Clinical Review & Education

JAMA | Special Communication

A Guideline for Reporting Mediation Analyses of Randomized Trials and Observational Studies
The AGReMA Statement

Hopin Lee, PhD; Aidan G. Cashin, PhD; Sarah E. Lamb, DPhil; Sally Hopewell, DPhil; Stijn Vansteelandt, PhD; Tyler J. VanderWeele, PhD; David P. MacKinnon, PhD; Gemma Mansell, PhD; Gary S. Collins, PhD; Robert M. Golub, MD; James H. McAuley, PhD; and the AGReMA group

JAMA September 21, 2021 Volume 326, Number 11

CHAIYAWAT SUPPASILP, M.D.

KAMOLPAT CHAIYAKITTISOPON, PHARM.D

ASST.PROF. PAWIN NUMTHAVAJ, M.D., PH.D.

THE AGREMA STATEMENT

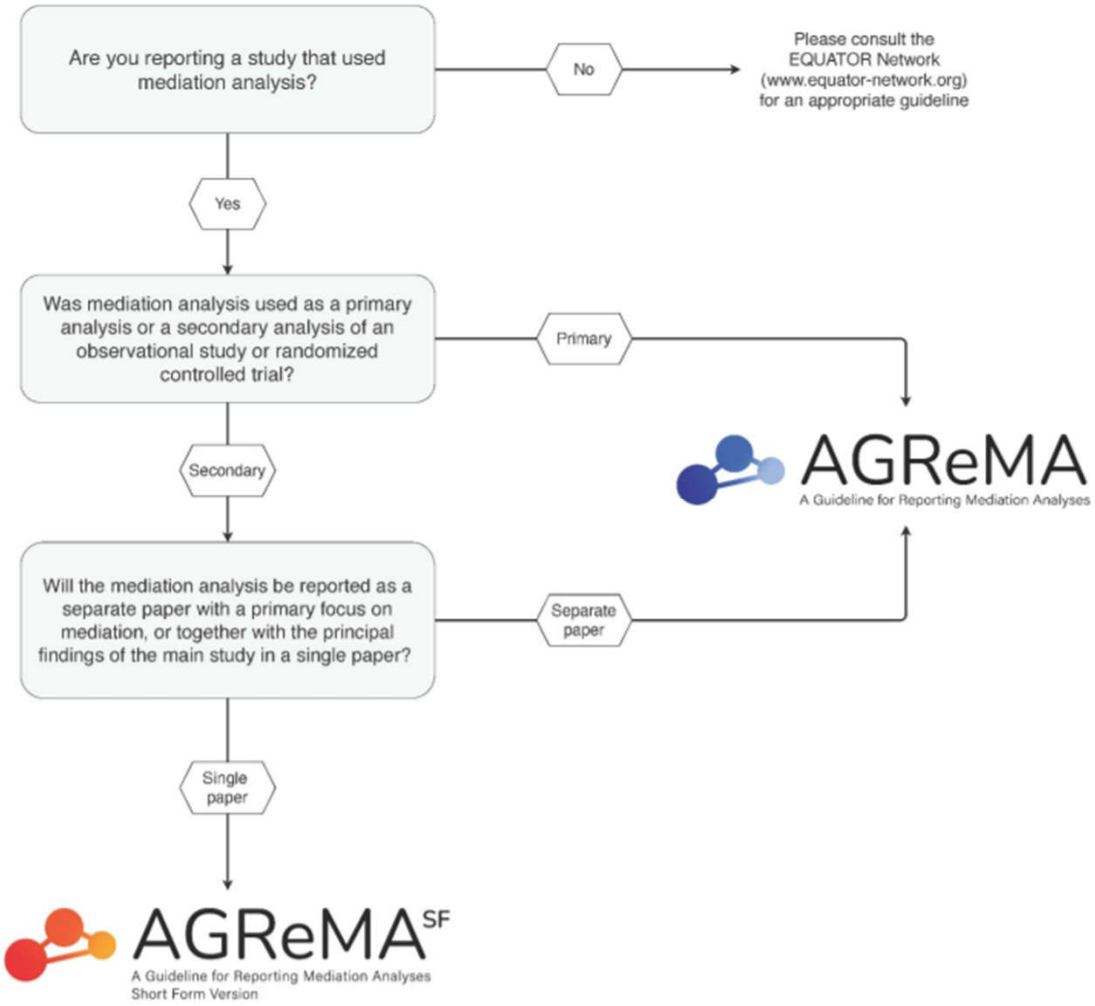
- Checklist Items and Explanation
- a 25-item AGReMA checklist statement: Long-form
  - Reporting guideline for primary reports of mediation analyses

