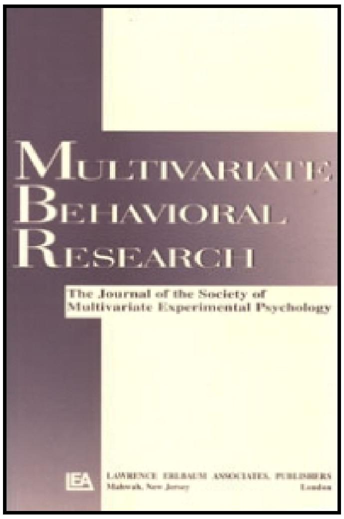

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Mediation and Moderation: Testing Relationships Between Symptom Status, Functional Health, and Quality of Life in HIV Patients

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Mediation and Moderation: Testing Relationships Between Symptom Status, Functional Health, and Quality of Life in HIV Patients

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We extended Wilson and Cleary's (1995) health-related quality of life model to examine the relationships among symptom status (Symptoms), functional health (Disability), and quality of life (QOL). Using a community sample ($N = 956$) of male HIV positive patients, we tested a mediation model in which the relationship between Symptoms and QOL is partially mediated by Disability. Common and unique ideas from 3 approaches to examining moderation of effects in mediational models (Edwards & Lambert, 2007; MacKinnon, 2008; Preacher, Rucker, & Hayes, 2007) were used to test whether (a) the direct relationship of Symptoms to QOL and (b) the relationship of Disability to QOL are moderated by age. In the mediation model, both the direct and the indirect (mediated) effects were significant. The direct relationship of Symptoms to QOL was significantly moderated by age, but the relationship of Disability to QOL was not. High Symptoms were associated with lower QOL at all ages, but this relationship became stronger at older ages. We compare the 3 approaches and consider their advantages over traditional approaches to combining mediation and moderation.

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The management of symptoms is important for the quality of life of patients. Wilson and Cleary (1995) proposed a health-related quality of life (HRQOL) conceptual model that suggests the relationship between symptom status and quality of life is mediated by an individual's functional health status (disability). Parts of this HRQOL conceptual model have been widely applied to different patient populations, including patients with HIV/AIDS (Cunningham, Crystal, Bozzette, & Hays, 2005; Sousa, Holzemer, Henry, Slaughter, 1999; Wilson & Cleary, 1997). In two previous studies, Sousa and Kwok (2005, 2006) found a significant relationship between symptom status and quality of life. It is important to more fully understand the relationships among symptom status, functional health, and quality of life in the HIV population, particularly given the wide range of ages now represented in this population. Determining the effects of age on the relationships between symptom status, functional health, and quality of life could provide beneficial information to develop interventions to support successful aging. We sought to answer four questions: (a) In the HIV/AIDS population, is functional health a mediator between symptom status and quality of life? (b) Is the relationship between symptom status and quality of life moderated by age? (c) Is the relationship between functional health and quality of life moderated by age?; and (d) Does age moderate the indirect relationship between symptom status and quality of life that is mediated by functional health?

A secondary goal of this article is to illustrate the application of new analytic approaches to the study of mediation and moderation. We briefly review mediation, moderation, and traditional approaches to combining mediation and moderation. We then consider three recent approaches (Edwards & Lambert, 2007; MacKinnon, 2008; Preacher, Rucker, & Hayes, 2007) that offer tests of combinations of mediation and moderation in the context of the standard three variable mediational models. These approaches overlap greatly, but each offers some unique features that may be useful in studying different questions involving mediation and moderation. We utilize relevant features from these approaches to test hypotheses about the potential moderation of both direct and indirect effects between symptom status and quality of life in a large sample of HIV/AIDS patients.

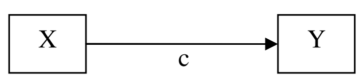
MEDIATION

When mediation is hypothesized, an independent variable (X) is expected to affect an intervening variable (M), which, in turn, is expected to affect a dependent variable (Y). For example, the relationship between neighborhood disadvantage (a single variable characterized by high rates of poverty, crime, and unemployment) and children's externalizing behavior is mediated by the intervening variable of parent-child conflict (Roosa et al., 2005); the relationship between neighborhood disadvantage and children's internalizing behavior is mediated by mothers' perceptions of neighborhood quality such as cleanliness (Deng et al., 2006). In the framework of path analysis, the mediated effect is referred to as an *indirect* effect (Alwin & Hauser, 1975; Bollen, 1987; Fox, 1980). Complete mediation requires that the full effect of the independent variable on the dependent variable be carried by the mediator. Partial mediation recognizes that independent variables may have their own direct effects on the dependent variable that are independent of the mediator. These direct effects may be theoretically important in some contexts and in practice are often larger in magnitude than the mediated effect.

