A New Class of Structural Equation Models for Longitudinal Mediation Analysis and a Multivariate Predictive Model for Laparoscopic vs. Open Appendectomy

Doug Gunzler

Department of Biostatistics and

Computational Biology

University of Rochester

Rochester, NY 14642

Friday, March 4^{th}, 2011

Outline

1. Introduction to Mediation Analysis and Structural Equation Models (SEM)
2. SEM for Mediation Analysis
3. Longitudinal Mediation Analysis and a New Class of SEM
4. Simulation Studies and Child Resilience Data Example
5. Discussion
6. Collaborative Projects
7. Department of Surgery Project

1 Mediation Analysis

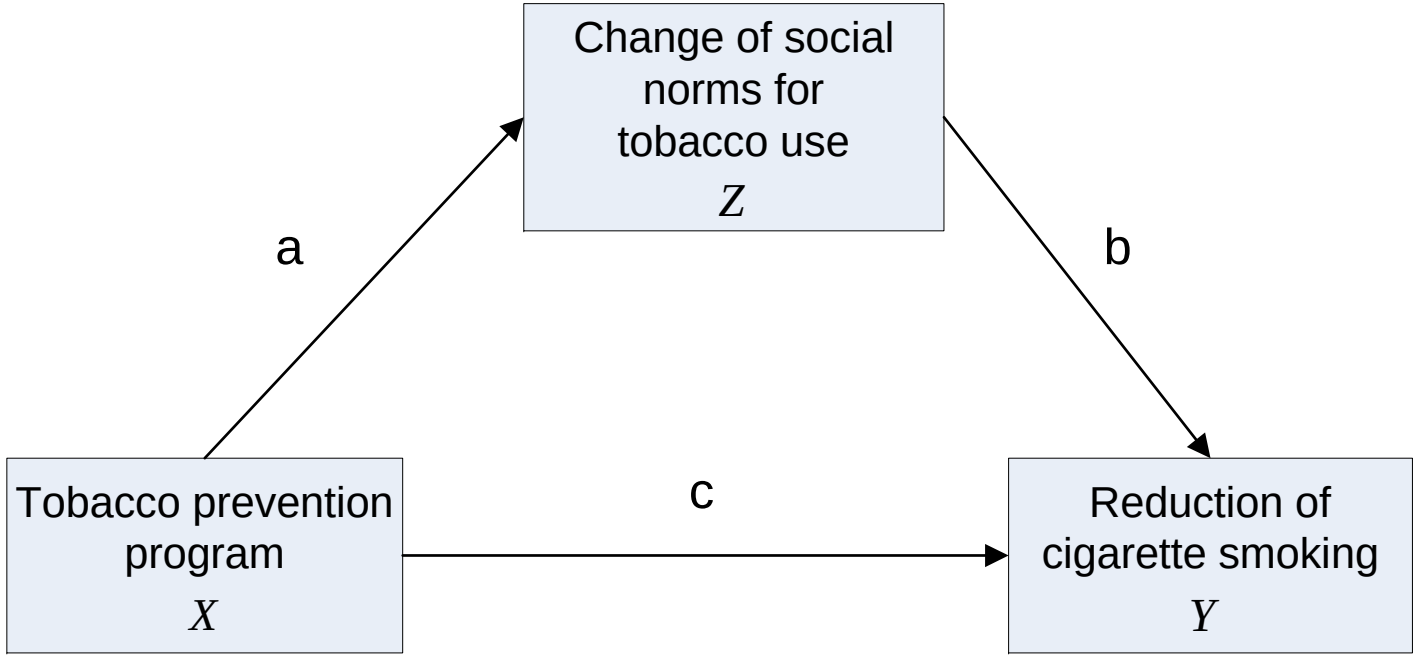
In treatment studies, it is often of great interest to identify and study mechanisms by which an intervention achieves its effect.

The mediational process is a cause and effect relationship between three variables.

Example:

Smoking is a health hazard, and since nonsmokers are healthier than smokers, not smoking would save money spent on health care.

A cost-effective tobacco prevention program reduces cigarette smoking.



Tobacco prevention program (X) changes the social norms for tobacco use (Z) and this change in social norms reduces cigarette smoking (Y)

Path Diagram

Tobacco prevention program (X) $\rightarrow$Reduces cigarette smoking (Y)

direct effect $= c$

Tobacco prevention program (X) $\rightarrow$Participants no longer take smoke breaks at work (Z) $\rightarrow$Reduces cigarette smoking (Y)

indirect effect $= ab$

total effect $= ab + c$

How does X affect Y?

Regression analysis is ill-suited for modeling such a causal relationship. Why?

2 Structural Equation Model (SEM)

What is a Structural Equation Model?