AGReMA
A Guideline for Reporting Mediation Analyses

- a 9-item AGReMA short-form (AGReMASF): Short-form
  - Reporting guideline for secondary reports of mediation analyses within reports of randomized trials or observational studies.

AGReMA SF
A Guideline for Reporting Mediation Analyses
Short Form Version

Decision tree to guide selection of appropriate version of AGReMA



THE AGREMA STATEMENT

Section and topic	AGReMA A Guideline for Reporting Mediation Analyses 25-item (Full- form)	AGReMA SF A Guideline for Reporting Mediation Analyses Short Form Version 9-item (Short- form)
Title and abstract	2	✖
Introduction	2	1
Methods	12	4
Results	3	2
Discussion	3	2
Other information	3	✖

EXAMPLE PAPER 1

Effects of Patient and Surgery Characteristics on Persistent Postoperative Pain

A Mediation Analysis

Xinlei Mi, PhD, Baiming Zou, PhD,*† Parisa Rashidi, PhD,‡§*
Raheleh Baharloo, BS,§ Roger B. Fillingim, PhD,‖
Margaret R. Wallace, PhD,¶ Paul L. Crispen, MD,#
*Hari K. Parvataneni, MD,** Hernan A. Prieto, MD,***
*Chancellor F. Gray, MD,** Tiago N. Machuca, MD, PhD,††*
Steven J. Hughes, MD,†† Gregory J.A. Murad, MD,‡‡
Elizabeth Thomas, DO,§§ Atif Iqbal, MD,‖‖ and Patrick J. Tighe, MD, MS,¶¶
for the Temporal Postoperative Pain Signatures (TEMPOS) Group

Clin J Pain 2021;37:803–81 (Impact Factor 2.893)

EXAMPLE PAPER 2

Gaming and Gaming Disorder: A Mediation Model Gender, Salience, Age of Gaming Onset, and Time Spent Gaming

Frank D. Buono, PhD,[1] Erina Paul, PhD,[2] Matthew E. Sprong, PhD,[3,4] Emma C. Smith, BA,[1] Amir Garakani, MD,[1] and Mark D. Griffiths, PhD[5]

CYBERPSYCHOLOGY, BEHAVIOR, AND SOCIAL NETWORKING
Volume 23, Number 9, 2020 (Impact Factor 4.157)

TITLE AND ABSTRACT

Title and abstract		
Title	1	• Identify that the study uses mediation analyses
Abstract	2	• Provide a structured summary of the objectives, methods, results, and conclusions specific to mediation analyses

- Provide a structured summary
- The study objectives (ideally supported by a brief statement of background and rationale for the mechanisms of interest),
- Methods (ideally including the setting, participants, sample size, exposure, mediator,outcome,andanalytic approach for mediation analyses),
- Results (including point estimates and uncertainty estimates)
- Main conclusion.
- Short-form dose not require these two items because it is used for secondary reports of mediation analyses within reports of randomized trials or observational studies.

Effects of Patient and Surgery Characteristics on Persistent Postoperative Pain

A Mediation Analysis

Objective: Acute postoperative pain intensity is associated with persistent postsurgical pain (PPP) risk. However, it remains unclear whether acute postoperative pain intensity mediates the relationship between clinical factors and persistent pain.

