Web Material

The Peril of Power: A Tutorial on Using Simulation to Better Understand When and How We Can Estimate Mediation

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Web Appendix: Description of Mediation Estimators

Baron and Kenny, original

The original Baron and Kenny method fits parametric regression generalized linear models for M and for Y (1). Under the assumptions listed in the Introduction section, the natural direct effect can be estimated as the coefficient on the A variable while controlling for the exposure A and covariates W. The natural indirect effect can be estimated by either 1) multiplying the coefficient on M in the outcome model by the coefficient on A in the mediator model or 2) take the difference in the value of the coefficient of A on Y in regressions that include versus exclude M. In the case of linear models, the two approaches will give the same estimate (2). For example, one would implement 1) by fitting the following models:

$$P(M = 1|a, w) = \beta_0 + \beta_1 a + \beta_{\mathbf{2}}\mathbf{w} \quad (1)$$
$$P(Y = 1|m, a, w) = \theta_0 + \theta_1 a + \theta_2 m + \theta_{\mathbf{3}}\mathbf{w}, \quad (2)$$

where the natural direct effect would be given by θ_1 and the natural indirect effect would be given by $\beta_1 \times \theta_2$, and where boldface indicates a vector. To estimate confidence bounds, one can either assume that the direct and indirect effects are normally distributed and calculate the variance using the Taylor series-derived large sample approximation in (3) (power for this version of the estimator can be calculated using the powerMediation R package (4)) or can use quantiles from bootstrapped replicates, which can better account for the asymmetry in the distribution of the indirect effect parameter in small samples (5), though this approach is also problematic (6). More guidance on how to implement this estimation approach can be found in the following tutorials (7, 8) and commented code can be found `https://github.com/kararudolph/MediationPowerTutorial/blob/master/step2_functions.R`.

Baron and Kenny, extension for $A - M$ interaction on Y

The extension of the Baron and Kenny method to allow for interaction between A and M on Y also fits parametric regression generalized linear models for M and for Y (9). For example, one would fit the following models:

$$\begin{aligned} P(M=1|a,w) &= \beta_0 + \beta_1 a + \boldsymbol{\beta_2}\mathbf{w} && (3)\\ P(Y=1|m,a,w) &= \theta_0 + \theta_1 a + \theta_2 m + \theta_3 am + \boldsymbol{\theta_4}\mathbf{w}, && (4)\end{aligned}$$

where the natural direct effect would be given by $\theta_1 + \theta_3(\beta_0 + \beta_2 w)$ and the natural indirect effect would be given by $\beta_1(\theta_2 + \theta_3)$ for binary A, and where boldface indicates a vector. To estimate confidence bounds, one can either assume that the direct and indirect effects are normally distributed and calculate the variance using the delta method given in (9) or can use quantiles from bootstrapped replicates, which can better account for the asymmetry in the distribution of the indirect effect parameter in small samples (5), though this approach is also problematic (6). More guidance on how to implement this estimation approach can be found in the following tutorials (9, 10) and commented code can be found `https://github.com/kararudolph/MediationPowerTutorial/blob/master/step2_functions.R`.

Inverse Odds Ratio Weighting

Inverse odds ratio weighting uses the invariance property of the odds ratio to estimate the relationship between the exposure and the mediator(s), and creates weights that function to block the indirect effect pathway (11). For those in the unexposed/control group, weights equal 1. For those in the exposed/treated group, weights are the inverse odds of exposure given mediators and covariates: e.g., $\frac{P(A=0|M,W)}{P(A=1|M,W)}$ for binary A. Alternatively, weights can be inverse odds ratios, e.g, $\frac{P(A=1|M=0,W)/P(A=0|M=0,W)}{P(A=1|M=1,W)/P(A=0|M=1,W)}$ but these are generally less efficient. The direct effect is calculated via a weighted regression of the outcome on the exposure and covariates, with the inverse odds ratio weight (12). The total effect is calculated using the same regression, but without the weight. The indirect effect is the difference between the total and direct effects. For inference, one can use the nonparametric bootstrap or the variance estimate as defined in the appendix of (11). More guidance on how to implement this estimation approach can be found in the following tutorials (8, 12) and commented code can be found `https://github.com/kararudolph/MediationPowerTutorial/blob/master/step2_functions.R`.

TMLE

We also include a doubly robust targeted minimum loss-based estimator (TMLE) that models the outcome, the exposure, and the mediator. It is unbiased if either the outcome model or both the exposure and mediator models are correctly specified. One can further relax the reliance on correct model specification by incorporating data-adaptive machine learning algorithms in model fitting. TMLE can be used to estimate the natural direct and indirect effects (NDE, NIE) (13) as well as the stochastic direct and indirect effects (SDE, SIE) (14, 15). We focus here on the TMLE for SDE and SIE to illustrate the potential value of choosing an SDE/SIE estimator in scenarios where there is a post-exposure confounder of the mediator-outcome relationship. In scenarios where there is no such post-exposure confounder, the SDE/SIE are aligned with the NDE/NIE. Thus, there may be little practical cost for estimating the SDE/SIE over the NDE/NIE, although the interpretations will differ. For inference, one can use the sample variance of the efficient influence curve for the parameter or if parametric models are used in fitting, one could alternatively use the bootstrap.

Guidance on how to implement this estimation approach can be found in the following tutorial (8) and example paper (16) and commented code can be found `https://github.com/kararudolph/MediationPowerTutorial/blob/master/step2_functions.R`.