Provides broad framework for modeling of means and covariance relationships in multivariate data

Generalizes many commonly-used statistical models from a simple ANOVA to complex models with observed and unobserved variables and correlations.

1) latent variables (i.e. happiness, quality of life, social norms)

2) **causal relationships** between **endogenous** and **exogenous** variables**.**

3 SEM for Mediation Analysis

Primary hypothesis of interest in a mediation analysis is to see whether the effect of a factor X (e.g., an intervention) on an outcome Y can be mediated by a change in the mediating variable Z.

First, check if path between X and Y is significant via linear regression.

Then, test if that significance changes (higher p-value, reduction in magnitude of parameter estimate) for the direct effect in the mediation model.

1) Full mediation process$\longrightarrow$dominant role

2) Partial mediation process$\longrightarrow$more complex relationship and need to explicate other mediators

3.1 Test of a Clinical Model of Drinking and Suicidal Risk

Project MATCH multi-site, randomized clinical trial.

1,726 participants of alcohol dependent individuals (ADIs) including 24% women and a mean age of 40.2$\pm$11.0 years

Pre-treatment interview (baseline) and three reassessments at 3-, 9-, and 15 months.

Suicidal behavior is known to occur during intense drinking bouts

Role of drinking in suicidal thoughts and behavior requires the understanding of the interrelationship of drinking with other risk factors, including potential mediator and **moderating** relationships.

Think of an interaction term in a regression model (i.e. **sex** by condition or **race** by condition). **When or for whom** does X affect Y?

Previous studies of ADIs: drinking promotes depressive symptoms and depressive disorders and that depression is a potent risk factor for suicidal thoughts and behavior.

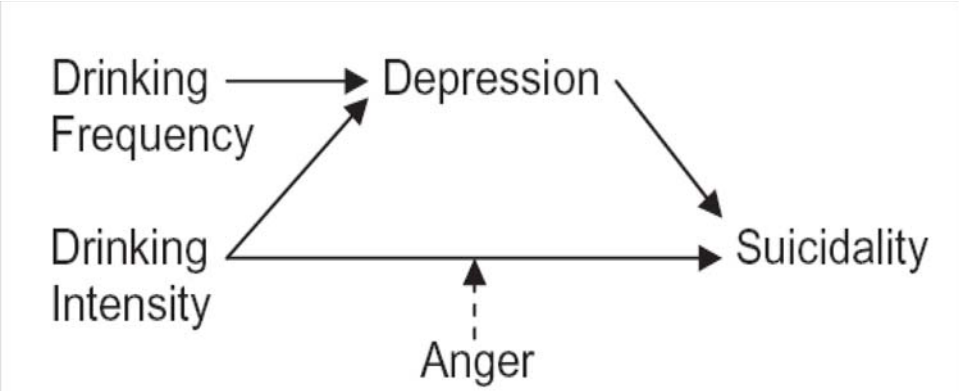
The extent to which depression mediates (full, partial) suicidal thoughts and behavior among ADIs is unknown, with implications for prevention and treatment.

Depression is internal, Aggression is external.

Aggression has been shown to confer suicide related risk in a variety of populations

Anger has been known to enhance the association between drinking and aggression.

Hypothesize anger moderates (increases) the risk for suicidal thoughts and behavior.



Clinical model of drinking and suicidality.

Variables used in models **:**

Average drinking intensity (drinks per drinking day or DDD) and average drinking frequency (percent days abstinent or PDA). Latent variables consisting of three months of drinking data.

Suicidal Ideation was dichotomous (Yes or No): Beck Depression Inventory (BDI; Beck et al.,1961) and Addiction Severity Index (ASI; McLellan et al., 1980).

Depression was a 20-item measure of depression severity from the BDI.

Anger was the total scores on the 44-item State-Trait Anger Expression Inventory (STAXI; Spielberger,1996).

age, sex, race (white, nonwhite), treatment assignment (cognitive behavioral treatment, motivational enhancement and 12-step facilitation), and study arm (aftercare, outpatient).

$\boldsymbol{Model\ used}$:

Logistic structural equation model with confirmatory factor analysis (CFI) implemented in MPlus, one of the most popular packages for SEM analysis (Muthen & Muthen, 2008).

Constrained each of the three time points to have the same estimates.

