Mediation and Moderation: Practical Approaches and Applications from Research Questions to Analysis and Interpretation in HIV Disparities Research

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Well Known Paper on Mediation and Moderation


• Cited by 58416 on Google Scholar
Common Kinds of Disparities
Research Questions

• Why are there disparities in health or health care?
  – Racial/ethnic, socioeconomic, insurance status, gender, age, or other disparities

• How do program/interventions achieve effects?
  – Process evaluation

• Are relationships in one group also seen another?

• For what group(s)/subgroups are effects on disparities more/less strong?
  – Are there differential relationships or interactions?
Role of Mediation and Moderation in Research Process

- Addresses the “3rd Variable” Problem
- Seeking to understand causality
- Need hypotheses:
  - Theory
  - Prior research, literature, clinical experience
- Pilot studies
- Quantitative analyses
- Qualitative studies
- Prospective studies, including interventions
- RCTs
- Secondary studies
3 Options for the 3rd Variable Relationship

**Effect of X on Y**

- **Z** - Covariate

**X**

**Y**

\[ c \]

Effect of X on Y
3 Options for the 3\textsuperscript{rd} Variable Relationship

- Confounder

Effect of X on Y
Path Diagram for the Single-Mediator Model

Total Effect of X on Y

X \rightarrow M \rightarrow Y

a \quad b

M - Mediator

c' \quad c

Total Effect of X on Y
Path Diagram for the Single-Moderator Model

Effect of X on Y

- Moderator

X → Y

Effect of X on Y
Path Diagram for the Single-Moderator Model

Moderator       Stratum-specific effects of X on Y

Z = 0          \[ \xrightarrow{c_0} \]

Z = 1          \[ \xrightarrow{c_1} \]
Mediation: v2.2
Regression Equations

- $Y = i_1 + cX + e_1$  
  $(Y = i + bM + e)$
- $M = i_2 + aX + e_2$
- $Y = i_3 + c'X + bM + e_3$  
  $*** c' < c$

Path diagram for the single-mediator model.
Statistical Assumptions of Mediation

1. Correct functional form of vars
2. No omitted variables
   - correct underlying model
3. Reliable and valid measures
4. Residual errors – uncorrelated with X, with each other, consistent variance
5. No moderation (interactions) of X, M
Effect size measures

1. Proportion or ratio: ab/c or ab/c’
2. $R^2$ measures
3. Standardized regression coefficients
   - Effect on $Y$ of 1 SD change in $X$
4. Standardized effect size: $ab/SD.Y$
   - change in $Y$ in SD units (Cohen 1988)
Significance Testing in Mediation

- Baron & Kenny approach notoriously low power, depends on sample size (N)
- Tests based on ab coefficient
- Confidence intervals, including one-tail tests; bootstrapping (binary outcome)
- In structural equation modeling (SEM), estimate indirect and direct effects, moderation, 3 fit indices (2 indep of N)
Behavioral Model of Health Services Utilization (Access)

- **Predisposing**
  - Demographic
  - Social Structure
  - Health Beliefs

- **Enabling**
  - Personal/family
  - Community

- **Need**
  - Perceived Health
  - Evaluated Health

- **Use**
  - Personal Health Practices
    - [Process]

- **Health Status**
- **Costs**
- **Satisfaction**

Adapted from Andersen 1968
Example Mediation Study 1

The association of stigma with self-reported access to medical care and antiretroviral therapy adherence in persons living with HIV/AIDS.

Sayles JN, Wong MD, Kinsler JJ, Martins D, Cunningham WE.

### Design and Data Collection

<table>
<thead>
<tr>
<th>Category</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study Design</strong></td>
<td>Cross sectional survey</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>202 HIV+ adults in Los Angeles County in 2007</td>
</tr>
<tr>
<td><strong>Setting</strong></td>
<td>5 HIV community organizations</td>
</tr>
<tr>
<td></td>
<td>2 HIV Clinics</td>
</tr>
<tr>
<td><strong>Data Collection</strong></td>
<td>154 item questionnaire</td>
</tr>
<tr>
<td></td>
<td>Refusal rates 10-30%</td>
</tr>
<tr>
<td><strong>Measurements</strong></td>
<td>Internalized HIV stigma, access to care, ART adherence, covariates</td>
</tr>
</tbody>
</table>
## Internalized HIV Stigma