Materials and Methods: Participants from a mixed surgical population completed the Brief Pain Inventory and Pain Catastrophizing Scale before surgery, and the Brief Pain Inventory daily after surgery for 7 days and at 30 and 90 days after surgery. We considered mediation models using the mean of the worst pain intensities collected daily on each of postoperative days (PODs) 1 to 7 against outcomes of worst pain intensity at the surgical site endpoints reflecting PPP (POD 90) and subacute pain (POD 30).

Results: The analyzed cohort included 284 participants for the POD 90 outcome. For every unit increase of maximum acute postoperative pain intensity through PODs 1 to 7, there was a statistically significant increase of mean POD 90 pain intensity by 0.287 after controlling for confounding effects. The effects of female versus male sex ($m=0.212$, $P=0.034$), pancreatic/biliary versus colorectal surgery ($m=0.459$, $P=0.012$), thoracic cardiovascular versus colorectal surgery ($m=0.31$, $P=0.038$), every minute increase of anesthesia time ($m=0.001$, $P=0.038$), every unit increase of preoperative average pain score ($m=0.012$, $P=0.015$), and every unit increase of catastrophizing ($m=0.044$, $P=0.042$) on POD 90 pain intensity were mediated through acute PODs 1 to 7 postoperative pain intensity.

Discussion: Our results suggest the mediating relationship of acute postoperative pain on PPP may be predicated on select patient and surgical factors.

Key Words: acute pai
operative, surgery

Abstract	Rank
Structured summary	☆☆☆
Study objectives	☆☆☆
Methods	☆☆
Results	☆☆☆
Main conclusion	☆☆☆

Gaming and Gaming Disorder: A Mediation Model Gender, Salience, Age of Gaming Onset, and Time Spent Gaming

Abstract

Females in empirically based peer-reviewed studies of Internet gaming disorder (IGD) are underrepresented, despite evidence that there are only minor gender disparities present in online gaming. Moreover, few studies have specifically evaluated adult gender effects, within a formal diagnosis of IGD, and behavioral motivation, as defined by the reinforcing behavioral function. A mediation analysis evaluated the relationship between gender, behavioral motivation, and the diagnostic features in online gaming among adults to understand the impact of motivation on videogame playing. This study interviewed 304 adults (aged >18 years) in which 178 identified as female. Participants completed the Video Game Functional Assessment-Revised (VGFA-R) and the 20-item Internet Gaming Disorder Test (IGDT-20) through an online survey. Results showed that number of hours played per week, and subfactors of the VGFA-R differed between gender, indicating that the function and the maintaining of videogame play are essential in evaluating videogame addiction. These findings support and extend the literature's limited findings concerning gender and online gaming.

Keywords: gender, Internet gaming disorder, motivation, diagnosis, mediation analysis

Abstract	Rank
Structured summary	☆
Study objectives	☆
Methods	☆
Results	☆
Main conclusion	☆

INTRODUCTION

Introduction		
Background and rationale	3	• Describe the study background and theoretical rationale for investigating the mechanisms of interest • Include supporting evidence or theoretical rationale for why the intervention or exposure might have a causal relationship with the proposed mediators • Include supporting evidence or theoretical rationale for why the mediators might have a causal relationship with the outcomes
Objectives	4	• State the objectives of the study specific to the mechanisms of interest • The objectives should specify whether the study aims to test or estimate the mechanistic effects

- Short-form: There is no item No.3.
- When mediation analyses are used to answer a secondary question, authors should clearly state the objectives but note that the objective of mediation analyses is secondary and place it within the context of the primary objective.

Effects of Patient and Surgery Characteristics on Persistent Postoperative Pain

A Mediation Analysis

Here, we examine the mediating role of acute postoperative pain intensity in the development of persistent postoperative pain in a mixed surgical cohort. We hypothesized that the effects of clinical factors (eg, age, sex, preoperative pain) on persistent postoperative pain could be mediated by acute postoperative pain intensity within the first 7 days following surgery, after controlling for confounding factors. To address this hypothesis, we considered mediation experiments using the mean of the worst pain intensities on each of postoperative days (PODs) 1 to 7, against outcomes of worst pain intensity at the surgical site endpoints reflecting PPP (POD 90) and subacute pain (POD 30).