$\boldsymbol{Results}$:

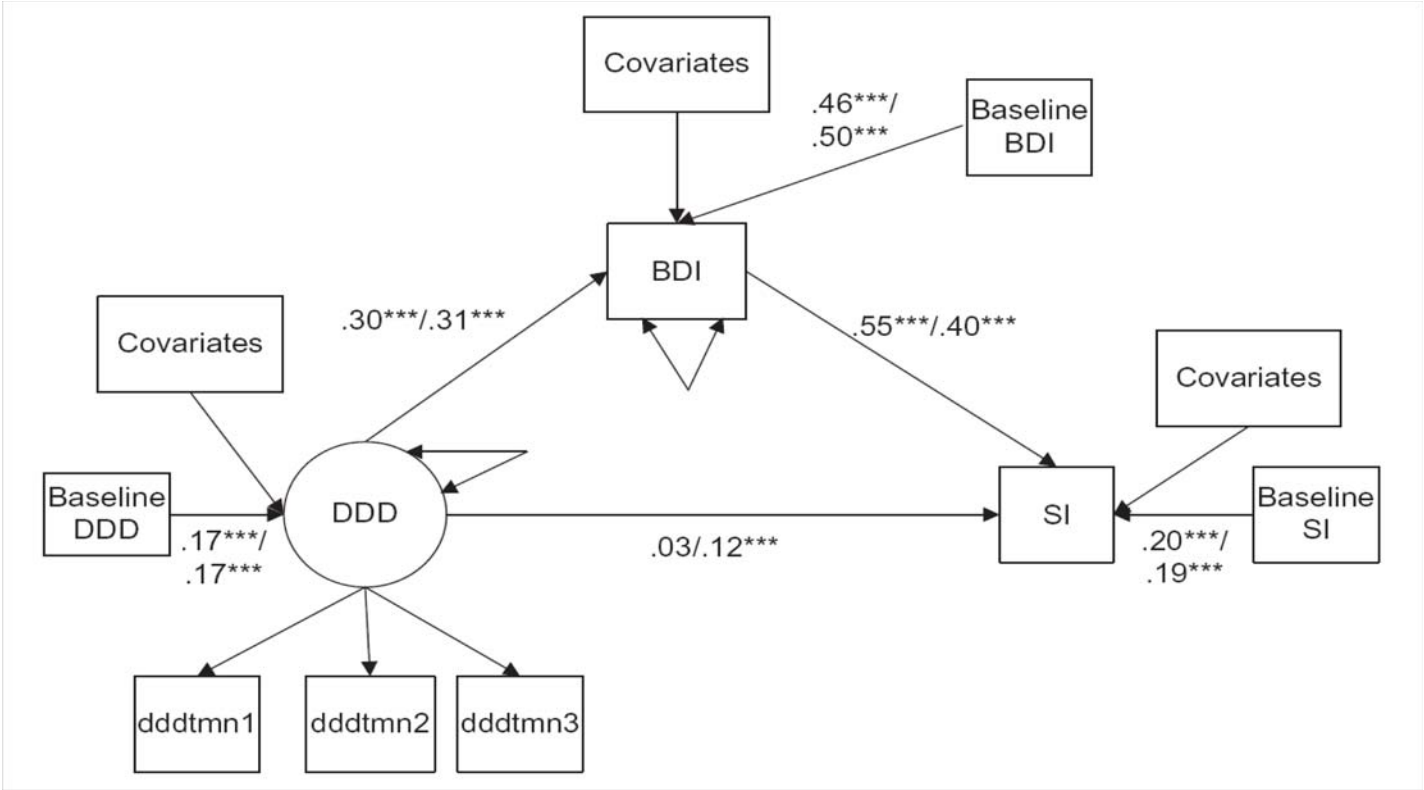
Both higher average drinking intensity (DDD) and greater drinking frequency (PDA) predicted greater likelihood of suicidal thoughts.

Depression mediates the relationship between drinking intensity and frequency and suicidal ideation.

BDI-SI outcome resulted in a full mediation ($p - value$ in direct model $\leq$ .001, mediation model $>$ .05)

ASI-SI outcome resulted in a partial mediation (direct model $\leq$ .001, mediation model$<$ .01).

Anger did not moderate the relationship (interactions of DDD/PDA and anger were not significant).



1) Is depression a partial or full mediator?

2) Generalizability to suicidal behavior (i.e. suicide attempt, suicide) is unclear.

Conner, KR, Gunzler, D, Tang, W, Tu, XM, Maisto, SA. (2011) Test of a Clinical Model of Drinking and Suicidal Risk. *Alcoholism: Clinical and Experimental Research.* 35(1):60-68.

4 Longitudinal Study Designs

Capture **both within-individual dynamics and between individuals differences over time**, offering the opportunity to study more complicated biological, psychological and behavioral processes and hypotheses.

Missing data is much more prevalent in longitudinal studies, which must also be addressed to ensure valid inference in the presence of incomplete observations.

Missing Completely at Random (MCAR) vs. Missing at Random (MAR)

Since temporal changes are important for modeling causal relationships, longitudinal data provides a new and more sensible setting for mediation analysis.

4.1 New Look for Longitudinal Mediation Analysis

Consider a longitudinal study with i=1,2,..,n subjects and 3 assessment times.