Kenny and his colleagues (Baron & Kenny, 1986; Judd & Kenny, 1981; Kenny, Kashy, & Bolger, 1998) have developed the most widely used procedure for testing for the existence of a mediational effect. Figure 1 illustrates the single mediator model and presents path diagrams illustrating the models and defining the following notation. Their procedure consists of four causal steps that are needed to establish mediation:

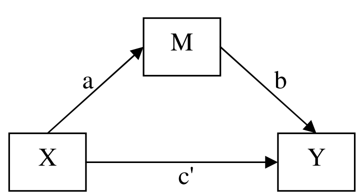
Step 1. Show that X and Y are related, that is, c is significant in (1).

$$Y = i_1 + cX + e_1 \tag{1}$$



$$Y = i_1 + cX + e_1$$

(a)



$$M = i_2 + aX + e_2$$
$$Y = i_3 + c'X + bM + e_3$$

(b)

FIGURE 1 Mediation model (Baron & Kenny, 1986; Judd & Kenny, 1981).

Step 2. Show that X and M are related, that is, a is significant in (2).

$$M = i_2 + aX + e_2 \tag{2}$$

Step 3. Show that M has an effect on Y over and above X, that is, b is significant in (3).

$$Y = i_3 + c'X + bM + e_3 \tag{3}$$

Step 4. Show that X has no direct effect on Y, that is, c' does not differ from zero in (3). This final step is a test that the effect is fully carried by the putative mediator (complete mediation).

In contrast, MacKinnon and colleagues (MacKinnon, 2008; MacKinnon, Lockwood, Hoffman, West, & Sheets, 2002) have emphasized focused tests of the indirect $X \rightarrow M \rightarrow Y$ effect. Focused tests provide estimates and tests of significance of the mediated effect, whereas the causal steps procedure only provides a binary conclusion that mediation exists or not. MacKinnon et al. (2002) showed that the causal steps procedure has low statistical power to detect the indirect effect. Correspondingly, Fritz and MacKinnon (2007) showed that exceedingly large sample sizes (e.g., $n > 20{,}000$) are required to achieve .80 power to detect an indirect effect in which both a and b are small in magnitude and there is no direct effect. Note further that Step 1 represents a test of the total effect, the combination of the direct effect of X on Y and the indirect effect of $X \rightarrow M \rightarrow Y$. Hence, the causal steps approach will fail to detect inconsistent mediation in which the direct and indirect effects are opposite in sign. In addition, given that in practice the magnitude of the direct effect is typically larger than that of the indirect effect, the outcome of this test will often be primarily determined by the magnitude of the direct effect, contrary to the hypothesis of interest. Consequently, Sobel (1982), MacKinnon et al. (2002), MacKinnon, Lockwood, and Williams (2004), and Shrout and Bolger (2002) proposed focused tests of the indirect effect. MacKinnon et al. (2002) provided analytic approaches that are expected to produce proper standard errors given the nonnormality of the *ab* product term, whereas MacKinnon et al. (2004) and Shrout and Bolger used bootstrapping procedures to achieve this same goal. By focusing on the indirect effect in the testing procedure, these approaches also help refocus attention on the direct effect when it may be of theoretical interest.

MODERATION

Moderation occurs when the direction, strength, or both of the relation between an independent and a dependent variable are affected by a third variable, which is termed a *moderator* (Baron & Kenny, 1986; Chaplin, 2007). For example, the efficacy of treatment for depression depends on patients' attachment insecurity, such that cognitive-behavioral therapy is more effective than interpersonal psychotherapy for patients who are higher in attachment avoidance (McBride, Atkinson, Quilty, & Bagby, 2006). In this example, the effect of therapy on depression reduction is *moderated* by patients' attachment insecurity. In multiple regression, moderation is typically represented as the linear by linear interaction between the independent variable and the moderator variable (Aiken & West, 1991), using Equation (4):

$$Y = b_0 + b_1X + b_2Z + b_3XZ + e, \tag{4}$$

where X is the independent variable and Z is the moderator. The test of the interaction term, b_3, represents the test of the moderation effect.

MODERATION OF INDIRECT AND DIRECT EFFECTS IN MEDIATIONAL MODELS

Research questions often require examination of moderation of effects in mediational models. As one example, the influence of ethnic cultural norms on cigarette use in Mexican American youth has been hypothesized to be mediated by self-efficacy. However, the magnitude of the indirect effect decreases as peer smoking increases (Morgan-Lopez, Castro, Chassin, & MacKinnon, 2003). As another example, the relationship between attention-deficit/hyperactivity disorder and depression is mediated by others' (e.g., teachers and parents) appraisals of social competence. However, the indirect effect holds only in younger children. In other words, the mediated effect of others' appraisals of social competence is moderated by children's age (Ostrander, Crystal, & August, 2006). Researchers have hypothesized a number of different models that combine mediation and moderation. These models have also more recently begun to include hypotheses about moderation of direct effects in mediational models.