Analytic Equation to Detect Any Effect

For comparison purposes, we also include the equation that estimates the power to detect a natural indirect effect under the assumptions listed in the Introduction (17). It is similar to the Baron and Kenny approach described above in that it uses a generalized linear model for Y and is a function of regression coefficient of M when A is also in the model (β_M). The function also requires the variance of M (σ_M^2), the residual variance of Y (σ_e^2), the correlation between A and M (ρ), sample size (n), and the quantile of the standard normal distribution for Type-I error, α (z_α).

$$z_\gamma = \sqrt{\frac{n(\beta_M \sigma_M)^2(1-\rho^2)}{\sigma_e^2}} - z_\alpha,$$

where z_γ is the quantile of the standard normal distribution for Type-II error, γ.

Commented code can be found `https://github.com/kararudolph/MediationPowerTutorial/blob/master/step2_functions.R`. We note that the powerMediation R package can also calculate this (4).

Web Table 1. Table of simulation results for data generating mechanisms (DGMs) 1-5 reflecting observed data O=(W,A,M,Y). BK=Baron and Kenny original estimator; BK Ixn=Baron and Kenny interaction estimator; IORW=inverse odds ratio weighting estimator; TMLE1=targeted minimum loss-based estimator using EIC for variance estimation; TMLE2=TMLE using bootstrapping for variance estimation.

DGM	N	Effect Type	Estimator	Power	Coverage	Effect Size
1	100	direct	BK	0.06	0.95	0.03
			BK Ixn	0.06	0.95	0.03
			IORW	0.03	0.97	0.03
			TMLE1	0.10	0.88	0.03
			TMLE2	0.02	0.98	0.03
		indirect	BK	0.08	0.94	0.03
			BK Ixn	0.08	0.94	0.03
			IORW	0.34	0.67	0.03
			TMLE1	0.86	0.83	0.03
			TMLE2	0.38	0.99	0.03
	1,000	direct	BK	0.22	0.93	0.03
			BK Ixn	0.22	0.94	0.03
			IORW	0.16	0.96	0.03
			TMLE1	0.19	0.95	0.03
			TMLE2	0.18	0.95	0.03
		indirect	BK	0.49	0.94	0.03
			BK Ixn	0.49	0.94	0.03
			IORW	0.87	0.59	0.03
			TMLE1	1.00	0.94	0.03
			TMLE2	1.00	0.94	0.03
	10,000	direct	BK	0.95	0.96	0.03
			BK Ixn	0.95	0.96	0.03
			IORW	0.93	0.97	0.03
			TMLE1	0.90	0.95	0.03
			TMLE2	0.90	0.95	0.03
		indirect	BK	1.00	0.95	0.03
			BK Ixn	1.00	0.95	0.03
			IORW	1.00	0.54	0.03
			TMLE1	1.00	0.94	0.03
			TMLE2	1.00	0.94	0.03
2	100	direct	BK	0.06	0.94	0.03
			BK Ixn	0.05	0.95	0.03
			IORW	0.05	0.93	0.03
			TMLE1	0.11	0.89	0.03
			TMLE2	0.10	0.91	0.03
		indirect	BK	0.004	0.99	0.001
			BK Ixn	0.003	0.99	0.001
			IORW	0.02	0.78	0.001
			TMLE1	0.03	0.84	0.001
			TMLE2	0.02	0.88	0.001
	1,000	direct	BK	0.21	0.94	0.03
			BK Ixn	0.18	0.96	0.03
			IORW	0.22	0.93	0.03
			TMLE1	0.18	0.94	0.03
			TMLE2	0.18	0.94	0.03
		indirect	BK	0.04	0.99	0.001

			BK Ixn	0.03	0.99	0.001
			IORW	0.04	0.90	0.001
			TMLE1	0.09	0.94	0.001
			TMLE2	0.10	0.94	0.001
	10,000	direct	BK	0.94	0.96	0.03
			BK Ixn	0.95	0.95	0.03
			IORW	0.95	0.95	0.03
			TMLE1	0.86	0.95	0.03
			TMLE2	0.86	0.95	0.03
		indirect	BK	0.90	0.95	0.001
			BK Ixn	0.70	0.95	0.001
			IORW	0.09	0.98	0.001
			TMLE1	0.64	0.94	0.001
			TMLE2	0.63	0.94	0.001
3	100	direct	BK	0.09	0.95	0.05
			BK Ixn	0.08	0.93	0.05
			IORW	0.08	0.93	0.05
			TMLE1	0.15	0.88	0.05
			TMLE2	0.11	0.92	0.05
		indirect	BK	0.007	0.99	0.001
			BK Ixn	0.003	0.99	0.001
			IORW	0.027	0.955	0.001
			TMLE1	0.087	0.782	0.001
			TMLE2	0.049	0.872	0.001
	1,000	direct	BK	0.36	0.95	0.05
			BK Ixn	0.40	0.94	0.05
			IORW	0.36	0.94	0.05
			TMLE1	0.30	0.94	0.05
			TMLE2	0.30	0.94	0.05
		indirect	BK	0.027	0.983	0.001
			BK Ixn	0.035	0.973	0.001
			IORW	0.068	0.933	0.001
			TMLE1	0.420	0.948	0.001
			TMLE2	0.419	0.949	0.001
	10,000	direct	BK	1.00	0.95	0.05
			BK Ixn	1.00	0.94	0.05
			IORW	1.00	0.94	0.05
			TMLE1	0.99	0.95	0.05
			TMLE2	0.99	0.95	0.05
		indirect	BK	0.273	0.874	0.001
			BK Ixn	0.268	0.950	0.001
			IORW	0.227	0.890	0.001
			TMLE1	1.000	0.956	0.001
			TMLE2	1.000	0.953	0.001