Tobacco prevention program (x_{i1}) changes the social norms for tobacco use (z_{i2}) and this change in social norms reduces cigarette smoking (y_{i3})

ID	$TIME$	X	Z	Y
1	$Baseline$	**Treatment**	4	10
1	6 $Months$	$Treatment$	**2**	6
1	18 $Months$	$Treatment$	0	**2**
2	$Baseline$	**Control**	3	8
2	6 $Months$	$Control$	4	12
2	18 $Months$	$Control$	4	**12**
3	$Baseline$	**Treatment**	5	11
3	6 $Months$	$Treatment$	4	10
3	18 $Months$	$Treatment$	NA	**NA**
.	.	.	.	.

4.2 Limitations of Classical Approaches for Longitudinal Data

Maximum Likelihood (ML) Inference (Parametric Approach)

Limitations of making the "bell-curve" assumption, as our data is typically non-normally distributed. ML is computationally complex. Incapable of handling non-normal variables.

Generalized Least Squares (GLS, Distribution-free!?!)

In theory addresses the bias of departures from model assumptions of ML to non-normal data. In SEM setting is theoretically equivalent to ML.

Weighted Least Squares (WLS, Distribution-free)

Addresses the lack of robustness of ML to non-normal data. Loss of efficiency from ML.

Missing Data

None of the approaches provide valid inference when distribution assumptions are not met in the presence of missing data when the missing data follows MAR, especially the case with longitudinal study data.

All except ML perform **listwise deletion** by removing the whole observation if data is missing at all.

5 A New Distribution-free SEM

Functional Response Model (FRM)

1) Provides a single distribution-free framework for modeling first and higher moments and extends such models to longitudinal data settings.

2) Addresses the inherent missing data issue under a unified paradigm.

Inference looks similar to Generalized Estimating Equations II (GEE II) and for longitudinal studies with missing data Weighted Generalized Estimating Equations II (WGEE II).

6 Simulation Studies

$n = 50$ and 500.

Simulations were performed with a Monte Carlo sample size of 1,000.

The data generated were fit by the classic methods GLS, WLS, MLE as well as FRM.

The FRM-based SEM was performed using the codes developed under the R programming language (R Development Core Team, 2008).

Analyses for GLS, MLE and WLS were carried out using the MPlus software (Muthen & Muthen, 2008).

The same random seed was used in each data set created using the R software.

Estimates, standard errors and type I errors based on normal error under complete data with 1000 MC replications								
	Estimate				Standard error			
$\boldsymbol{\theta}$	Method				Method			
					Asymptotic			
	FRM	MLE	GLS	WLS	FRM	MLE	GLS	WLS
Sample size $= 50$								
$b = 1$	0.998	0.998	0.998	0.997	0.149	0.142	0.143	0.135
$c = 1$	1.007	1.007	1.007	1.000	0.209	0.200	0.202	0.193
$a = 1$	0.996	0.996	0.996	1.005	0.146	0.141	0.142	0.135
Type I α for H_0: $c = 1$					0.050	0.052	0.050	0.074
Sample size of 500								
$b = 1$	1.000	1.000	1.000	1.000	0.044	0.045	0.045	0.045
$c = 1$	0.998	0.998	0.998	1.001	0.063	0.063	0.063	0.063
$a = 1$	1.001	1.001	1.001	0.999	0.045	0.045	0.045	0.044
Type I α for H_0: $c = 1$					0.048	0.054	0.054	0.049

Missing data (15%/30% at time 2/3) with correlated normal error terms				
	Estimate		Standard error	
$\boldsymbol{\theta}$	Method		Method	
			Asymptotic	
	FRM	MLE	FRM	MLE
Sample size $= 50$				
$b = 1$	1.070	1.113	0.263	0.184
$c = 1$	0.939	0.888	0.568	0.394
$a = 1$	1.010	1.060	0.349	0.291
Type I α for H_0: $c = 1$			0.067	0.081
Sample size of 500				
$b = 1$	1.031	1.117	0.135	0.058
$c = 1$	0.975	0.873	0.313	0.125
$a = 1$	1.011	1.073	0.131	0.092
Type I α for H_0: $c = 1$			0.060	0.177

7 Child Resilience Project (Wyman et al., 2010) Example

401 students from first up to third grade in five Rochester City School District elementary schools.

Examines how children with a higher risk of developing behavioral problems with a mentor socially improve compared to the control and lower risk children over periods of 6 and 18 months.

Multilevel models with two-level random effects to accommodate the nesting of children within mentor within school.