Building on initial work by Baron and Kenny (1986) in the causal steps tradition, researchers have historically conducted analyses combining mediation and moderation using one of three general approaches (Edwards & Lambert, 2007). In the *piecemeal approach*, researchers have conducted mediation analysis and moderation analysis separately on the same data set. Mediation is usually tested using the causal steps approach and moderation is tested using analysis of variance or regression analysis. The results of the two sets of analysis are interpreted together. In the *subgroup approach*, the sample is typically dichotomized into subgroups based on the moderator variable (e.g., younger/older children) and a mediational analysis is conducted separately in each subgroup. If the mediation effect differs between subgroups (e.g., mediation effect is significant in one group but not in the other; the magnitude of mediation effect differs between the subgroups), then an inference is made that mediation is moderated. In the *moderated causal steps approach*, mediation analysis is conducted following the causal steps procedure with the product term of independent variable × moderator added (Baron & Kenny, 1986; Muller, Judd, & Yzerbyt, 2005).

These earlier methods all inherit the shortcomings of the causal steps approach (Baron & Kenny, 1986; Judd & Kenny, 1981) identified previously. All of these earlier methods require a significant total X to Y relationship in Step 1, which (a) is often highly dependent on the existence of a direct effect from X to Y and (b) is often not fulfilled under inconsistent mediation. None of the approaches introduced earlier provide a direct test of indirect effect or provide an estimate of the magnitude of the indirect effect conditioned on the level of the moderator. None of these traditional general methods provide a clear mechanism for modeling which paths (e.g., X to M, M to Y, or X to Y) are affected by the moderator. None of the approaches consider potential moderation of the direct effect. Finally, in the subgroup approach, continuous moderators are dichotomized and moderation is often inferred when an effect is statistically significant in one group but not in the other, two practices that can be problematic (MacCallum, Zhang, Preacher, & Rucker, 2002; McNemar, 1960).

In response to limitations of previous approaches, Edwards and Lambert (2007), MacKinnon (2008, chap. 10), and Preacher et al. (2007) have independently proposed general frameworks for considering moderated effects in mediational models. Each of the approaches uses a general path analytic framework and develops the regression equations necessary to specify potential models of interest. Consequently, there is considerable overlap among the three approaches. The approaches differ in the models that are emphasized and in subsidiary procedures used in model testing and interpretation.

Edwards and Lambert (2007) argued that prior research and theory might lead researchers to hypothesize that any of the paths in Figure 1 (B) might be moderated or not moderated. Given the three potential paths in the basic mediational model, $X \to Y$, $X \to M$, $M \to Y$, eight ($2 \times 2 \times 2$) potential models may be described, the basic mediational model plus seven additional models that involve moderation of one, two, or all three paths. Unlike Preacher et al. (2007), they explicitly emphasized models that involve the moderation of direct as well as indirect effects. They developed reduced form equations for each of the models that involve the product of the two path coefficients and they recommended the use of bootstrapping methods to construct confidence limits for the product of the two path coefficients. They also extended procedures developed by Aiken and West (1991) to plot and test how indirect and direct effects vary across levels of the moderator by calculating conditional indirect and direct effects.

Preacher et al. (2007) took a similar general approach to combining moderation and mediation. Preacher et al. (2007, p. 194) considered five models, three of which were identical to models considered in detail by Edwards and Lambert (2007): Model 2, moderation of the a path from the independent variable X to the mediator M by the moderator variable W; Model 3, moderation of the b path from the mediator M to the dependent variable Y by the moderator variable W; and Model 5, simultaneous moderation of both the X to M and M to Y paths by the common moderator W. In addition, Preacher et al. (2007) proposed two models not considered by Edwards and Lambert. Model 4 is a small variant of Model 5 in which W moderates the X to M path and Z moderates the M to Y path. In Model 1, the independent variable X moderates the path from M to Y, a case emphasized by Kraemer, Wilson, Fairburn, and Agras (2002) and discussed earlier by Baron and Kenny (1986). Even though Preacher et al.'s (2007) two additional models were not presented in Edwards and Lambert, the general framework of Edwards and Lambert can be easily extended to include these models. For the significance tests of the conditional indirect effects, Preacher et al. (2007) proposed using bootstrapping methods to construct confidence intervals. They also provided the formulas to obtain asymptotic normal-theory standard errors for key parameters in each of the five models. In addition to the methods presented by Edwards and Lambert for plotting and testing conditional indirect effects, Preacher et al. (2007) also proposed an extension of the Johnson and Neyman (1936) procedure that determines the regions of significance over which the conditional indirect effect will be significant.

Finally, MacKinnon (2008) presents a complete volume devoted to mediational analysis. He presents the most general approach (pp. 286–287) using two general algebraic equations that encompass nearly all possible models involving mediation and moderation. All but one of the models proposed by either Edwards and Lambert (2007) or Preacher et al. (2007) can be considered special cases of MacKinnon's general approach.

