \rightarrow Y$ link (case B) are moderated by X_2. The relevant equations are

$$Y = \gamma_4 + \tau_1 X_1 + \tau_2 X_2 + \tau_{12} X_1 X_2 + \varepsilon_4 \quad (5)$$

$$Y = \gamma_5 + \tau'_1 X_1 + \tau'_2 X_2 + \tau'_{12} X_1 X_2 + \beta_m X_m + \boldsymbol{\beta_{m2} X_m X_2} + \varepsilon_5 \quad (6)$$

$$X_m = \gamma_6 + \alpha_1 X_1 + \alpha_2 X_2 + \boldsymbol{\alpha_{12} X_1 X_2} + \varepsilon_6, \quad (7)$$

and the indirect effect is computed as $\beta_m \alpha_{12} + \beta_{m2} \alpha_1$. If only case A applies, β_{m2} equals zero (bold part in equation 6). If only case B applies, α_{12} equals zero (bold part in equation 7). This would simplify the estimate of the indirect effect. If both case A and B apply, β_{m2} and α_{12} are non-zero.

The present work is aimed at showing the advantage of using improved methods for analyzing data. Using a valuable set of longitudinal data, unfortunately small in size, we provide an independent example of using an optimal method such as the bias-corrected

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bootstrap rather than the traditional method to investigate indirect effects. Due to their asymptotic nature, traditional statistics can be particularly dangerous when used on small data sets. Our example deals with mediated moderation. We compare the results for the traditional significance test (p-value and 95% CI) with results from the methods for confidence interval computation as discussed in [5].

Data, hypotheses, and statistical analysis

A longitudinal study was set up to investigate the effects of maternal anxiety during pregnancy on the child's behavior and personality [27-29]. Eighty-six healthy mothers who where pregnant of their first child were enrolled in the study. Fourteen to fifteen years later, 68 mother-adolescent pairs were still participating. One of the aims of the study was to investigate whether adolescents' cortisol profile mediates an effect of maternal antenatal anxiety on pathological depression in the adolescent [30]. To this end, the mother's anxiety during pregnancy was measured with the State-Trait Anxiety Inventory (STAI), the adolescent's level of depression was measured with Beck's Depression Inventory for Children (CDI) and their cortisol profile was measured through saliva samples delivered at awakening and approximately four and twelve hours later on a control day. We will focus on the mother's anxiety level as measured in the first trimester of pregnancy. Gender differences were suspected, for example in the effect of maternal anxiety on depression since depression is more prevalent in females than in males. Thus, in our analyses the independent variable X_1 is the antenatal maternal anxiety level, the mediator X_m is the cortisol profile and the dependent variable Y is the CDI score of the child at age 14-15 years.

All analyses are performed with SAS9 (SAS Institute, Cary, NC, USA). We will first discuss the regression models, which are fitted using ordinary least squares regression (PROC GLM in SAS). The ω^2 measure of effect size [31] is the main measure of performance. Additionally, p-values are reported. Then, we proceed to estimate the indirect effect itself. All 95% confidence intervals are computed using a self-written macro, except that for the M-test which is computed using a macro written by [32], and

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that for the empirical *M*-test which is computed using the reference values mentioned in [5].

Results and discussion

First, we checked for an overall effect of antenatal maternal anxiety in the first trimester of pregnancy on the child's CDI level of depression around 15 years after birth. This yielded a moderation effect of gender (cf equation 5), $\hat{\tau}_{12}$ = 0.083, se = 0.0352, $t(54)$ = 2.36, ω^2 = 0.07, p = 0.0220. It turns out that antenatal maternal anxiety influences the child's depression for girls (slope = 0.078, ω^2 = 0.14, p = 0.0027) but not for boys (slope = -0.0048, ω^2 = 0.00, p = 0.8470). No main effects were present (ω^2's = 0.00, p's > 0.80).