Overall measure 28-items, Cronbach’s alpha = 0.93

<table>
<thead>
<tr>
<th>SUBSCALES</th>
<th>EXAMPLE ITEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stereotypes</td>
<td>People assume I have done something bad to get HIV</td>
</tr>
<tr>
<td>Disclosure</td>
<td>If I go to the HIV clinic someone I know might see me</td>
</tr>
<tr>
<td>Concerns</td>
<td>I feel abandoned by family members because I have HIV</td>
</tr>
<tr>
<td>Social Relationships</td>
<td></td>
</tr>
<tr>
<td>Self-Acceptance</td>
<td>I feel ashamed when telling others I have HIV</td>
</tr>
</tbody>
</table>

Sayles et al., *J Urban Health* 2006; Sayles et al. *AIDS and Behavior*, 2008
Outcome: Access to Care

- Example item: I am able to get medical care whenever I need it (six item scale); alpha = 0.75
- Response scale: strongly / somewhat agree, unsure, strongly / somewhat disagree
- Poor access to care: answer strongly or somewhat disagree on average to six items
- Overall and dichotomized measures reliable and predictive of health outcome in PLHA

Cunningham et al., JAIDS 1996; Cunningham et al., Med Care 1998; Med Care 1999
Outcome: ART Adherence

“How often in the last week were you able to take your antiretroviral medications exactly as your doctor or nurse told you to?”

- Response: none, a little, some, most, all the time
- Community programs for clinical research on AIDS (CPCRA) antiretroviral medication self report
- Suboptimal adherence: less than all time
- associated with viral load, CD4 count, and quality of life

Mannheimer et al., CID 2002; Mannheimer et al., AIDS Care 2005
## Multivariate Associations of Internalized Stigma with Outcomes Odds Ratio (95% CI)

<table>
<thead>
<tr>
<th></th>
<th>Poor access to care (n=202)</th>
<th>Suboptimal adherence (n=142)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High Internalized Stigma</strong></td>
<td>5.15 (2.39-11.09)$</td>
<td>3.15 (1.35-7.36)*</td>
</tr>
</tbody>
</table>

Model adjusted for age, gender, race/ethnicity, education, income, insurance, HIV risk category, years since HIV diagnosis, CD4 count

$p <0.0001$; $*p<0.01$
Mediation Model To Explore Associations Between Internalized HIV Stigma, Mental Health and Adherence to ART

**Mediator:**
Mental health status – SF-12 MCS

AOR=2.90 (95% CI=1.45–5.78)***

AOR=7.86 (95% CI=1.90–14.49)****

**Independent variable:**
Internalized HIV stigma

3.15 (1.35-7.36)**

**Dependent variable:**
ART adherence

AOR=1.57 (95% CI=0.95–2.58)

\[ a \quad b \quad c \quad c' \]
Interpretation

• Mental health status mediates the effect of stigma on ART adherence
Example Mediation Study 2

Effect of a Laboratory Health Information Exchange Intervention on Racial/Ethnic Disparities in Antiretroviral Therapy and Viral Suppression

Cunningham WE, Kinsler JJ, Seiden D, Cima L, Nakazono T, Bell DS.

In Preparation
Effect of Health IT System Intervention on Racial/Ethnic Disparities in ART & VS

• Objectives:
  1. Examine disparities in ART and viral suppression (VS)
  2. Examine effect of the laboratory health data exchange intervention on disparities in ART use and VS
Background on Disparities Evaluation

- ART can be life saving, but many do not receive ART or adhere, esp. minorities and the poor
- Interventions are needed to improve delivery of ART, improve outcomes and reduce disparities
- Health IT interventions are increasingly emphasized as a way to deliver care, but it is unknown how they may impact HIV care, outcomes and disparities
Traditional Lab-Work System

Doctor examines patient, writes a lab order, hands it to patient to take to the lab

Patient hopefully takes slip to the lab, hands it to Lab-Tech

Lab-Tech performs test

Lab-Tech enters test result into EMR, Nurse prints the test results

Nurse hands the test results to the Doctor
HIT Network Enhanced Lab-Work System

Doctor examines patient, decides to order lab tests

Doctor enters test order through the EMR, Lab-Tech accesses the test ordered when patient comes to lab

Lab-Tech performs test at the lab

Lab-Tech enters results into the EMR, doctor gets a message once results are in, has immediate access to results
Evaluation Design