In MacKinnon's (2008) approach, the first equation for predicting the mediator is

$$M = i_2 + a_1 X + a_2 Z + a_3 XZ + e_2. \tag{5}$$

In this equation the test of a_3 represents the test of the moderation of the X to M path. The second equation for predicting the dependent variable Y is

$$Y = i_3 + c_1' X + c_2' Z + c_3' XZ + b_1 M + b_2 MZ + hXM + jXMZ + e_3. \tag{6}$$

In this equation, b_2 represents the test of moderation of the M to Y path by Z at $X = 0$, h represents the test of moderation of the M to Y path by X at $Z = 0$, and j represents the possibility that X and Z combine to moderate the M to Y path, an effect not considered by Edwards and Lambert (2007) or Preacher et al. (2007). Note also that c_3' represents the moderated direct effect emphasized by Edwards and Lambert. Although MacKinnon presents the most general framework, he does not discuss each of the possible submodels in the depth of Edwards and Lambert or Preacher et al. (2007). MacKinnon also makes a clear distinction between the individual tests of the X to M and M to Y paths involved in the indirect effect and the tests of the overall indirect effect: they test different hypotheses.

In this study we draw on these three general approaches to test a hypothesized model in which the direct relationship between symptoms and quality of life and indirect relationship between these two variables through disability may be moderated by age. We also utilize graphical and statistical procedures extended from Aiken and West (1991) to provide a further understanding of the effects we obtain.

Hypotheses

Mediation. The hypothesized basic (i.e., unconditional) mediation model is depicted in Figure 2. We hypothesized that the effect of symptom status (Symptoms) on quality of life (QOL) would be partially mediated by functional health (Disability). We expected that there would be an indirect relationship in which the changes in the level of Symptoms would be related to the level of Disability, which, in turn, would be related to QOL. We also expected that Symptoms would have a direct effect on QOL in addition to its effect through Disability. We expected that this general pattern of direct and indirect relationships would exist over the full range of ages represented in our adult sample.

Moderated direct and indirect effects. In addition to the unconditional mediation model, we hypothesized that the direct relationship of Symptoms to QOL and the relationship of Disability to QOL would be moderated by patient's age in years (Age), such that the relationships would be *stronger* for older relative

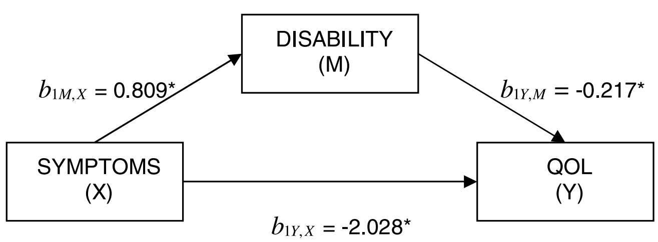


FIGURE 2 Mediation: Effects of Symptoms on QOL partially mediated by Disability. Unstandardized estimates are shown. * indicates $p < .05$; Symptoms = proportion of 23 symptoms reported; Disability = mean difficulty carrying out 8 daily life tasks; QOL = mean of 4 quality of life subscales (cognition, vitality, mental health, disease worry).

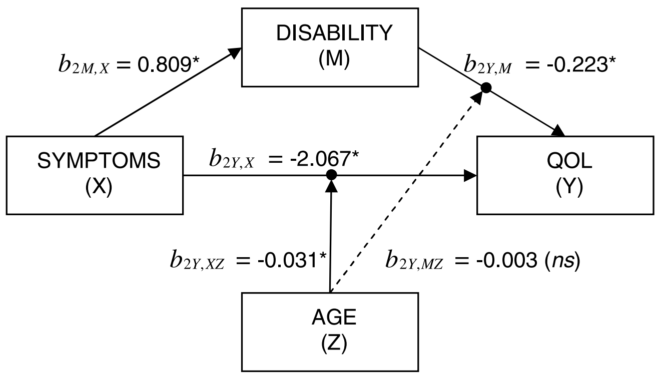


FIGURE 3 Moderated direct and indirect effects: Direct effect of Symptoms on QOL moderated by Age. Unstandardized estimates are shown. $*p < .05$. *ns* = nonsignificant. Dashed arrow represents nonsignificant path. Symptoms = proportion of 23 symptoms reported; Disability = mean difficulty carrying out 8 daily life tasks; QOL = mean of 4 quality of life subscales (cognition, vitality, mental health, disease worry); Age = patient's age in years.

to younger patients. The moderated direct and indirect effects model is shown in Figure 3. A large number of studies have shown relationships between age and symptom severity in various populations with medical conditions (e.g., cancer, Walsh, Donnelly, & Rybicki, 2000; depression, Prince et al., 1999; premenstrual symptoms, Freeman, Rickels, Schweizer, & Ting, 1995). A smaller number of studies have investigated relationships between age and quality of life, including one showing a negative relationship in HIV patients (Piette, Wachtel, Mor, & Mayer, 1995). However, with one exception, we were unable to locate any studies that have investigated age as a putative moderator of the *relationships* between symptoms, functional health, and quality of life. For the relationship of Disability to QOL, Masoudi et al. (2004) found in a population of heart disease patients that decreased functional health was associated with declines in health-related QOL in the older (age > 65) but not in the younger patients.