Objective	Rank
Specific to the mechanism of interest	☆☆☆
Specify whether "to test" or "to estimate" the mechanistic effects	☆ (stated in Method)

Gaming and Gaming Disorder: A Mediation Model Gender, Salience, Age of Gaming Onset, and Time Spent Gaming

Therefore, this study examined the impact of behavioral motivation utilizing the Video Game Functional Assessment-Revised (VGFA-R[18]) in relation to duration of time impact of hours of play, gender, and the risk of IGD utilizing the IGDT-20. Based on previous research[5,19] it was hypothesized that females would have higher levels of attention-maintained behavioral motivation, whereas males would have higher escape-maintained behavioral motivation.

Objective	Rank
Specific to the mechanism of interest	☆☆
Specify whether "to test" or "to estimate" the mechanistic effects	☆ (stated in Method)

METHOD: LONG-FORM

	Methods		
	Study registration	5	• If applicable, provide references to any protocols or study registrations specific to mediation analyses and highlight any deviations from the planned protocol
	Study design and source of data	6	• Specify the design of the original study that was used in mediation analyses and where the details can be accessed, supported by a reference • If applicable, describe study design features that are relevant to mediation analyses
	Participants	7	• Describe the target population, eligibility criteria specific to mediation analyses, study locations, and study dates (start of participant enrollment and end of follow-up)
	Sample size	8	• State whether a sample size calculation was conducted for mediation analyses • If so, explain how it was calculated
✓	Effects of interest	9	• Specify the effects of interest
	Assumed causal model	10	• Include a graphic representation of the assumed causal model including the exposure, mediator, outcome, and possible confounders
✓	Causal assumptions	11	• Specify assumptions about the causal model
✓	Measurement	12	• Clearly describe the interventions or exposures, mediators, outcomes, confounders, and moderators that were used in the analyses • Specify how and when they were measured, the measurement properties, and whether blinded assessment was used
	Measurement levels	13	• If relevant, describe the levels at which the exposure, mediator, and outcome were measured
✓	Statistical methods	14	• Describe the statistical methods used to estimate the causal relationships of interest • This description should specify analytic strategies used to reduce confounding, model building procedures, justification for the inclusion or exclusion of possible interaction terms, modeling assumptions, and methods used to handle missing data • Provide a reference to the statistical software and package used
	Sensitivity analyses	15	• Describe any sensitivity analyses that were used to explore causal or statistical assumptions and the influence of missing data
	Ethical approval	16	• Name the institutional research board or ethics committee that approved the study • Provide a description of participant informed consent or ethics committee waiver of informed consent

METHOD: SHORT-FORM

Methods		
Effects of interest	2	• Specify the effects of interest
Causal assumptions	3	• Specify assumptions about the causal model
Measurement	4	• Clearly describe the interventions or exposures, mediators, outcomes, confounders, and moderators that were used in the analyses • Specify how and when they were measured, the measurement properties, and whether blinded assessment was used
Statistical methods	5	• Describe the statistical methods used to estimate the causal relationships of interest • This description should specify analytic strategies used to reduce confounding, model building procedures, justification for the inclusion or exclusion of possible interaction terms, modeling assumptions, and methods used to handle missing data • Provide reference to the statistical software and package used