With respect to the effect of X_1 (antenatal maternal anxiety) on the mediator (the cortisol profile), preliminary repeated measurements regression analyses pointed out that antenatal anxiety has mainly an effect on the diurnal cortisol decrease, which can be computed by subtracting the evening cortisol level from the morning cortisol level. This difference, called DIF, serves as the mediator X_m. Antenatal maternal anxiety has an effect on the child's diurnal cortisol decrease, irrespective of gender (i.e., α_{12} and α_2 in equation 7 are zero; ω^2 for $\hat{\alpha}_{12}$ and $\hat{\alpha}_2$ were both 0.00), $\hat{\alpha}_1$ = -0.21, se = 0.103, $t(56)$ = -2.03, ω^2 = 0.05, p = 0.0467. Higher antenatal maternal anxiety is related to a lower decrease in the child's diurnal cortisol profile.

Since the $X_1 \rightarrow X_m$ path did not differ for boys and girls (the moderator), one would expect a gender-moderated effect of X_m on Y, when controlling for the moderated effect of X_1 (i.e., the gender-anxiety interaction). In the final analysis, the dependent (Y; the CDI depression level) is regressed on antenatal maternal anxiety (X_1), gender (X_2), the gender-anxiety interaction, DIF (X_m), and the gender-DIF interaction (cf. equation 7). The effect of X_m on Y is only weakly moderated by gender, $\hat{\beta}_{m2}$ = -0.090, se = 0.0524, $t(52)$ = -1.71, ω^2 = 0.03, p = 0.0933. While diurnal cortisol decrease tends to exhibit a negative effect on CDI for girls (slope = -0.063, ω^2 = 0.08, p = 0.0130), there tends to be no effect for

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boys (slope = 0.026, ω^2 = 0.00, p = 0.5705). We do observe that the gender-anxiety effect has decreased when the gender-DIF interaction is added, $\hat{\tau}'_{12}$ = 0.062, se = 0.0348, $t(52)$ = 1.78, ω^2 = 0.03, p = 0.0812 (girls: slope = 0.060, ω^2 = 0.07, p = 0.0200; boys: slope = -0.0022, ω^2 = 0.00, p = 0.9293). If we use Baron and Kenny's [2] method for deciding on mediation effects we would not be tempted to conclude that a strong mediated moderation effect exists. However, note that this method has low power. Since our focus is on methods that are based on a direct estimate of the indirect effect, we will not discuss this issue any further.

As discussed above, the mediated moderation effect equals $\beta_m\alpha_{12} + \beta_{m2}\alpha_1$. Since we do not have any evidence to conclude that α_{12} is non-zero, we can simplify the formula to $\beta_{m2}\alpha_1$. Based on the regression analyses, the mediated moderation effect can be estimated as (-0.21)*(-0.090) = 0.0188. Using equation 4 as suggested by the Sobel test, the standard error of the effect is estimated to be 0.01438, leading to a weak mediated moderation effect (z = 1.31, p = 0.1911) with the 95% CI being [-0.0094; 0.0470].

To further investigate the mediated moderation effect, we performed bootstrap analyses. Figure 2 clearly shows that the bootstrap estimate of the indirect effect distribution is positively skewed. The superimposed normal distribution using the Sobel standard error further demonstrates that the traditional CI will be too wide to the left, making it hard to obtain evidence for an indirect effect. Methods that take this skewness into account, such as the ones discussed in [5], are thus better suited to estimate the magnitude of an indirect effect such as the mediated moderation effect in our dataset. Confidence intervals for all tested methods are shown in Figure 3. The bias-corrected and BC_a intervals, which are the most powerful methods, most convincingly suggest that mediated moderation is present. The 95% CI for the bias-corrected bootstrap is [0.0008; 0.0618]. All other methods produced intervals containing zero but, apart from the jackknife and Monte Carlo methods, the obtained CIs are much closer to zero than the z-test CI. The jackknife and Monte Carlo methods, probably not by coincidence, came out as the least performing alternatives in [5]. Notice in this regard that the jackknife's CI is nearly symmetrical around the estimate of the mediated moderation effect.