METHODS

Data and Measures

The data were collected from HIV positive patients recruited through clinics in San Francisco, Los Angeles, and San Diego.[1] The sample we used in this

[1]The data were collected from six locations corresponding to large geographic areas (communities) within these cities. We calculated the intraclass correlations for Symptoms, Disability, QOL,

analysis was $N = 956$ males collected between 1992 and 1994 prior to the introduction of the current treatment regimen for HIV introduced in 1998. All participants had complete responses on Symptoms, Functional Health, and Health-Related QOL items. Symptoms were measured using a 23-item checklist indicating whether each symptom occurred during the past week (e.g., have had fever, night sweats, nausea) with the response options being "yes" or "no." Disability was measured by 8 items asking whether they have had any difficulty carrying out daily tasks or activities (e.g., dress yourself, open a new carton of milk, climb up five steps). Disability items were scaled 0 (without any difficulty) to 3 (unable to do) so that higher numbers indicated more difficulty. Health-Related Quality of Life (QOL) was measured by four subscales based on 17 items measuring cognition (e.g., react slowly), vitality (e.g., feel worn out), mental health (e.g., feel nervous), and disease worry (e.g., frustrated about his health). QOL subscales were scaled from 1 to 5 with higher numbers indicating better quality of life.

We took the average of the 23 symptom items and the 8 functional health items to compute composite scores for Symptoms and Disability, respectively. We took the average of the four QOL subscale scores to compute composite scores for QOL. Coefficient alpha (Cronbach, 1951) was .876, .913, and .937 for Symptoms, Disability, and QOL, respectively. Previous work by Sousa and colleagues on this sample of patients has established the measurement structure underlying each of the three scales. Sousa, Tann, and Kwok (2006) showed that a second order factor model with a strong general second order factor (and six first order factors) fit the data well for the measure of symptoms in the HIV population. Sousa, Kwok, and Ryu (2008) showed that a single general factor underlies the functional health items in the HIV population. Chen, West, and Sousa (2006) showed a bifactor model with a strong general factor and much smaller specific factors associated with each subscale fit these data well in the HIV population. The means, standard deviations, and correlations of Symptoms, Disability, QOL, and Age are shown in Table 1. Following Aiken and West (1991), all of the composite scores for the independent variables (Symptoms, Disability, and Age) were centered at the mean. QOL was not centered.

Models

Mediation. The hypothesized mediational model presented in Figure 2 is expressed by the two regression equations as shown in (7) and (8). Recall that

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and Age. The intraclass correlations ranged from 0.04 to 0.08. We used the Complex procedure in Mplus to produce correct standard errors that take into account this dependency in the data. Because of the concerns about participant anonymity, identification numbers for individual clinics were not typically available in the data set.

TABLE 1
Means, Standard Deviations, and Correlations of Symptoms, Disability, QOL, and Age

			Correlation			
	M	*SD*	*Symptoms*	*Disability*	*QOL*	*Age*
Symptoms	0.208	0.208	1.000			
Disability	0.147	0.275	0.611	1.000		
QOL	3.306	0.683	−0.669	−0.464	1.000	
Age	39.386	8.141	−0.113	−0.032	0.113	1.000

Note. $N = 956$. Symptoms = proportion of 23 symptoms reported; Disability = mean difficulty carrying out 8 daily life tasks; QOL = mean of 4 quality of life subscales (cognition, vitality, mental health, disease worry); Age = patient's age in years.

we expected that direct and indirect relationships would exist over the full range of ages represented in our adult sample.

$$M = a_{11} + b_{1M,X}X + e_{11} \tag{7}$$

$$Y = a_{12} + b_{1Y,X}X + b_{1Y,M}M + e_{12} \tag{8}$$

Substituting (7) into (8) yields the reduced form Equation (9).

$$Y = (a_{12} + b_{1Y,M}a_{11}) + (b_{1Y,X} + b_{1Y,M}b_{1M,X})X + b_{1Y,M}e_{11} + e_{12} \tag{9}$$

In Equation (7), the effects of X (Symptoms) on Y (QOL) consist of two additive components: the direct effect ($b_{1Y,X}$) and the indirect effect ($b_{1Y,M}b_{1M,X}$). The indirect effect is the product of the path coefficient from X (Symptoms) to M (Disability) and the path coefficient from M (Disability) to Y (QOL).[2] We used three different methods to test the significance of the indirect effect: Sobel (1982) standard error, bias-corrected bootstrap confidence interval (MacKinnon et al., 2004), and asymmetric confidence interval produced by the PRODCLIN program (MacKinnon, Fritz, Williams, & Lockwood, 2007). The three methods are reported for the purpose of illustration. In practice, researchers should choose one of the methods depending on the availability of the methods for their mediational model. The bias-corrected bootstrap method and the PRODCLIN program produce asymmetric confidence limits of the indirect effect. Both methods are more exact and have greater statistical power than those based on the

[2]The indirect or mediated effect can be calculated in two ways: (a) difference between total effect (regression of Y on X) and direct effect (regression of Y on X controlling for M) and (b) product of path coefficient from X to M and path coefficient from M to Y. These two methods yield identical estimates of mediated effect when the dependent variable is continuous and ordinary least squares regression is used (MacKinnon, Warsi, & Dwyer, 1995).