Quasi-experimental interrupted time series
– Electronic medical record (ENS) abstraction
– Followed 1,181 HIV-positive patients from St. Mary’s CARE Clinic over a period of 3 years
## Evaluation Conceptual Framework

### ENS Structure

#### IT Network Enhancements:
- Bi-directional lab interface
- E-prescriptions ordering and re-fill interface (eRx)

### Process of Care
- CD4 testing
- Viral load testing
- Ordering and obtaining lab results
- E-prescribing
- Referrals

### Patient Characteristics
- Age
- Race/ethnicity
- Gender
- Risk group
- Income
- Education
- Insurance
- CD4
- AIDS DX

### Outcomes
- ART Rx/adherence
- Viral load suppression
- Ratings of care (CAHPS)
- Hospitalizations/ER visits
- Access to care
- Stigma
- Trust
- Willingness to share PHI
- HRQOL (SF-12)

Conceptual model adapted from Donabedian
Data Analysis Plan

• Bivariate analysis
  – repeated measures, logistic GEE regression: 1. ART; 2. VL < 75

• Multivariate analysis
  – Controlling for covariates
  – repeated measures, logistic GEE regression: 1. ART; 2. VL < 75
Multiple logistic GEE regressions of ART use on race/ethnicity, the laboratory health information exchange intervention, sociodemographics, and CD4 count (n=1181)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Bivariate Regressions†</th>
<th>Multivariate Regressions†</th>
</tr>
</thead>
<tbody>
<tr>
<td>(reference group)</td>
<td>OR (95%CI)</td>
<td>aOR (95%CI)</td>
</tr>
<tr>
<td>Race/ethnicity (White*)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>African American / Black</td>
<td>0.75 (0.58-0.98) ‡</td>
<td>0.83 (0.65-1.07)</td>
</tr>
<tr>
<td>Latino / Hispanic</td>
<td>1.13 (0.88-1.45) §</td>
<td>1.22 (0.97-1.54)</td>
</tr>
<tr>
<td>LHIE intervention</td>
<td>2.22 (2.07-2.39) ‖</td>
<td>2.26 (2.09-2.43) ‖</td>
</tr>
</tbody>
</table>

†Bivariate GEE regressions including only the predictor variables shown in each row. Multivariate GEE regressions including covariates as shown in each model - Model A: Race/ethnicity, Intervention; Model B: Race/ethnicity, Intervention, CD4, Age, Gender, Risk Group; Model C: Race/ethnicity, Intervention, CD4, Age, Gender, Risk Group, FPL, Insurance Type, Visits.
‡p < .05, §p < .01, ‖p < .001
Interpretation of Mediation Effect

• Racial disparities in ART use were reduced/ outcomes improved for blacks, mediated by the LHIE intervention
Example Mediation Study 3


Research Questions

• Are there racial/ethnic disparities in use of HAART in a nationally representative sample of the US (HCSUS)?

• Do sociodemographic and clinical characteristics help explain (mediate) those disparities?
Multiple logistic regression analysis of the effect of patient characteristic on current use of HAART (n=2263)

<table>
<thead>
<tr>
<th>Characteristics (reference group)</th>
<th>Model A OR (95% CI)</th>
<th>Model C aOR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Race/Ethnicity (White)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>0.60 (0.46, 0.80) ***</td>
<td>0.74 (0.51, 1.07)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>0.85 (0.63, 1.14)</td>
<td>1.10 (0.81, 1.42)</td>
</tr>
</tbody>
</table>

| **Insurance Status (Private)**   |                     |                      |
| Private/HMO                      | ----- --------------- | 0.83 (0.56, 1.24)    |
| Medicare                         | ----- --------------- | 0.70 (0.47, 1.05)    |
| Medicaid                         | ----- --------------- | 0.68 (0.46, 1.00)*   |
| None                             | ----- --------------- | 0.71 (0.53, 0.95)*   |

Values are adjusted odds ratios and 95% CIs in logistic regression models including, Age, Gender, Risk Group, income, education, insurance status, CD4 count.

1There were 4 missing values on independent variables.

* p<0.05, ** p<0.01, *** p<0.001, **** p<0.0001
Moderation

\[ Y = b_1 X + b_2 \]

Diagram showing a regression line with coefficients \( b_1 \) and \( b_2 \).
The prospective effect of access to medical care on health-related quality of life outcomes in patients with symptomatic HIV disease.