DGM	N	Effect Type	Estimator	Power	Coverage	Effect Size
4	100	direct	BK	0.86	0.93	0.30
			BK Ixn	0.84	0.96	0.30
			IORW	0.81	0.95	0.30
			TMLE1	0.80	0.90	0.30
			TMLE2	0.72	0.94	0.30
		indirect	BK	0.06	0.96	0.02
			BK Ixn	0.056	0.98	0.02
			IORW	0.08	0.97	0.02
			TMLE1	0.24	0.91	0.02
			TMLE2	0.13	0.95	0.02
	1,000	direct	BK	1.00	0.94	0.30
			BK Ixn	1.00	0.94	0.30
			IORW	1.00	0.96	0.30
			TMLE1	1.00	0.95	0.30
			TMLE2	1.00	0.95	0.30
		indirect	BK	0.96	0.96	0.02
			BK Ixn	0.959	0.95	0.02
			IORW	0.65	0.97	0.02
			TMLE1	0.96	0.94	0.02
			TMLE2	0.96	0.94	0.02
	10,000	direct	BK	1.00	0.94	0.30
			BK Ixn	1.00	0.95	0.30
			IORW	1.00	0.96	0.30
			TMLE1	1.00	0.96	0.30
			TMLE2	1.00	0.95	0.30
		indirect	BK	1.00	0.95	0.02
			BK Ixn	1.000	0.95	0.020
			IORW	1.00	0.97	0.02
			TMLE1	1.00	0.96	0.02
			TMLE2	1.00	0.96	0.02
5	100	direct	BK	0.93	0.91	0.33
			BK Ixn	0.89	0.92	0.33
			IORW	0.86	0.93	0.33
			TMLE1	0.84	0.67	0.33
			TMLE2	0.39	0.94	0.33
		indirect	BK	0.164	0.915	0.035
			BK Ixn	0.168	0.943	0.035
			IORW	0.296	0.812	0.035
			TMLE1	0.421	0.741	0.035
			TMLE2	0.038	0.960	0.035

DGM	N	Effect Type	Estimator	Power	Coverage	Effect Size
5	1,000	direct	BK	1.00	0.92	0.33
			BK Ixn	1.00	0.94	0.33
			IORW	1.00	0.94	0.33
			TMLE1	1.00	0.94	0.33
			TMLE2	1.00	0.94	0.33
		indirect	BK	0.971	0.871	0.035
			BK Ixn	0.976	0.956	0.035
			IORW	0.975	0.830	0.035
			TMLE1	1.00	0.951	0.035
			TMLE2	1.00	0.948	0.035
	10,000	direct	BK	1.00	0.90	0.33
			BK Ixn	1.00	0.94	0.33
			IORW	1.00	0.91	0.33
			TMLE1	1.00	0.94	0.33
			TMLE2	1.00	0.94	0.33
		indirect	BK	1.00	0.23	0.035
			BK Ixn	1.00	0.95	0.035
			IORW	1.00	0.80	0.035
			TMLE1	1.00	0.95	0.035
			TMLE2	1.00	0.94	0.035

Web Table 2. Table of simulation results for data generating mechanisms (DGMs) 6-13 reflecting observed data O=(W,A,Z,M,Y). BK1=Baron and Kenny estimator omitting Z; BK2=Baron and Kenny estimator controlling for Z; BK Ixn1 = Baron and Kenny interaction estimator omitting Z; BK Ixn2 = Baron and Kenny interaction estimator controlling for Z; IORW1=inverse odds ratio weighting estimator omitting Z; IORW2=inverse odds ratio weighting estimator controlling for Z; TMLE1=targeted minimum loss-based estimator using EIC for variance estimation; TMLE2=TMLE using bootstrapping for variance estimation.

DGM	N	Effect Type	Estimator	Power	Coverage	Effect Size
6	100	direct	BK1	0.05	0.95	0.03
			BK2	0.05	0.95	0.03
			BK Ixn1	0.07	0.94	0.03
			BK Ixn2	0.06	0.94	0.03
			IORW1	0.05	0.93	0.03
			IORW2	0.04	0.92	0.03
			TMLE1	0.13	0.88	0.03
			TMLE2	0.10	0.92	0.03
		indirect	BK1	0.001	0.997	0.002
			BK2	0.001	1.000	0.002
			BK Ixn1	0.000	0.998	0.002
			BK Ixn2	0.000	0.997	0.002
			IORW1	0.024	0.785	0.002
			IORW2	0.026	0.799	0.002
			TMLE1	0.033	0.880	0.002
			TMLE2	0.023	0.950	0.002
	1,000	direct	BK1	0.23	0.96	0.03
			BK2	0.20	0.95	0.03
			BK Ixn1	0.40	0.95	0.03
			BK Ixn2	0.33	0.95	0.03
			IORW1	0.25	0.95	0.03
			IORW2	0.21	0.94	0.03
			TMLE1	0.22	0.93	0.03
			TMLE2	0.21	0.93	0.03
		indirect	BK1	0.134	0.944	0.002
			BK2	0.048	0.887	0.002
			BK Ixn1	0.033	0.941	0.002
			BK Ixn2	0.027	0.941	0.002
			IORW1	0.085	0.932	0.002
			IORW2	0.048	0.936	0.002
			TMLE1	0.122	0.938	0.002
			TMLE2	0.124	0.937	0.002
	10,000	direct	BK1	0.99	0.96	0.03
			BK2	0.97	0.95	0.03
			BK Ixn1	1.00	0.96	0.03
			BK Ixn2	1.00	0.93	0.03
			IORW1	1.00	0.95	0.03
			IORW2	0.99	0.93	0.03
			TMLE1	0.92	0.96	0.03
			TMLE2	0.92	0.96	0.03