normal distribution (e.g., Sobel method). For the two-path mediated effects, PRODCLIN may have trivially greater power than the bias-corrected bootstrap method. The bias-corrected bootstrap method also requires raw data that may sometimes be unavailable; it can also be computationally cumbersome. However, the PRODCLIN confidence limits cannot presently be computed for indirect effects consisting of more than two paths (e.g., three-path mediated effect: $X \rightarrow M1 \rightarrow M2 \rightarrow Y$), whereas the bias-corrected bootstrap method can be extended to more complicated cases. Although the least accurate, the Sobel method is easy to compute as it is now implemented in nearly all structural equation modeling software.

Moderated direct and indirect effects. The hypothesized moderated direct and indirect effects model presented in Figure 3 is expressed by the two regression Equations (10) and (11). We tested the moderating effects of Age by adding the interaction terms (XZ = Symptoms $\times$ Age and MZ = Disability $\times$ Age) as shown in (11).

$$M = a_{21} + b_{2M,X}X + e_{21} \tag{10}$$

$$Y = a_{22} + b_{2Y,X}X + b_{2Y,M}M + b_{2Y,Z}Z + b_{2Y,XZ}XZ + b_{2Y,MZ}MZ + e_{22} \tag{11}$$

Substituting (10) into (11) gives (12), in which the effects of X (Symptoms) on Y (QOL) consist of two additive components: the direct effect $(b_{2Y,X} + b_{2Y,XZ}Z)$ and the indirect effect $(b_{2M,X}(b_{2Y,M} + B_{2Y,MZ}Z))$.

$$\begin{aligned} Y = {} & [a_{22} + b_{2Y,M}a_{21} + (b_{2Y,Z} + b_{2Y,MZ}a_{21})Z] \\ & + [(b_{2Y,X} + b_{2Y,XZ}Z) + b_{2M,X}(b_{2Y,M} + b_{2Y,MZ}Z)]X \\ & + (b_{2Y,M} + b_{2Y,MZ}Z)e_{21} + e_{22} \end{aligned} \tag{12}$$

The direct effect is a function of the moderating variable Age. If $b_{2Y,XZ}$ is significant, it means that the strength of the direct effect of Symptoms on QOL differs depending on how old the patient is. The indirect effect is also a function of the moderating variable Age. If $b_{2Y,MZ}$ is significant, it indicates that the Disability $\rightarrow$ QOL relationship differs depending on the patient's age. The significance of the moderation of Age on the indirect effect[3] (Symptoms $\rightarrow$ Disability $\rightarrow$ QOL) can be tested by testing the significance of the product term $b_{2M,X}b_{2Y,MZ}$. We obtained the bias-corrected bootstrap confidence interval to test

[3]We thank an anonymous reviewer for suggesting this test.

the significance by utilizing the SAS macro provided by Taylor, MacKinnon, and Tein (2008). We used Mplus 5 to estimate the model.[4]

Results

Unconditional mediation model. Using Sobel's (1982) standard error, both the direct effect (unstandardized estimate $b_{1Y,X} = -2.028$, SE = 0.167, $p < .001$) and the indirect effect (unstandardized estimate $b_{1Y,M}b_{1M,X} = -0.217 * 0.809 = -0.176$, SE = 0.048, $p < .001$) of Symptoms on QOL were significant. The estimates indicated that patients having higher scores on the symptoms checklist had lower scores on QOL. As noted earlier, the Sobel method for testing the indirect effect is asymptotically correct but fails to represent the asymmetric nonnormal distribution of the product term at realistic sample sizes. In practice, this typically means that the Sobel method will have reduced power to test the indirect effect that may be appreciable with small effect sizes or small sample sizes (MacKinnon et al., 2002). Following recommendations by Edwards and Lambert (2007) and Preacher et al. (2007), we also used the bias-corrected bootstrapping method to construct the 95% confidence interval for the indirect effect. The 95% confidence interval for the indirect effect was [−0.309, −0.039] and did not include zero. We can conclude that the indirect effect is significantly different from zero at $\alpha = .05$. Finally, we also used MacKinnon et al.'s (2007) PRODCLIN program, which implements work by Aroian (1944; see also Meeker, Cornwell, & Aroian, 1981) on the distribution of the product of two normally distributed random variables. PRODCLIN produces asymmetric confidence intervals for the indirect effect at a specified level of $1 - \alpha$. If the confidence interval does *not* contain zero, the null hypothesis that the indirect effect equals zero can be rejected at the corresponding level of α. In the present case, PRODCLIN produced lower and upper 95% confidence limits of −0.301 and −0.061; we can again conclude there is a significant indirect effect at $\alpha = .05$. All three methods indicated that the indirect effect of Symptoms on QOL through Disability was significantly different from zero.