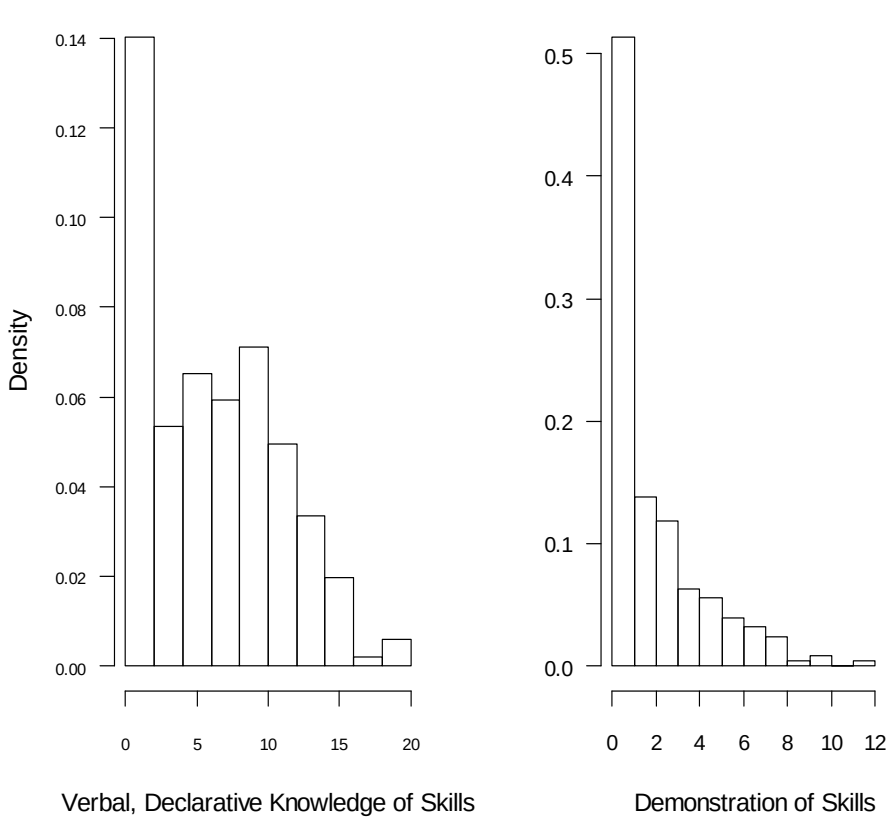
Both the mediator and response were focused on helping children to manage challenging emotions- emotion self-regulation in a complete subset of 251 students.

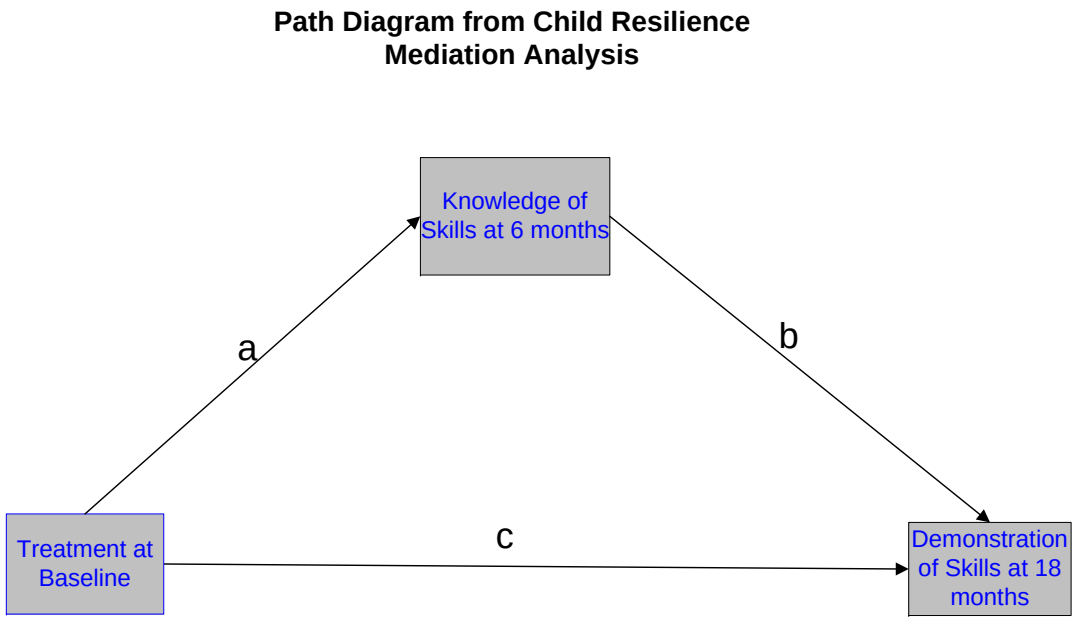
X=treatment at baseline (mentor or no mentor)

Z=self-reported verbal, declarative knowledge of the skills the child is learning in the Resilience Project at 6 months

Y=child's self-initiated demonstration of skills he/she is learning, at 18 months.