DGM	N	Effect Type	Estimator	Power	Coverage	Effect Size
6	10,0000	indirect	BK1	0.997	0.950	0.002
			BK2	0.916	0.488	0.002
			BK Ixn1	0.904	0.709	0.002
			BK Ixn2	0.816	0.592	0.002
			IORW1	0.249	0.970	0.002
			IORW2	0.078	0.992	0.002
			TMLE1	0.830	0.944	0.002
			TMLE2	0.830	0.947	0.002
7	100	direct	BK1	0.06	0.96	0.03
			BK2	0.04	0.95	0.03
			BK Ixn1	0.07	0.94	0.03
			BK Ixn2	0.03	0.92	0.03
			IORW1	0.06	0.94	0.03
			IORW2	0.01	0.74	0.03
			TMLE1	0.12	0.88	0.03
			TMLE2	0.09	0.93	0.03
		indirect	BK1	0.007	0.986	0.002
			BK2	0.001	0.999	0.002
			BK Ixn1	0.001	0.997	0.002
			BK Ixn2	0.001	0.997	0.002
			IORW1	0.012	0.822	0.002
			IORW2	0.056	0.816	0.002
			TMLE1	0.031	0.914	0.002
			TMLE2	0.012	0.976	0.002
	1,000	direct	BK1	0.17	0.96	0.03
			BK2	0.04	0.92	0.03
			BK Ixn1	0.27	0.94	0.03
			BK Ixn2	0.06	0.89	0.03
			IORW1	0.19	0.95	0.03
			IORW2	0.04	0.88	0.03
			TMLE1	0.16	0.94	0.03
			TMLE2	0.15	0.94	0.03
		indirect	BK1	0.076	0.941	0.002
			BK2	0.008	0.960	0.002
			BK Ixn1	0.002	0.984	0.002
			BK Ixn2	0.002	0.985	0.002
			IORW1	0.057	0.925	0.002
			IORW2	0.031	0.878	0.002
			TMLE1	0.042	0.938	0.002
			TMLE2	0.045	0.934	0.002
	10,000	direct	BK1	0.94	0.95	0.03
			BK2	0.15	0.57	0.03
			BK Ixn1	0.99	0.94	0.03
			BK Ixn2	0.25	0.33	0.03
			IORW1	0.95	0.95	0.03
			IORW2	0.14	0.57	0.03
			TMLE1	0.80	0.95	0.03
			TMLE2	0.80	0.95	0.03

DGM	N	Effect Type	Estimator	Power	Coverage	Effect Size
7	10,000	indirect	BK1	0.362	0.930	0.002
			BK2	0.119	0.111	0.002
			BK Ixn1	0.193	0.231	0.002
			BK Ixn2	0.108	0.154	0.002
			IORW1	0.138	0.962	0.002
			IORW2	0.026	0.964	0.002
			TMLE1	0.119	0.952	0.002
			TMLE2	0.127	0.952	0.002
8	100	direct	BK1	0.09	0.97	0.05
			BK2	0.07	0.97	0.05
			BK Ixn1	0.12	0.94	0.05
			BK Ixn2	0.09	0.95	0.05
			IORW1	0.08	0.92	0.05
			IORW2	0.06	0.89	0.05
			TMLE1	0.23	0.87	0.05
			TMLE2	0.13	0.94	0.05
		indirect	BK1	0.004	0.997	0.001
			BK2	0.005	0.996	0.001
			BK Ixn1	0.006	0.993	0.001
			BK Ixn2	0.005	0.993	0.001
			IORW1	0.019	0.964	0.001
			IORW2	0.019	0.971	0.001
			TMLE1	0.064	0.762	0.001
			TMLE2	0.015	0.890	0.001
	1,000	direct	BK1	0.62	0.96	0.05
			BK2	0.56	0.96	0.05
			BK Ixn1	0.71	0.95	0.05
			BK Ixn2	0.66	0.95	0.05
			IORW1	0.69	0.95	0.05
			IORW2	0.62	0.94	0.05
			TMLE1	0.51	0.94	0.05
			TMLE2	0.50	0.93	0.05
		indirect	BK1	0.046	0.966	0.001
			BK2	0.040	0.965	0.001
			BK Ixn1	0.040	0.970	0.001
			BK Ixn2	0.046	0.970	0.001
			IORW1	0.091	0.925	0.001
			IORW2	0.068	0.942	0.001
			TMLE1	0.556	0.935	0.001
			TMLE2	0.554	0.932	0.001
	10,000	direct	BK1	1.00	0.95	0.05
			BK2	1.00	0.90	0.05
			BK Ixn1	1.00	0.94	0.05
			BK Ixn2	1.00	0.92	0.05
			IORW1	1.00	0.91	0.05
			IORW2	1.00	0.81	0.05
			TMLE1	1.00	0.95	0.05
			TMLE2	1.00	0.95	0.05