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Finally, note that the results as presented in [30] are different in that a covariate was included to account for the mother's anxiety after childbearing. For reason of clarity, we chose not to incorporate this variable in the present paper.

Conclusion

The results show that the traditional method fails to clearly detect mediated moderation while the methods demonstrated to be superior consider the presence of mediated moderation more likely. Interestingly, methods that were not among the best according to the simulation studies also yielded less evidence for an indirect effect. For such a longitudinal data set involving ample work and time, it would be a pity not to discover the evidence of the mediated moderation effect when the traditional method is used without further inquiry. Yet, the resampling alternatives to the traditional *z*-test and Baron and Kenny's [2] approach appear to be underused [33] although there are some exceptions [6,15,34]. Our application also shows the straightforward extension of the resampling techniques to more complex mediation situations such as mediated moderation.

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FIGURE 1 Graphical presentation of the overall effect (panel A), of a mediation effect (panel B) and of mediated moderation examples according to [24], with gender as moderating variable (C). The thickness of the solid arrows is related to the strength of the effect, the thickness of the dashed arrows is related to the strength of the accompanying overall effect.

FIGURE 2 Bootstrap estimated distribution of the mediated moderation effect. The superimposed full line represents a kernel estimation of this distribution, the dashed line represents the normal distribution used in the traditional *z*-test.

FIGURE 3 Graphical presentation of the 95% confidence intervals as obtained by various methods. The horizontal lines represent the confidence intervals and the full vertical line represents zero, the dashed vertical line represents the mediated moderation effect as estimated by the data (0.0188). Thick lines represent CIs that do not contain zero.

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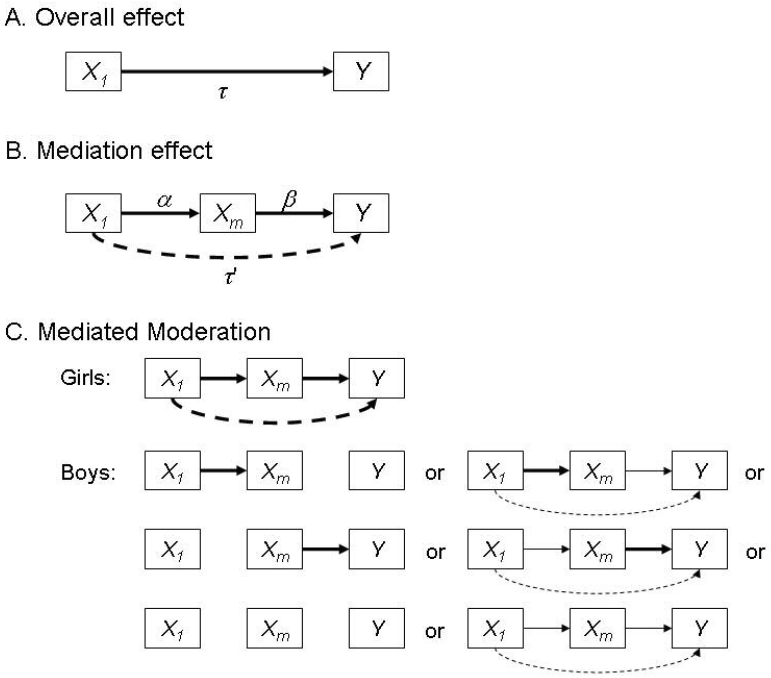