The treatment would be expected to predict a higher knowledge of skills which would then predict a higher demonstration of skills which would indicate that the children receiving a mentor improved their social skills over time given an increase in the mediator.


Histograms of Probability Density
Density
0.14
0.12
0.10
0.08
0.06
0.04
0.02
0.00
0
5
10
15
20
Verbal, Declarative Knowledge of Skills
0.5
0.4
0.3
0.2
0.1
0.0
0
2
4
6
8
10
12
Demonstration of Skills


Path Diagram from Child Resilience
Mediation Analysis
Knowledge of
Skills at 6 months
a
b
Treatment at
Baseline
c
Demonstration
of Skills at 18
months

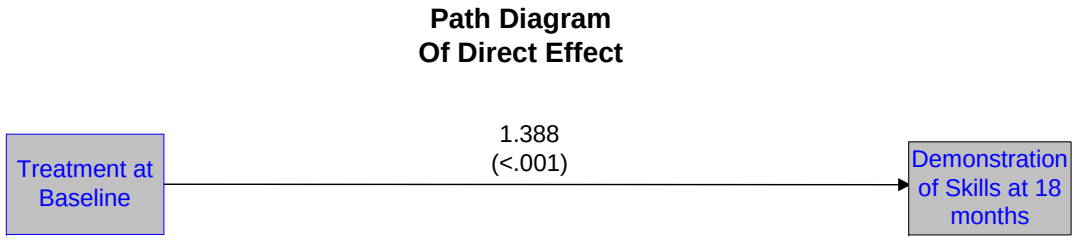

Path Diagram
Of Direct Effect
Treatment at
Baseline
1.388
(<.001)
Demonstration
of Skills at 18
months

Figure 1:

Estimates, standard errors and type I errors						
child resilience study example under complete data						
	Estimate			Standard error		
$\boldsymbol{\theta}$	Method			Method		
				Asymptotic		
	FRM	MLE	GLS	FRM	MLE	GLS
Sample size $= 251$						
b	0.231	0.231	0.231	$\mathbf{0.035}$	0.053	0.053
c	0.371	0.371	0.371	$\mathbf{0.354}$	0.449	0.450
a	4.390	4.390	4.390	0.527	0.529	0.530
Type I α for H_0: $c = 0$				$\mathbf{0.295}$	0.409	0.409

8 Discussion

Mediation analysis is a critical component of many studies in biomedical, psychosocial and related services research to investigate the causal mechanism of interventions.

Structural equation model (SEM) provides an ideal conceptual framework.

By taking advantage of the functional response models (FRM), I have developed a distribution-free approach to systematically address the limitations of SEM as it applies to longitudinal mediation analysis; valid inference under MAR.

Double Robust Method (Robins et al., 1995).

9 Collaborative Projects

1) Serum urate (UA) is associated with a slower rate of cognitive loss in patients with Parkinson's Disease (PD)?

DATATOP dataset of 800 subjects that confirmed the efficacy of deprenyl in fighting the progression of PD

linear regression, repeated measures ANOVA, **stratification**

$\boldsymbol{major\ finding}$

not on α-tocopherol, higher urate concentrations were associated with a slower rate of decline in the UPDRS mental score

2) Seychelles Child Development Study main cohort consists of 779 children born to mothers who consumed sufficient fish meals during pregnancy to result in high Methylmercury exposure

Does either a prenatal Methylmercury by gender interaction or a postnatal Methylmercury by gender interaction have a significant effect on the standardized test scores of subjects?

linear regression

$$major\ finding$$

Significant adverse associations between examination scores and postnatal exposure in boys for a subgroup of 215 students who participated in a regional achievement test called SACMEQ.

3) Department of Surgery Projects

10 Department of Surgery Projects

10.1 Background

The National Surgical Quality Improvement Program (NSQIP) of the American College of Surgeons

Retrieving observations from 2005-2008, including 39,950 appendectomy cases, this data set includes over 239 variables covering pre-operative patient factors, procedure related factors, and post-operative outcomes.

Appendicitis is the most common general surgical emergency in developed countries (estimated 252,682 appendicitis-related hospitalizations in the United States in 1997).

Aim of the study: to determine if a laparoscopic approach was associated with an increased risk of postoperative organ space (intraperitoneal) infection (OSI) in a large patient cohort, while controlling for well-known surgical risk factors.

23% (9375/39,950) were open approach cases.

Laparoscopic appendectomy has been widely adopted in the management of acute appendicitis because of its demonstrated advantages over open appendectomy.

1) shorter length of hospital stay

2) reduced superficial wound infection

3) reduced postoperative ileus

Laparoscopic approach was associated with a 2- to 3-fold increased risk of post-operative organ space (intraperitoneal) infection (OSI) compared with the open approach in meta-analyses.