DGM	N	Effect Type	Estimator	Power	Coverage	Effect Size
8	10,000	indirect	BK1	0.312	0.847	0.001
8	10,000	indirect	BK2	0.272	0.824	0.001
8	10,000	indirect	BK Ixn1	0.275	0.936	0.001
8	10,000	indirect	BK Ixn2	0.276	0.939	0.001
8	10,000	indirect	IORW1	0.319	0.863	0.001
8	10,000	indirect	IORW2	0.248	0.894	0.001
8	10,000	indirect	TMLE1	1.000	0.950	0.001
8	10,000	indirect	TMLE2	1.000	0.950	0.001
9	100	direct	BK1	0.08	0.95	0.05
9	100	direct	BK2	0.03	0.96	0.05
9	100	direct	BK Ixn1	0.10	0.92	0.05
9	100	direct	BK Ixn2	0.05	0.91	0.05
9	100	direct	IORW1	0.09	0.90	0.05
9	100	direct	IORW2	0.01	0.63	0.05
9	100	direct	TMLE1	0.24	0.84	0.05
9	100	direct	TMLE2	0.12	0.93	0.05
9	100	indirect	BK1	0.002	0.998	0.002
9	100	indirect	BK2	0.001	0.996	0.002
9	100	indirect	BK Ixn1	0.001	0.998	0.002
9	100	indirect	BK Ixn2	0.002	0.998	0.002
9	100	indirect	IORW1	0.029	0.959	0.002
9	100	indirect	IORW2	0.044	0.956	0.002
9	100	indirect	TMLE1	0.077	0.791	0.002
9	100	indirect	TMLE2	0.018	0.914	0.002
9	1,000	direct	BK1	0.62	0.97	0.05
9	1,000	direct	BK2	0.16	0.90	0.05
9	1,000	direct	BK Ixn1	0.70	0.95	0.05
9	1,000	direct	BK Ixn2	0.23	0.89	0.05
9	1,000	direct	IORW1	0.67	0.94	0.05
9	1,000	direct	IORW2	0.12	0.81	0.05
9	1,000	direct	TMLE1	0.48	0.94	0.05
9	1,000	direct	TMLE2	0.47	0.94	0.05
9	1,000	indirect	BK1	0.046	0.924	0.002
9	1,000	indirect	BK2	0.025	0.927	0.002
9	1,000	indirect	BK Ixn1	0.026	0.963	0.002
9	1,000	indirect	BK Ixn2	0.025	0.963	0.002
9	1,000	indirect	IORW1	0.112	0.920	0.002
9	1,000	indirect	IORW2	0.058	0.934	0.002
9	1,000	indirect	TMLE1	0.594	0.938	0.002
9	1,000	indirect	TMLE2	0.590	0.940	0.002
9	10,000	direct	BK1	1.00	0.97	0.05
9	10,000	direct	BK2	0.95	0.35	0.05
9	10,000	direct	BK Ixn1	1.00	0.96	0.05
9	10,000	direct	BK Ixn2	0.98	0.42	0.05
9	10,000	direct	IORW1	1.00	0.93	0.05
9	10,000	direct	IORW2	0.94	0.28	0.05
9	10,000	direct	TMLE1	1.00	0.96	0.05
9	10,000	direct	TMLE2	1.00	0.96	0.05

DGM	N	Effect Type	Estimator	Power	Coverage	Effect Size
9	10,000	indirect	BK1	0.561	0.724	0.002
			BK2	0.171	0.552	0.002
			BK Ixn1	0.168	0.878	0.002
			BK Ixn2	0.169	0.875	0.002
			IORW1	0.390	0.909	0.002
			IORW2	0.064	0.953	0.002
			TMLE1	1.000	0.943	0.002
			TMLE2	1.000	0.939	0.002
10	100	direct	BK1	0.32	0.95	0.13
			BK2	0.23	0.93	0.13
			BK Ixn1	0.30	0.93	0.13
			BK Ixn2	0.20	0.92	0.13
			IORW1	0.28	0.95	0.13
			IORW2	0.20	0.92	0.13
			TMLE1	0.41	0.89	0.13
			TMLE2	0.35	0.94	0.13
		indirect	BK1	0.13	0.94	0.02
			BK2	0.07	0.91	0.02
			BK Ixn1	0.07	0.96	0.02
			BK Ixn2	0.06	0.95	0.02
			IORW1	0.17	0.93	0.02
			IORW2	0.08	0.94	0.02
			TMLE1	0.23	0.91	0.02
			TMLE2	0.17	0.94	0.02
	1,000	direct	BK1	1.00	0.94	0.13
			BK2	0.97	0.77	0.13
			BK Ixn1	1.00	0.94	0.13
			BK Ixn2	0.97	0.81	0.13
			IORW1	1.00	0.94	0.13
			IORW2	0.99	0.77	0.13
			TMLE1	0.98	0.95	0.13
			TMLE2	0.98	0.96	0.13
		indirect	BK1	0.98	0.92	0.02
			BK2	0.94	0.87	0.02
			BK Ixn1	0.94	0.95	0.02
			BK Ixn2	0.93	0.88	0.02
			IORW1	0.92	0.88	0.02
			IORW2	0.61	0.99	0.02
			TMLE1	0.99	0.96	0.02
			TMLE2	0.99	0.96	0.02
	10,000	direct	BK1	1.00	0.88	0.13
			BK2	1.00	0.04	0.13
			BK Ixn1	1.00	0.87	0.13
			BK Ixn2	1.00	0.04	0.13
			IORW1	1.00	0.89	0.13
			IORW2	1.00	0.04	0.13
			TMLE1	1.00	0.94	0.13
			TMLE2	1.00	0.95	0.13