Main Study Question

• Does the effect of access to care on health-related quality of life (HRQOL) depend on the initial level of HRQOL?

• Hypothesis: effect greatest when HRQOL is low enough that care matters, but not so low that care is futile
  – When people are really sick is when our health care system tends to provide greatest access to care
Approach: Access & HRQOL

- Stratify into 3 tertiles by level of baseline HRQOL
- Run separate multiple linear regressions in each strata
- Equivalent to interactions of all IVs by baseline HRQOL
- Outcome is change score (FU-Baseline HRQOL score)
Mean Changes in HRQOL Scores, Stratified by Level of Baseline Access and by Tertile of Baseline HRQOL

<table>
<thead>
<tr>
<th>HRQOL Composite Measures*</th>
<th>High Access (n=142)</th>
<th>Low Access (n=54)</th>
<th>Difference in Change for High vs Low Access (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Base-line 3 mo Change</td>
<td>Base-line 3 mo Change</td>
<td></td>
</tr>
<tr>
<td>Physical health composite</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Middle tertile</td>
<td>48.1 54.8 6.7**</td>
<td>48.3 44.8 -3.5</td>
<td>10.2 (3.0-17.0)**</td>
</tr>
<tr>
<td>Overall</td>
<td>50.4 56.9 6.6*</td>
<td>45.1 47.0 1.9</td>
<td>4.7 (-1.2-10.2)</td>
</tr>
</tbody>
</table>

The high access group is defined by scores above 48 (<25th percentile) on the 0 to 100 range, and the low access group had scores of 48 or below (≤25th percentile). Change was computed by subtracting baseline scores form 3-mo scores, with 95% CI shown. Difference of change was computed by subtracting low access group scores from high access group scores within each row, with 95% CI shown.

**p <0.001, *p<0.01
Effect of Baseline Access on 3-month Health-related Quality of Life (HRQOL) Outcomes, by Tertile of Baseline HRQOL:

<table>
<thead>
<tr>
<th>Tertile</th>
<th>Physical Health</th>
<th>Mental Health</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Tertile</td>
<td>0.15</td>
<td>0.38</td>
</tr>
<tr>
<td>Middle Tertile</td>
<td>0.51</td>
<td>0.30</td>
</tr>
<tr>
<td>High Tertile</td>
<td>0.22</td>
<td>0.05</td>
</tr>
<tr>
<td>Overall</td>
<td>0.23</td>
<td>0.20</td>
</tr>
</tbody>
</table>
Interpretation of Moderation in Example Paper 1

• Access to care had moderate-size effect on physical HRQOL, but only among those in middle tertile of HRQOL at baseline
  – Similar effect size in lowest tertile of MH
Comparison of health-related quality of life among clinical trial and non-clinical trial HIV-infected cohorts.

Cunningham WE, Bozzette SA, Hays RD, Kanouse DE, Shapiro MF.

HRQOL of Patients in Clinical Trial versus Public Hospital Samples

Adjusted Scale Scores

- Health Index
- Current Health
- Physical Function
- Energy/Fatigue
- Low Pain
- Emotional Well-being
- Social Function
- Role Function
- Cognitive Function

Trial vs. Non-trial
Regression of Perceived Health Index on Characteristics by Sample (t-Statistic)\(^a\)

<table>
<thead>
<tr>
<th>Demographic Characteristic</th>
<th>Clinical Trial (n= 1,193)</th>
<th>Nonclinical Trial (n = 180)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonhispanic black</td>
<td>1.1</td>
<td>-1.2</td>
</tr>
<tr>
<td>Latino</td>
<td>0.7</td>
<td>1.7</td>
</tr>
<tr>
<td>Median annual income</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$10,001-30,000</td>
<td>-2.2(^*)</td>
<td>0.05</td>
</tr>
<tr>
<td>$5,000-10,000</td>
<td>-3.9(^{**})</td>
<td>1.4</td>
</tr>
</tbody>
</table>

\(^a\)Each health-related quality-of-life scale score directly adjusted for log age, race, insurance status, education, income, CD4 level, square root number of medications, and square root number of symptoms. \(^*\)p< 0.05, \(^{**}\)p<0.001
Interpretation of Moderation - Example 2

• The relationships of sample characteristics variables with HRQOL are quite different in clinical trial vs public hospital patients.