OSI postappendectomy occurs in approximately 1.6% to 3.0% of all cases;

In patients with complicated appendicitis postoperative OSI rates of 7.0% to 15% have been reported.

Problems with studies thus far in the context of complicated appendicitis conversion to open appendectomy:

1) Only small patient populations where total number of events (90 postappendectomy operative OSIs) in the meta-analyses is relatively small.

2) Many of the studies have not controlled for potential confounding factors such as wound class, operative time, obesity and smoking history.

10.2 Statistical Procedure

Datasets were originally compiled in SPSS (Copyright IBM Corporation 2009).

Using DBMS-COPY Version 8 (Conceptual Software, Inc.), these datasets were converted into SAS datasets.

All merging, concatenating and analyses were carried out at the University of Rochester using SAS 9.2 (Copyright 2009 SAS Institute Inc. Cary North Carolina 27513, USA) on a Windows XP Pro platform (Microsoft Corp.).

TABLE 1. Clinical Characteristics of the Patient Group Based on Operative Procedure

	Laparoscopic Group*	Open Group	*P*
Total group	30,575 (77%)	9375 (23%)	
Male gender, N (%)	15,623 (51.1%)	5305 (56.6%)	<0.0001
Mean age in years (± SD)	38 (± 16)	41 (± 18)	<0.0001
Mean body mass index (± SD)	27.5 (± 6.5)	27.2 (± 6.3)	<0.0001
History of diabetes mellitus, N (%)	1242 (4.1%)	483 (5.2%)	<0.0001
Steroid use for chronic condition, N (%)	235 (0.8%)	108 (1.2%)	<0.0001
Current smoker within 1 year, N (%)	6739 (22%)	2045 (21.8%)	0.64

Ex: more patients who underwent open appendectomy were male and older, had a higher incidence of comorbid conditions, had an increased rate of preoperative sepsis, had a higher ASA class and were more likely to have a grossly contaminated wound.

Surgical infections postappendectomy (OSI as well as incisional infection) were evaluated independently as binary outcomes, and the associations of operative approach and surgical risk.

TABLE 2. Univariate Analysis of Clinical Factors and Operative Procedures Associated With Incisional and Organ Space Wound Infection

Variable	Incisional Infection, n = 1001	No Incisional Infection, n n= 38,941	*P*	Organ Space Infection, n = 722	No Organ Space Infection, n = 39,228	*P*
Laparoscopic technique, N (%)	512 (51.0%)	30,063 (77.2%)	<0.0001	547 (75.8%)	30,028 (76.6%)	0.62
Male gender, N (%)	576 (57.5%)	20,352 (50.9%)	0.009	439 (60.8%)	20,489 (52.2%)	<0.0001
Mean age in years (±SD)	43.2 (± 16.6)	38.6 (± 16.4)	<0.0001	41.6 (± 17.1)	38.7 (± 16.5)	<0.0001
Mean body mass index (±SD)	29.8 (± 7.8)	27.4 (± 6.4)	<0.0001	27.9 (± 6.3)	27.4 (± 6.5)	0.1
Diabetes mellitus, N (%)	103 (10.3%)	1622 (4.2%)	<0.0001	41 (5.7%)	1684 (4.3%)	0.07
Steroid use, N (%)	16 (1.6%)	327 (0.8%)	0.01	7 (1.0%)	336 (0.9%)	0.74
Bleeding disorder, N (%)	37 (3.7%)	821 (2.1%)	0.006	22 (3.1%)	836 (2.1%)	<0.0001
Current smoker within 1 year, N (%)	261 (26.1%)	8523 (21.9%)	0.0016	204 (28.3%)	8580 (21.9%)	<0.0001
Preoperative SIRS, N (%)	442 (44.2%)	12,889 (33.1%)	<0.0001	400 (55.4%)	12,931 (33.0%)	<0.0001

Those variables with a P $\leq$ 0.10 in a univariate model were selected for inclusion in a multivariate logistic regressions.

"*Heart and Soul*" *of this large sample study* :

A **predictive model** incorporating the preoperative and intraoperative factors was used to evaluate the probability of infection for sample patient scenarios.

10.3 Results

Compared with the open approach in the multivariate analysis:

1) Laparoscopic approach was associated with a reduced incidence of incisional infection.

2) Independently, laparoscopic approach was associated with an increased incidence of OSI.

In further analyses models:

1) Laparoscopic approach was associated with a lower rate of any infection (cumulative events of incisional and OSI).

2) Protective effect of laparoscopy seen for all wound classes.