DGM	N	Effect Type	Estimator	Power	Coverage	Effect Size
10	10,000	indirect	BK1	1.00	0.43	0.02
10	10,000	indirect	BK2	1.00	0.45	0.02
10	10,000	indirect	BK Ixn1	1.00	0.96	0.03
10	10,000	indirect	BK Ixn2	1.00	0.42	0.03
10	10,000	indirect	IORW1	1.00	0.57	0.02
10	10,000	indirect	IORW2	1.00	1.00	0.02
10	10,000	indirect	TMLE1	1.00	0.95	0.02
10	10,000	indirect	TMLE2	1.00	0.95	0.02
11	100	direct	BK1	0.93	0.89	0.33
11	100	direct	BK2	0.34	0.53	0.33
11	100	direct	BK Ixn1	0.91	0.94	0.33
11	100	direct	BK Ixn2	0.22	0.68	0.33
11	100	direct	IORW1	0.87	0.93	0.33
11	100	direct	IORW2	0.13	0.64	0.33
11	100	direct	TMLE1	0.87	0.88	0.33
11	100	direct	TMLE2	0.57	0.97	0.33
11	100	indirect	BK1	0.57	0.95	0.07
11	100	indirect	BK2	0.09	0.81	0.07
11	100	indirect	BK Ixn1	0.07	0.82	0.07
11	100	indirect	BK Ixn2	0.06	0.79	0.07
11	100	indirect	IORW1	0.48	0.93	0.07
11	100	indirect	IORW2	0.10	0.94	0.07
11	100	indirect	TMLE1	0.57	0.91	0.07
11	100	indirect	TMLE2	0.08	0.99	0.07
11	1,000	direct	BK1	1.00	0.89	0.33
11	1,000	direct	BK2	0.99	0.00	0.33
11	1,000	direct	BK Ixn1	1.00	0.94	0.33
11	1,000	direct	BK Ixn2	0.98	0.00	0.33
11	1,000	direct	IORW1	1.00	0.94	0.33
11	1,000	direct	IORW2	0.98	0.01	0.33
11	1,000	direct	TMLE1	1.00	0.96	0.33
11	1,000	direct	TMLE2	1.00	0.96	0.33
11	1,000	indirect	BK1	1.00	0.92	0.07
11	1,000	indirect	BK2	0.72	0.13	0.07
11	1,000	indirect	BK Ixn1	0.77	0.29	0.07
11	1,000	indirect	BK Ixn2	0.77	0.18	0.07
11	1,000	indirect	IORW1	1.00	0.86	0.07
11	1,000	indirect	IORW2	0.23	1.00	0.07
11	1,000	indirect	TMLE1	1.00	0.96	0.07
11	1,000	indirect	TMLE2	1.00	0.95	0.07
11	10,000	direct	BK1	1.00	0.71	0.33
11	10,000	direct	BK2	1.00	0.00	0.33
11	10,000	direct	BK Ixn1	1.00	0.78	0.33
11	10,000	direct	BK Ixn2	1.00	0.00	0.33
11	10,000	direct	IORW1	1.00	0.78	0.33
11	10,000	direct	IORW2	1.00	0.00	0.33
11	10,000	direct	TMLE1	1.00	0.96	0.33
11	10,000	direct	TMLE2	1.00	0.95	0.33

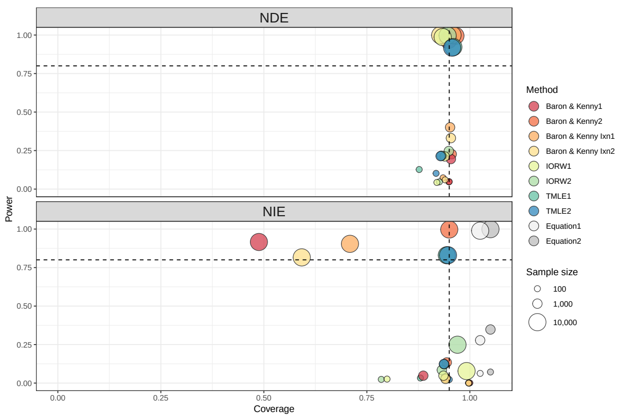
DGM	N	Effect Type	Estimator	Power	Coverage	Effect Size
11	10,000	indirect	BK1	1.00	0.44	0.07
11	10,000	indirect	BK2	1.00	0.00	0.07
11	10,000	indirect	BK Ixn1	1.00	0.00	0.07
11	10,000	indirect	BK Ixn2	1.00	0.00	0.07
11	10,000	indirect	IORW1	1.00	0.34	0.07
11	10,000	indirect	IORW2	0.95	1.00	0.07
11	10,000	indirect	TMLE1	1.00	0.96	0.07
11	10,000	indirect	TMLE2	1.00	0.95	0.07
12	100	direct	BK1	0.46	0.94	0.15
12	100	direct	BK2	0.41	0.94	0.15
12	100	direct	BK Ixn1	0.41	0.95	0.15
12	100	direct	BK Ixn2	0.38	0.94	0.15
12	100	direct	IORW1	0.38	0.95	0.15
12	100	direct	IORW2	0.32	0.92	0.15
12	100	direct	TMLE1	0.52	0.89	0.15
12	100	direct	TMLE2	0.41	0.97	0.15
12	100	indirect	BK1	0.18	0.92	0.04
12	100	indirect	BK2	0.14	0.90	0.04
12	100	indirect	BK Ixn1	0.13	0.94	0.04
12	100	indirect	BK Ixn2	0.13	0.93	0.04
12	100	indirect	IORW1	0.29	0.81	0.04
12	100	indirect	IORW2	0.22	0.85	0.04
12	100	indirect	TMLE1	0.55	0.90	0.04
12	100	indirect	TMLE2	0.26	0.97	0.04
12	1,000	direct	BK1	1.00	0.95	0.15
12	1,000	direct	BK2	1.00	0.91	0.15
12	1,000	direct	BK Ixn1	1.00	0.95	0.15
12	1,000	direct	BK Ixn2	1.00	0.91	0.15
12	1,000	direct	IORW1	1.00	0.94	0.15
12	1,000	direct	IORW2	1.00	0.86	0.15
12	1,000	direct	TMLE1	1.00	0.95	0.15
12	1,000	direct	TMLE2	1.00	0.96	0.15
12	1,000	indirect	BK1	0.98	0.86	0.04
12	1,000	indirect	BK2	0.94	0.67	0.04
12	1,000	indirect	BK Ixn1	0.94	0.92	0.04
12	1,000	indirect	BK Ixn2	0.94	0.89	0.04
12	1,000	indirect	IORW1	0.99	0.80	0.04
12	1,000	indirect	IORW2	0.95	0.79	0.04
12	1,000	indirect	TMLE1	1.00	0.96	0.04
12	1,000	indirect	TMLE2	1.00	0.95	0.04
12	10,000	direct	BK1	1.00	0.93	0.15
12	10,000	direct	BK2	1.00	0.65	0.15
12	10,000	direct	BK Ixn1	1.00	0.84	0.15
12	10,000	direct	BK Ixn2	1.00	0.58	0.15
12	10,000	direct	IORW1	1.00	0.77	0.15
12	10,000	direct	IORW2	1.00	0.22	0.15
12	10,000	direct	TMLE1	1.00	0.95	0.15
12	10,000	direct	TMLE2	1.00	0.95	0.15