Effects of Patient and Surgery Characteristics on Persistent Postoperative Pain

A Mediation Analysis

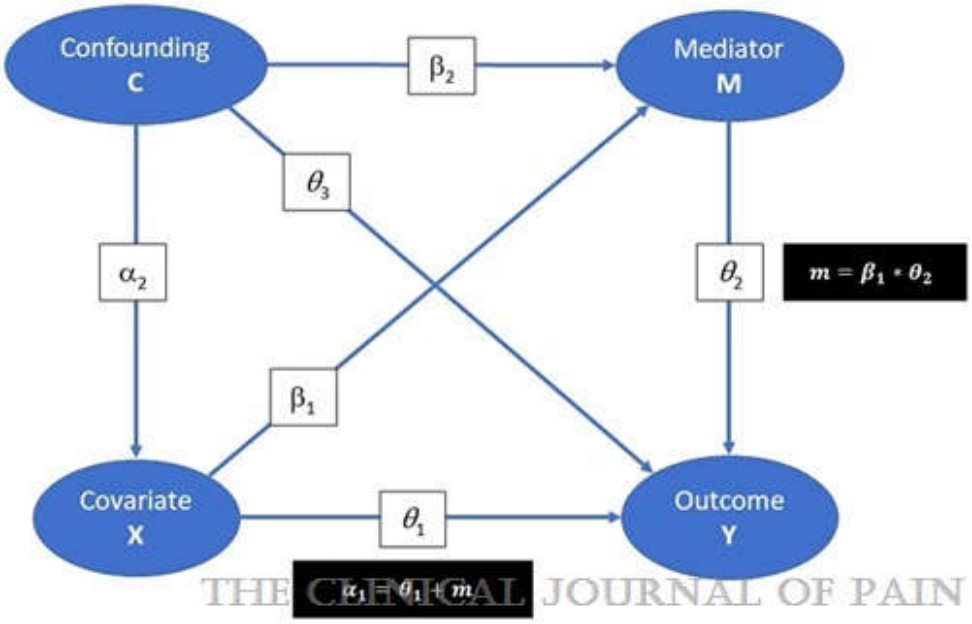
MATERIALS AND METHODS

This study was a prospective cohort of a mixed surgical population that aimed to investigate how the temporal dynamics of acute postoperative pain are associated with the development of persistent postoperative pain. The protocol (IRB 201500153) was approved by the University of Florida Institutional Review Board-01 and registered at ClinicalTrials.gov (NCT02407743; date of registration: April 3, 2015) before study initiation, participant enrollment, and data collection. This analysis represented an interim report while awaiting follow-up at longer-term endpoints. This article adhered to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[23]

Methods	Rank
Study registration	☆☆☆
Study design and Source of data	☆☆☆
Participants	☆☆☆
Sample size	☆
Effect of interest	☆☆☆
Assumed causal model	☆☆☆
Causal assumption	☆☆☆
Measurement	☆☆☆
Measurement level	NA
Statistical methods	☆☆☆
Sensitivity analyses	☆☆☆
Ethical approval	☆☆☆

Effects of Patient and Surgery Characteristics on Persistent Postoperative Pain

A Mediation Analysis



THE CLINICAL JOURNAL OF PAIN

Overview of the approach to mediation analysis. After accounting for confounding factors (C), patient and clinical covariates (X) were examined for both direct association with the outcome of persistent postoperative pain at 30 days following surgery (Y) as well as through a mediating effect (M) of acute postoperative pain intensity in postoperative days 1 to 7.

$$(1)\ E(Y|X,\ C) = \alpha_0 + \alpha_1 X + \alpha_2' C$$

$$(2)\ E(M|X,\ C) = \beta_0 + \beta_1 X + \beta_2' C$$

$$(3)\ E(Y|X,\ M,\ C) = \theta_0 + \theta_1 X + \theta_2 M + \theta_3' C$$

Gaming and Gaming Disorder: A Mediation Model Gender, Salience, Age of Gaming Onset, and Time Spent Gaming

Methods

Participants

A total of 320 participants met inclusion criteria (see Sprong et al.[19]) and volunteered to participate in the study; 304 remained after data cleaning. The average age of the total participants who completed the study was 29.8 years (standard deviation = 9.82), and 178 identified as female (56 percent). The remaining demographic information is shown in Table 1.

Procedure

This study was approved by the research team's institutional review board before participant recruitment. All participants received a recruitment e-mail that provided information about the study, including its purpose, the length of participation in the study, the inclusion criteria (e.g., being aged $\geq$18 years), and information about study discontinuation and reimbursement for participation. The e-mail included the recruitment script and the individuals interested in participating in the study were instructed to click a link at the end of the recruitment script that directed them to the study materials through the *Qualtrics* software program. All participants were debriefed after completion of the assessments and were entered in a prize draw for five $50(US) *Amazon* gift cards.