TABLE 3. Multivariate Analysis of Clinical Factors and Operative Procedures Associated With Incisional and Organ Space Wound Infection

	Incisional Infection		Organ Space Infection	
Variable	**OR (CI 95%)**	***P***	**OR (CI 95%)**	***P***
Laparoscopic technique (vs. open)	0.37 (0.32–0.43)	<0.0001	1.44 (1.21–1.73)	<0.0001
Male gender	1.12 (0.97–1.29)	0.1290	1.33 (1.14–1.55)	0.0004
Mean age in years	1.04 (0.99 –1.01)	0.0916	1.00 (0.99–1.01)	0.8676
Mean body mass index	1.03 (1.02–1.04)	<0.0001	–	–
History of diabetes mellitus	1.49 (1.15–1.92)	0.0024	0.94 (0.66–1.31)	0.7090
History smoking	1.09 (0.92–1.29)	0.34	1.24 (1.04–1.48)	0.0154
History bleeding disorder	1.05 (0.70–1.51)	0.8129	0.96 (0.59–1.50)	0.8854
SIRS	1.26 (1.08–1.48)	0.0040	1.49 (1.26–1.77)	<0.0001
Mean preoperative serum WBC count per 1000 WBC/mm^3	1.02 (1.01–1.04)	0.0162	1.03 (1.01–1.05)	0.0002
ASA class II vs. I	1.09 (0.92–1.32)	0.3090	1.15 (0.95–1.39)	0.1540
ASA class (III + IV + V vs. I)	1.18 (0.90–1.53)	0.2302	1.21 (0.90–1.60)	0.2013
Emergency case	–	–	1.31 (1.07–1.62)	0.0093
Wound class III vs. II	1.01 (0.84–1.22)	0.8981	1.76 (1.34–2.32)	<0.0001
Wound class IV vs. II	1.70 (1.39 –2.03)	<0.0001	7.90 (6.16–10.27)	<0.0001
Total operation time ≥60 min	1.89 (1.63–2.18)	<0.0001	1.53 (1.31–1.79)	<0.0001

SIRS, systemic inflammatory response syndrome; WBC, white blood cell.

TABLE 4. Clinical Patient Scenarios With Probability of OSI Stratified for by Laparoscopic (lap) and Open Approach (open)

Case	Sex	Age	Diabetes	Smoker	Bleeding Disorder	Preop Sepsis	Preop WBC	ASA Class	Emergency	Wound Class	OR Time minutes	Procedure	Probability OSI
1a	M	18	No	Yes	No	SIRS	15	1	Yes	IV	<60	Lap	7.1%
												Open	5.0%
1b	M	18	No	Yes	No	SIRS	15	1	Yes	IV	≥60	Lap	10.4%
												Open	7.4%
2a	F	23	No	No	No	None	13	1	Yes	II	<60	Lap	0.4%
												Open	0.3%
2b	F	23	No	No	No	None	13	1	Yes	IV	<60	Lap	2.8%
												Open	2.0%
3a	M	77	Yes	Yes	No	Sepsis	17	4	Yes	II	<60	Lap	1.2%
												Open	0.8%
3b	M	77	Yes	Yes	No	Sepsis	17	4	Yes	IV	<60	Lap	8.4%
												Open	6.0%
3c	M	77	Yes	Yes	No	Sepsis	17	4	Yes	IV	≥60	Lap	12.3%
												Open	8.9%

F, female; M, male; OR, operating room; preop, preoperative; SIRS, systemic inflammatory response syndrome; WBC, white blood cell.

10.4 Conclusions

Laparoscopic approach, sex, smoking, preoperative sepsis, wound class, and operative time were all associated with OSI postappendectomy.

Risk of OSI with laparoscopic appendectomy will, therefore, vary depending on particular patient scenarios.

Given the demonstrated benefit of laparoscopy for incisional infections postappendectomy in all scenarios, the findings from this study can aid clinicians in balancing both categories of infectious risk to choose the most appropriate operative technique for their patients.

10.5 Further Studies

Examined the effect of laporascopic vs. open surgery on other surgical procedures: splenectomy, dialysis, prolapse, and ileal pouch.

We aimed to establish the relationship between operative approach (laparoscopic or open) and subsequent surgical infection post surgical procedure, independent of potential confounding factors, using logistic and linear regression models.

Power analysis to calculate the minimum acceptable sample size.

We found that laparoscopic procedures were associated with an increased incidence of OSI.

10.6 References

Fleming, FJ, Kim, MJ, Messing, S, Gunzler, D, Salloum, R, Monson, JRT. (2010) Balancing the Risk of Post-operative Surgical Infections: A Multivariate Analysis of Factors Associated with Laparoscopic Appendectomy from the NSQIP Database. Annals of Surgery. 252(6):895-900.

Fleming, FJ, Francone, TD, Kim, MJ, Gunzler, D, Messing, S, Monson, JRT. (2011) A Laparoscopic Approach Does Reduce Short-Term Complications in Patients Undergoing Ileal Pouch-Anal Anastomosis. Diseases of the Colon & Rectum. 54, in press.

Thank You!