DGM	N	Effect Type	Estimator	Power	Coverage	Effect Size
12	10,000	indirect	BK1	1.00	0.38	0.04
			BK2	1.00	0.01	0.04
			BK Ixn1	1.00	0.78	0.04
			BK Ixn2	1.00	0.59	0.04
			IORW1	1.00	0.69	0.04
			IORW2	1.00	0.63	0.04
			TMLE1	1.00	0.95	0.04
			TMLE2	1.00	0.94	0.04
13	100	direct	BK1	0.98	0.91	0.36
			BK2	0.63	0.73	0.36
			BK Ixn1	0.95	0.95	0.36
			BK Ixn2	0.51	0.82	0.36
			IORW1	0.94	0.95	0.36
			IORW2	0.30	0.74	0.36
			TMLE1	0.90	0.85	0.36
			TMLE2	0.45	0.98	0.36
		indirect	BK1	0.52	0.91	0.08
			BK2	0.09	0.70	0.08
			BK Ixn1	0.09	0.81	0.08
			BK Ixn2	0.07	0.78	0.08
			IORW1	0.53	0.83	0.08
			IORW2	0.12	0.90	0.08
			TMLE1	0.62	0.86	0.08
			TMLE2	0.03	0.99	0.08
	1,000	direct	BK1	1.00	0.90	0.36
			BK2	1.00	0.11	0.36
			BK Ixn1	1.00	0.93	0.36
			BK Ixn2	1.00	0.22	0.36
			IORW1	1.00	0.92	0.36
			IORW2	1.00	0.22	0.36
			TMLE1	1.00	0.96	0.36
			TMLE2	1.00	0.95	0.36
		indirect	BK1	1.00	0.85	0.08
			BK2	0.79	0.02	0.08
			BK Ixn1	0.79	0.24	0.08
			BK Ixn2	0.79	0.18	0.08
			IORW1	1.00	0.85	0.08
			IORW2	0.45	0.64	0.08
			TMLE1	1.00	0.94	0.08
			TMLE2	1.00	0.94	0.08
	10,000	direct	BK1	1.00	0.87	0.36
			BK2	1.00	0.00	0.36
			BK Ixn1	1.00	0.76	0.36
			BK Ixn2	1.00	0.00	0.36
			IORW1	1.00	0.70	0.36
			IORW2	1.00	0.00	0.36
			TMLE1	1.00	0.96	0.36
			TMLE2	1.00	0.95	0.36
		indirect	BK1	1.00	0.22	0.08
			BK2	1.00	0.00	0.08
			BK Ixn1	1.00	0.00	0.08
			BK Ixn2	1.00	0.00	0.08

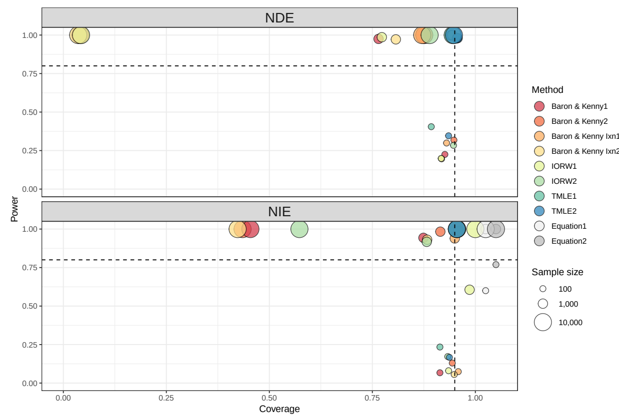
			IORW1	1.00	0.52	0.08
			IORW2	1.00	0.01	0.08
			TMLE1	1.00	0.94	0.08
			TMLE2	1.00	0.94	0.08

Web Figure 1. Power and coverage of natural direct and indirect effects by sample size, estimation method, and effect size for DGMs reflecting a weak effect of Z and no $A - M$ interaction.

a. DGM 6: Small effect size.



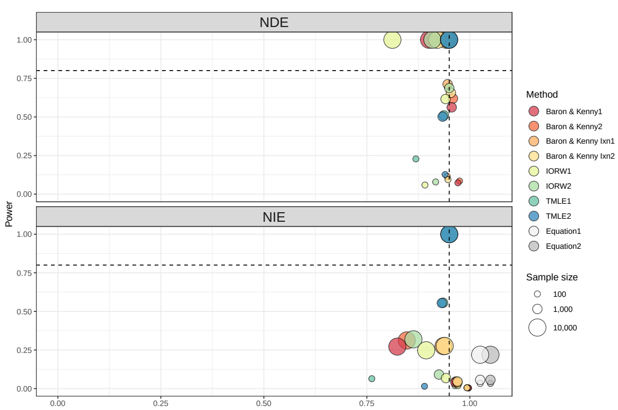
b. DGM 10: Large effect size.



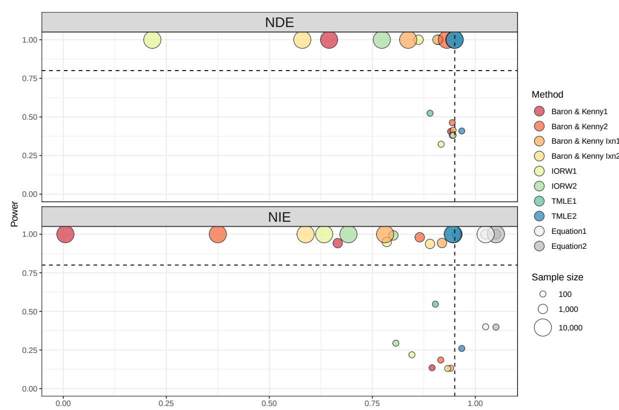
Note: Baron & Kenny corresponds to the original version of the estimator. Baron & Kenny Ixn corresponds to the extension that allows for $A - M$ interaction. Baron & Kenny1, IORW1, and Equation1 correspond to omitting Z. Baron & Kenny2, IORW2, and Equation2 correspond to controlling for Z. TMLE1 corresponds to variance estimated using the EIC and TMLE2 represents variance calculated using the bootstrap.