Methods	Rank
Study registration	0
Study design and Source of data	☆☆
Participants	☆
Sample size	0
Effect of interest	☆
Assumed causal model	☆
Causal assumption	☆☆
Measurement	☆☆
Measurement level	NA
Statistical methods	☆
Sensitivity analyses	NA
Ethical approval	☆

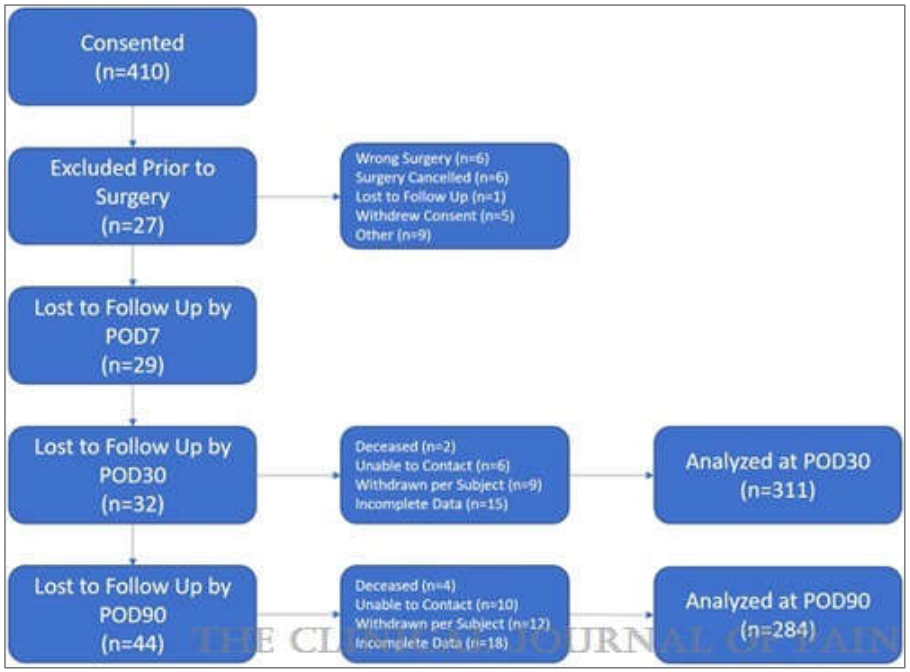
RESULTS

Results		
Participants	17	• Describe baseline characteristics of participants included in mediation analyses • Report the total sample size and number of participants lost during follow-up or with missing data
Outcomes and estimates	18	• Report point estimates and uncertainty estimates for the exposure-mediator and mediator-outcome relationships • If inference concerning the causal relationship of interest is considered feasible given the causal assumptions, report the point estimate and uncertainty estimate
Sensitivity parameters	19	• Report the results from any sensitivity analyses used to assess robustness of the causal or statistical assumptions and the influence of missing data

Effects of Patient and Surgery Characteristics on Persistent Postoperative Pain

A Mediation Analysis

Participant flow through study (POD indicates postoperative day.)



Results	Rank
Baseline Characteristic	☆☆
Total sample size and missing data	☆☆☆
Outcome with Point estimates and uncertainty estimates	☆☆
Sensitivity analyses	NA

Effects of Patient and Surgery Characteristics on Persistent Postoperative Pain

A Mediation Analysis

TABLE 3. Sociodemographic and Pain Characteristics of Study Cohort

	Postoperative Day 90				Postoperative Day 30			
Variable	**Count**	**Percentage**			**Count**	**Percentage**		
Participants	284				311			
Sex								
Female	144	50.7			160	51.4		
Male	140	49.3			151	48.6		
Surgery								
Colorectal	72	25.4			77	24.8		
Spine	21	7.4			23	7.4		
Orthopedics	45	15.8			52	16.7		
Pancreas and biliary	41	14.4			45	14.5		
Thoracic	53	18.7			60	19.3		
Urology	52	18.3			54	17.4		
Variable	Mean	SD	Minimum	Maximum	Mean	SD	Minimum	Maximum
Age (y)	58.7	12.5	22	83	58.8	12.5	22	83
Duration of surgery (min)	190.4	94.8	13	523	189.7	95.9	13	523
Charlson Comorbidity Index	2.4	2.9	0	11	2.5	2.9	0	11
Preoperative mean pain intensity (BPI)	2.3	2.9	0	10	2.4	3	0	10
Catastrophizing (PCS-13)	12.7	11.9	0	52	13.4	12.4	0	52
Worst pain intensity on postoperative day 90 (BPI)	1.9	2.9	0	10	3.20	3.3	0	10

BPI indicates Brief Pain Inventory; PCS, pain catastrophizing scale.