• These differences call into question the generalizability of findings from AIDS clinical trials to other samples (which have more ppl of color, the poor).
Example Moderators
Paper 3

Health services utilization for people with HIV infection: Comparison of a population targeted for outreach with U.S. population in care.

Cunningham WE, Sohler NL, Tobias C, Drainoni M, Bradford J, Davis C, Cabral HJ, Cunningham CO, Eldred L, Wong MD.

Medical Care. 2006;44(11):1038-1047.
Comparison of Outreach and HCSUS Samples, Stratified by Ambulatory Medical Visits in Last 6 Mo

<table>
<thead>
<tr>
<th></th>
<th>0–1 Ambulatory Visits in Last 6 Mo</th>
<th>2 or More Ambulatory Visits in last 6 Mo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Outreach %</td>
<td>HCSUS %</td>
</tr>
<tr>
<td>White</td>
<td>16.8</td>
<td>36.8**</td>
</tr>
<tr>
<td>Black</td>
<td>64.0</td>
<td>38.1</td>
</tr>
<tr>
<td>Hispanic</td>
<td>16.8</td>
<td>22.5</td>
</tr>
<tr>
<td>Spanish language</td>
<td>6.9</td>
<td>5.7</td>
</tr>
<tr>
<td>CD4 count &lt;50</td>
<td>10.2</td>
<td>9.0*</td>
</tr>
<tr>
<td>Used heroin or cocaine ever</td>
<td>50.5</td>
<td>48.0</td>
</tr>
</tbody>
</table>

p values for differences in proportions across categories: *p<0.05; **p<0.01; ****p<0.0001.
For HCSUS values, all percentages are weighted to account for the complex sampling design, but numbers are unweighted; all numbers and percentages for Outreach are unweighted.
Multivariate Associations and Interactions of Sample Characteristics with Ambulatory Medical Visits, Comparing Outreach and HCSUS samples

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Outreach</th>
<th>HCSUS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(Odds Ratio 95% CI)</td>
<td>(Odds Ratio 95% CI)</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>1.21 (0.75–1.94)</td>
<td>1.71 (1.18–2.49)**†</td>
</tr>
<tr>
<td>Latino</td>
<td>0.81 (0.39–1.69)</td>
<td>2.34 (1.56–3.52)***‡</td>
</tr>
<tr>
<td>Annual income &lt; $10,000</td>
<td>0.73 (0.56–0.96)**†</td>
<td>1.35 (1.04–1.75)**†</td>
</tr>
<tr>
<td>Heavy alcohol use in past 30 days(^a)</td>
<td>1.74 (1.23–2.45)**‡</td>
<td>1.00 (0.73–1.37)</td>
</tr>
</tbody>
</table>

P Values for significant odds ratios in logistic regressions for separate samples are indicated by: *p<0.05; **p<0.01; ***p<0.0001.

\(^a\)Five or more drinks in a day.

Interaction P values indicated by: †0.24; ‡0.02; ‼0.002;
Cross-over Interaction

Factor A

A1 A2

B1

B2

Y
Suggested Steps Using Mediation/Moderation in the Research Process

1. Define the outcome measure. Investigate the epidemiology of the outcome. Identify high-risk groups.

2. Identify the conceptual theory of how the outcome occurs. Identify correlates of the outcome variables by theory and empirical studies. Review literature for ideas on what is related to the outcome. Create a list of candidate mediators. Ideally, identify two or more theories about the mechanism by which the outcome occurs that have different predictions regarding mediating processes.

3. Link the mediators with the action needed to affect the mediator. Identify program components of studies that have attempted to change the outcome measure and related outcome measures. Is it reasonable to change the mediator given the resources available? Create an action theory table that lists the action that will change each mediator.
Steps Using Mediation/Moderation in the Research Process (cont.)

4. Study potential moderation effects of the intervention with subgroups. Are there groups for whom the action and conceptual theory make the most sense? Consider whether the effect of the intervention will be greatest for those persons lowest or highest on mediators at baseline.

5. Design the intervention to have the greatest chance of success by documenting and ensuring adequate implementation and measurement of variables.

6. Conduct the study and evaluate action and conceptual theory of the program.

7. Repeat the study and improve the intervention by selecting effective components or adding new components.

8. Design a study in which subjects are randomly assigned to levels of mediating variables to more clearly understand the mechanism by which the intervention worked.
References