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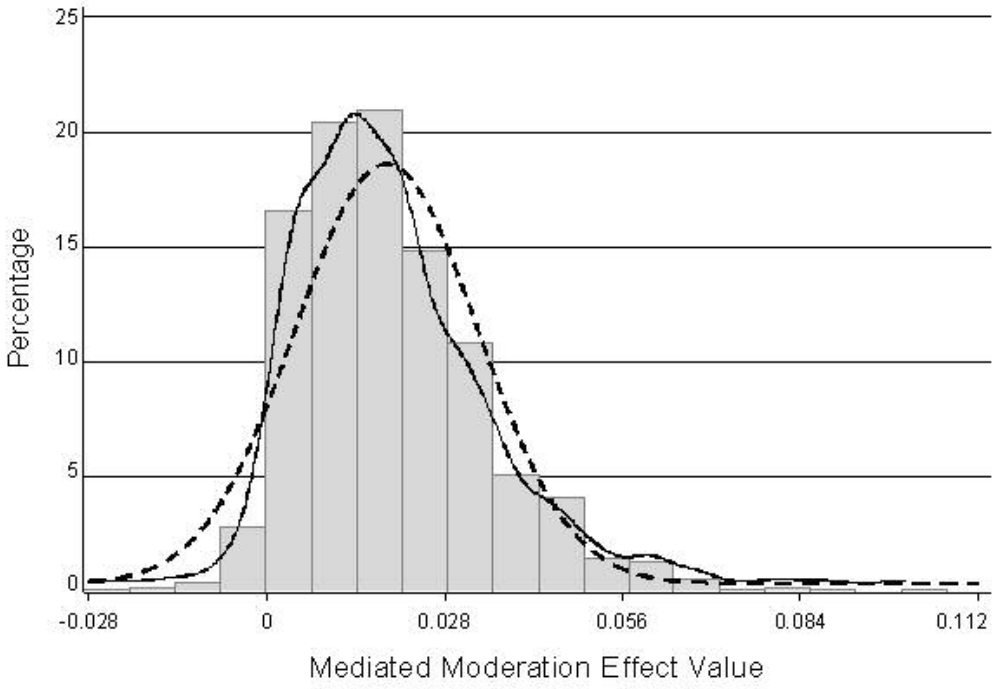

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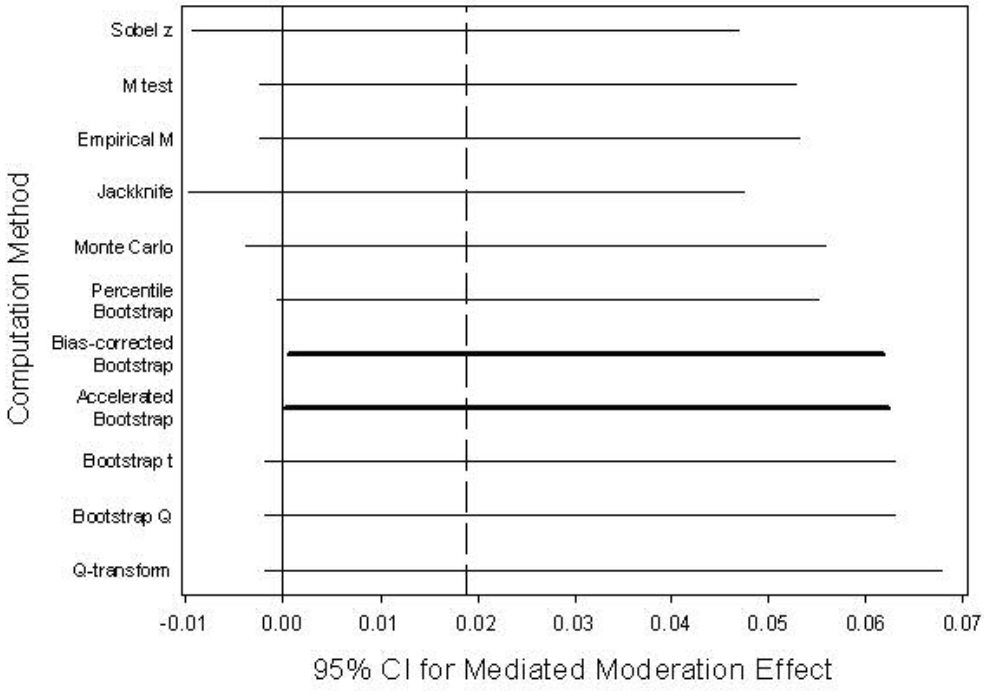

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