The negative sign of the estimate of the direct effect ($b_{1Y,X} = -2.028$) indicates that patients who have more symptoms have lower QOL. The significant indirect effect ($b_{1Y,M}b_{1M,X} = -0.176$) indicates that in addition to the direct effect of Symptoms on QOL, there is a second, independent process in which Symptoms is related to increasing Disability ($b_{1M,X} = 0.809$, positive), which,

[4]Other statistical programs (e.g., SPSS, SAS, LISREL, EQS) can be used to estimate the models presented here. Edwards and Lambert (2007) provide SPSS syntax in their appendix; SPSS macros to perform analyses from Preacher et al. (2007) are available at www.quantpsy.org; and the CD accompanying MacKinnon (2008) contains computer script and outputs from SPSS, SAS, LISREL, EQS, MPLUS, and CALIS programs.

in turn, is related to lower QOL ($b_{1Y.M} = -0.217$, negative). Approximately 8% of the total effect of Symptoms on QOL is mediated through Disability.

Moderated direct and indirect effects. Recall that we hypothesized that age would moderate two of the paths in our mediational model. As shown in Figure 3, Age significantly moderated the direct effect of Symptoms on QOL ($b_{2Y.XZ} = -0.031$, SE = 0.005, $p < .001$). The estimate indicated that the direct negative relationship of Symptoms to QOL became stronger by 0.031 for each 1 year increase in Age. Contrary to our second hypothesis, we found no evidence for a moderating effect of age on the relationship between Disability and QOL ($b_{2Y.MZ} = -0.003$, SE = 0.007, *ns*). The estimated moderating effect of Age on the indirect effect was −0.002 (= 0.809 × (−0.003)). The bias-corrected 95% confidence interval was [−0.007, 0.021]. Therefore the moderation of Age on the indirect effect was also not significant.

In order to understand how the direct effect of Symptoms on QOL varies at different Age values, we estimated simple (conditional) slopes for the direct effect of Symptoms on QOL at different levels of Age (sample range = 21 to 69). We chose values of Age of 24, 32, 40, 48, and 56, which represent approximate values of the Mean Age $-$ 2*SD*, M $-$ 1*SD*, M, M + 1*SD*, and M + 2*SD*, respectively. Following procedures described by Aiken and West (1991) and by Preacher, Curran, and Bauer (2006), we tested each of the conditional slopes. As shown in Figure 4, the estimated simple slopes were negative and statistically significant at all Age values (−1.590, −1.838, −2.086, −2.334, and −2.582 at age = 24, 32, 40, 48, and 56, respectively; all ps $< .05$); the simple slopes became increasingly negative as Age increased. Otherwise stated, higher levels of Symptoms were associated with lower QOL at *all* ages, but this relationship became stronger as age increased. Indeed, when we used the extension of the Johnson-Neyman procedure (Preacher et al., 2006) to calculate the range of ages over which the conditional slopes between symptoms and quality of life is statistically significant, we found that this relationship was significant at the full range of values of age included in the study. Solution of the Johnson-Neyman equation showed mathematically that the effect became nonsignificant at age = −21, representing an impossible value of age.

DISCUSSION

Symptom status was found to be negatively related to the quality of life (QOL) of HIV patients. This relationship is partially mediated by the functional health (Disability) in that having more symptoms increased the levels of Disability, which, in turn, lowered QOL. The direct relationship between Symptoms and