Web Figure 2. Power and coverage of natural direct and indirect effects by sample size, estimation method, and effect size for DGMs reflecting a weak effect of Z and $A - M$ interaction.

c. DGM 8: Small effect size.



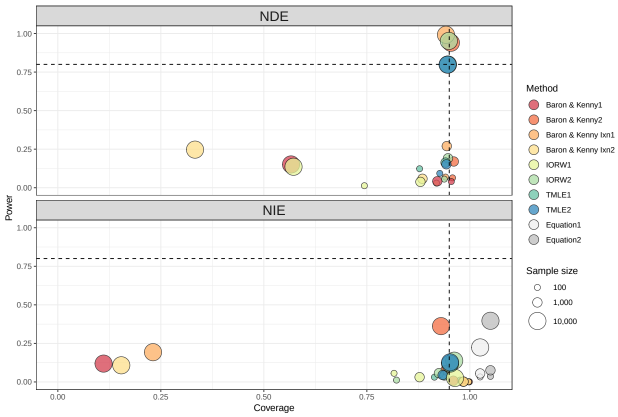
d. DGM 12: Large effect size.



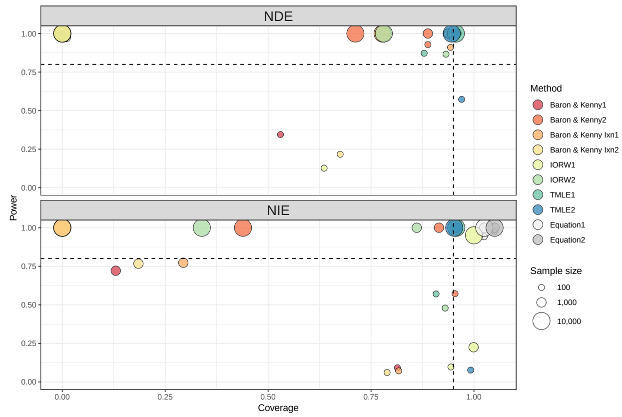
Note: Baron & Kenny corresponds to the original version of the estimator. Baron & Kenny Ixn corresponds to the extension that allows for $A - M$ interaction. Baron & Kenny1, IORW1, and Equation1 correspond to omitting Z. Baron & Kenny2, IORW2, and Equation2 correspond to controlling for Z. TMLE1 corresponds to variance estimated using the EIC and TMLE2 represents variance calculated using the bootstrap.

Web Figure 3. Power and coverage of natural direct and indirect effects by sample size, estimation method, and effect size for DGMs reflecting a strong effect of Z and no $A-M$ interaction.

e. DGM 7: Small effect size.



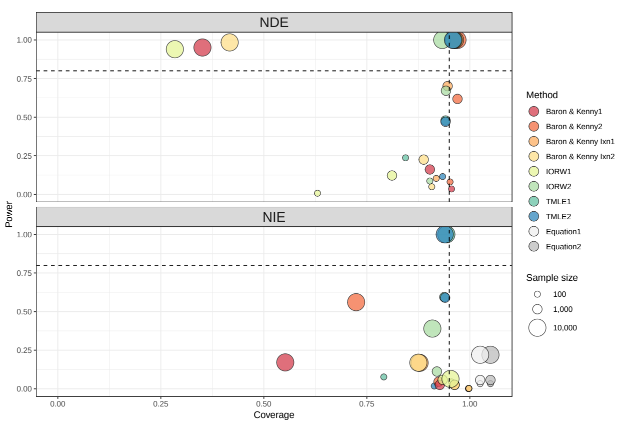
f. DGM 11: Large effect size.



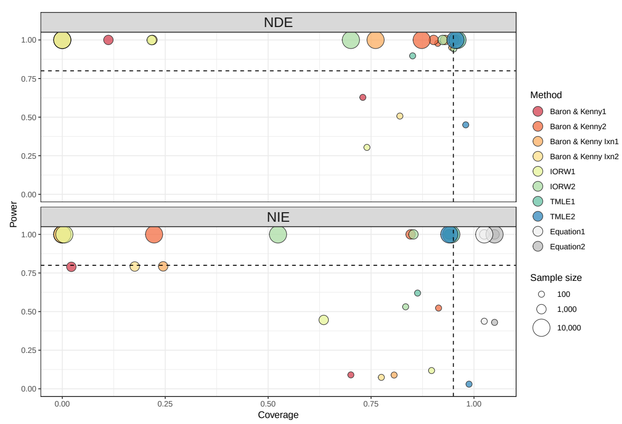
Note: Baron & Kenny corresponds to the original version of the estimator. Baron & Kenny Ixn corresponds to the extension that allows for $A-M$ interaction. Baron & Kenny1, IORW1, and Equation1 correspond to omitting Z. Baron & Kenny2, IORW2, and Equation2 correspond to controlling for Z. TMLE1 corresponds to variance estimated using the EIC and TMLE2 represents variance calculated using the bootstrap.

Web Figure 4. Power and coverage of natural direct and indirect effects by sample size, estimation method, and effect size for DGMs reflecting a strong effect of Z and $A-M$ interaction.

g. DGM 9: Small effect size.



h. DGM 13: Large effect size.



Note: Baron & Kenny corresponds to the original version of the estimator. Baron & Kenny Ixn corresponds to the extension that allows for $A-M$ interaction. Baron & Kenny1, IORW1, and Equation1 correspond to omitting Z. Baron & Kenny2, IORW2, and Equation2 correspond to controlling for Z. TMLE1 corresponds to variance estimated using the EIC and TMLE2 represents variance calculated using the bootstrap.

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