Results	Rank
Baseline Characteristic	☆☆
Total sample size and missing data	☆☆☆
Outcome with Point estimates and uncertainty estimates	☆☆
Sensitivity analyses	NA

Effects of Patient and Surgery Characteristics on Persistent Postoperative Pain

A Mediation Analysis

TABLE 2. Parameter Estimates of Direct and Mediated Modeling Effects on Worst Pain at Postoperative Day 30

Covariate	α_1	*P*	β_1	*P*	θ_1	*P*	θ_2	*P*	*m*	*P*
Age	−0.061	<0.001	−0.008	0.445	−0.058	<0.001	0.415	<0.001	−0.003	0.462
Male	−1.067	0.003	−0.633	0.009	−0.805	0.022	0.415	<0.001	−0.26	0.022
Spine surgery	1.207	0.126	0.26	0.621	1.1	0.147	0.415	<0.001	0.102	0.632
Orthopedic surgery	1.63	0.009	−0.225	0.589	1.723	0.004	0.415	<0.001	−0.097	0.568
Pancreas and biliary surgery	0.255	0.663	1.348	0.001	−0.304	0.597	0.415	<0.001	0.56	0.005
Thoracic surgery	1.954	<0.001	0.867	0.017	1.594	0.003	0.415	<0.001	0.365	0.034
Urologic surgery	0.137	0.811	−0.15	0.696	0.199	0.718	0.415	<0.001	−0.065	0.697
Duration of surgery	0.006	0.001	0.003	0.011	0.005	0.008	0.415	<0.001	0.001	0.038
CCI	−0.111	0.087	−0.073	0.091	−0.081	0.198	0.415	<0.001	−0.03	0.168
Preoperative mean pain intensity (BPI)	−0.003	0.869	0.033	0.004	−0.017	0.319	0.415	<0.001	0.014	0.012
Catastrophizing (PCS-13)	0.183	0.022	0.133	0.012	0.127	0.099	0.415	<0.001	0.056	0.032

Surgical procedure covariates use colorectal surgery as reference class.
BPI indicates Brief Pain Inventory; CCI, Charlson Comorbidity Index; PCS, Pain Catastrophizing Scale.

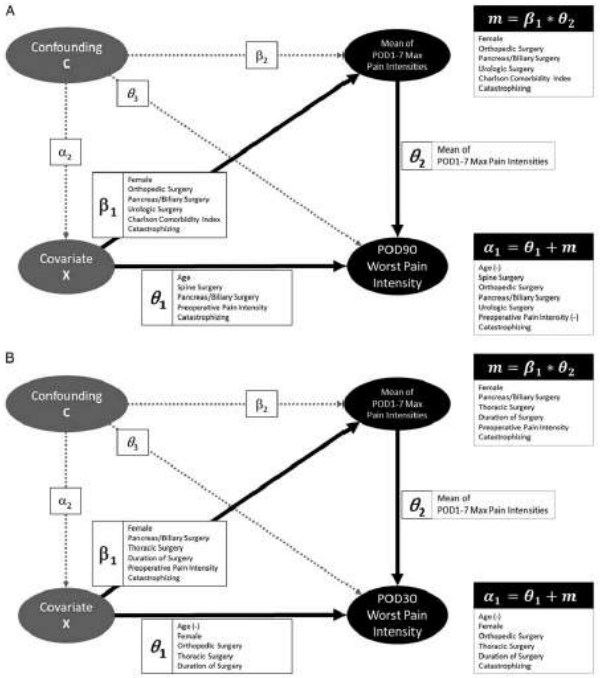


FIGURE 4. Relationships among contributing factors for mediating and direct effects. Features with statistically significant coefficients of the mediating model are listed for each term in the mediating model for postoperative day (POD) 90 (A) and POD 30 (B) outcomes.