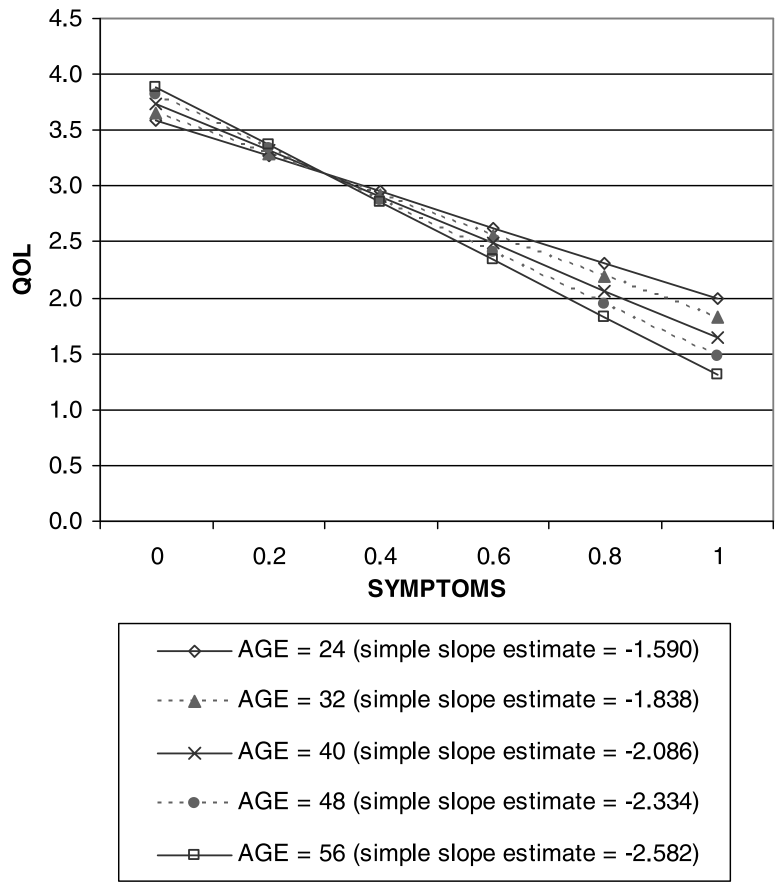

FIGURE 4 Estimated direct effects of Symptoms on QOL at different Age values. Each of the conditional direct effects is significant at $p < .05$. Symptoms = proportion of 23 symptoms reported; QOL = mean of 4 quality of life subscales (cognition, vitality, mental health, disease worry); Age = patient's age in years.

QOL was also significant. We also tested whether the direct and indirect effects of Symptoms on QOL varied depending on Age (i.e., were moderated by Age). We found that only the direct effect was moderated by Age. The relationship between Symptoms and QOL was negative, with a higher level of Symptoms being associated with a lower QOL at all ages. However, the magnitude of the negative relationship became stronger in older patients. One possible explanation is that the patients' coping strategies decrease and their social support diminishes as they age. Studies have shown that active coping and social support are associated with good quality of life in patients with HIV (Friedland, Renwick, & McColl, 1996; Leiberich et al., 1997; Swindells et al., 1999). However, studies also have shown that older persons with HIV have limited social support and coping strategies (Heckman et al., 2002; Pitts, Grierson, & Misson, 2005).

The moderated path analysis approach presented here based on work by Edwards and Lambert (2007), Preacher et al. (2008), and MacKinnon (2007) has advantages over traditional approaches to moderated mediation. We were able to develop focused tests of a priori hypotheses about the forms of moderation of the direct and indirect effects that might be present. This ability contrasts with traditional approaches to moderated mediation in three important ways.

First, the traditional moderated causal steps procedure (Baron & Kenny, 1986; Muller et al., 2005) can provide only a binary decision whether the combined mediation-moderation effect is present. The general approach illustrated here provides estimates of the direct and indirect effects, and it shows how these effects vary as a function of the moderator. In our data, we did not find a moderated indirect effect, but bootstrapping methods described by Edwards and Lambert (2007) and Preacher et al. (2007) are available to provide tests of conditional indirect effects.

Second, some traditional models have combined mediation and moderation by adding the moderator (Z) and the product of the independent variable $\times$ moderator (XZ), as if there are three independent variables in the model (Baron & Kenny, 1986; Morgan-Lopez et al., 2003; Morgan-Lopez & MacKinnon, 2006). In this model, which has often been termed *mediated moderation* model, the three independent variables (X, Z, and XZ) predict both M and Y. However, this mediated moderation model is equivalent to a particular case of the moderated path analysis model in which the $X \rightarrow M$ path and the $X \rightarrow Y$ path are *both* moderated by Z. In contrast, the use of approach described in this article has greater flexibility in that it permits tests of moderation in which the $X \rightarrow M$ path, $M \rightarrow Y$ path, or $X \rightarrow Y$ path or any combination thereof are hypothesized to be moderated by Z. In addition, both the Preacher et al. (2007) and MacKinnon (2008) approaches permit X to moderate the $M \rightarrow Y$ path.

Third, particularly in the Edwards and Lambert (2007) approach, the moderated direct effect, here an effect of central interest, is emphasized as well as the moderated indirect effect. Traditional approaches to combining mediation and moderation have disregarded the direct effect. Preacher et al. (2007) also do not consider this type of effect and MacKinnon (2008) includes it in his general model but does not develop its possibilities. When there is partial mediation, the relationship between the two variables is accounted for by two additive components—direct and indirect effects. In our analysis, the moderated direct effect has an important clinical implication. The impact of symptoms on QOL is greater for older patients. Therefore, symptom management is more crucial for older patients to help them maintain good quality of life.

We caution that our findings are based on a cross-sectional analysis like many other mediational analyses. Maxwell and Cole (2007) note that estimates based on cross-sectional data may be biased relative to estimates based on longitudinal data sets because of the failure to allow for autoregressive effects of the mediator and outcome variables. Baron and Kenny (1986), Holland (1988), and MacKinnon (2008) all note that in the absence of a randomized experiment we cannot rule out the possibility that other alternative explanations may also account for the present results. However, in the present context manipulation of chronic symptom status and disability status is clearly precluded by important ethical concerns. Fortunately, in the present case some prominent alternative models are implausible: for example, current theory and research do not provide an account suggesting how quality of life could produce disability or symptoms. Another issue is that the present results imply a comparison between younger and older cohorts of patients, not the change of the relationship between Symptoms and QOL within patients as they age. Further research using focused tests associated with the moderated path analysis approach on longitudinal data sets can help us better understand and reach stronger conclusions about some of the mechanisms involved in the relationship between symptom status and quality of life in HIV patients.

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