Gaming and Gaming Disorder: A Mediation Model Gender, Salience, Age of Gaming Onset, and Time Spent Gaming

TABLE 1. DEMOGRAPHIC INFORMATION OF VIDEO GAMING PARTICIPANTS ($n=304$)

	n	*% of population*
Gender		
Male	126	41
Female	176	59
Ethnicity		
White	190	63
African American	37	12
Asian	23	8
Hispanic/Latino	30	10
Mixed/other	24	8
Hours played/week		
0–5	88	29
6–11	83	27
12–17	57	19
18–23	32	11
≥24	44	14
Reported type of games played[a]		
Role-playing	191	34
First-person shooter	194	34
Real-time strategy	131	22
Turn-base	99	24
Simulation	187	24
Sports	117	15
Facebook	154	15

[a]Multiple individuals self-reported using more than one type of video gaming genre.

Results	Rank
Baseline Characteristic	☆☆
Total sample size and missing data	☆
Outcome with Point estimates and uncertainty estimates	☆☆
Sensitivity analyses	NA

Gaming and Gaming Disorder: A Mediation Model Gender, Salience, Age of Gaming Onset, and Time Spent Gaming

TABLE 2. RESULTS OF MEDIATION ANALYSIS FOR FUNCTIONS OF VIDEO GAME FUNCTIONAL ASSESSMENT-REVISED (INDEPENDENT VARIABLES), GENDER AND TIME SPENT GAMING (MEDIATING VARIABLES), FOR TOTAL INTERNET GAMING DISORDER-20 SCORE (DEPENDENT VARIABLE)

	Mediator variable models							
	Gender				*Time spent gaming*			
	B	SE	t	p	B	SE	t	p
Attention	0.640	0.095	6.72	<0.0001	3.89	0.586	6.63	<0.0001
Escape/avoidance	−2.62	1.29	−2.02	<0.0001	1.77	0.494	3.57	<0.0001
Sensory	−1.17	1.60	−0.733	0.462	3.46	0.554	6.25	<0.0001
Tangible/intangible	−1.84	1.66	−1.11	0.269	3.41	0.595	5.72	<0.0001
	Dependent variable							
	IGD-20—total							
	Gender				*Time spent gaming*			
	R^2	SE	F	p	R^2	SE	F	p
Attention	0.13	14.64	22.6	<0.0001	0.24	13.69	47.6	<0.0001
Escape/avoidance	0.50	11.07	152.2	<0.0001	0.52	10.92	160.8	<0.0001
Sensory	0.24	13.70	47.3	<0.0001	0.33	12.90	72.6	<0.0001
Tangible/intangible	0.19	14.17	34.2	<0.0001	0.26	13.49	53.5	<0.0001

IGD, Internet Gaming Disorder.

Results	Rank
Baseline Characteristic	☆☆
Total sample size and missing data	☆
Outcome with Point estimates and uncertainty estimates	☆☆
Sensitivity analyses	NA

DISCUSSION & OTHER INFORMATION

Discussion		
Limitations	20	• Discuss the limitations of the study including potential sources of bias
Interpretation	21	• Interpret the estimated effects considering the study's magnitude and uncertainty, plausibility of the causal assumptions, limitations, generalizability of the findings, and results from relevant studies
Implications	22	• Discuss the implications of the overall results for clinical practice, policy, and science

Other information		
Funding and role of sponsor	23	• List all sources of funding or sponsorship for mediation analyses and the role of the funders/sponsors in the conduct of the study, writing of the manuscript, and decision to submit the manuscript for publication
Conflicts of interest and financial disclosures	24	• State any conflicts of interest and financial disclosures for all authors
Data and code	25	• Authors are encouraged to provide a statement for sharing data and code for mediation analyses

THANK YOU