was absent, however, for most of these relationships.

The present study, though hampered by a small sample size, identified selected variables as being candidate confounders and mediators in studies of sperm concentration and disease risk.

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Controlled Mediation as a Generalization of Interventional Mediation

To the Editor:

Moreno-Betancur and Carlin contrast interventional with natural mediation excellently.[1] They did not discuss the policy-relevant controlled mediation.[2] I illustrate how controlled is a generalization of interventional mediation, at least in simple settings, using Moreno-Betancur and Carlin's directed acyclic graph (DAG) in part A of their Figure that contains an outcome (Y), an exposure (A), and a mediator (M). Assumptions are no uncontrolled confounding of exposure and outcome, mediator and outcome, and exposure and mediator.[3] With a binary exposure, the interventional effects are estimated from a hypothetical three-arm trial with exposure, control, and exposure then mediator intervention arms. The interventional effects arising are defined as potential outcomes weighted by the distribution of the mediator. The total effect is $\sum_m E(Y_{1m}) * P(M_1 = m) - \sum_m E(Y_{0m}) * P(M_0 = m)$; the direct effect is $\sum_m E(Y_{1m}) * P(M_0 = m) - \sum_m E(Y_{0m}) * P(M_0 = m)$; and the indirect effect is $\sum_m E(Y_{1m}) * \mathrm{P}(M_1 = m) - \sum_m E(Y_{1m}) * P(M_0 = m)$. The mediator intervention in the third arm changes the distribution to the control group's.[1] Although the controlled direct effect is defined at the individual level,[4] the group-level interventional effect has been defined as a controlled direct effect under a stochastic intervention.[3] Generalizing to include mediator change in the control group means adding a fourth arm to the trial, control then mediator intervention. The total effect is the same, but now the direct effect is $\sum_m E(Y_{1m}) * P(M_i = m) - \sum_m E(Y_{0m}) * P(M_i = m)$, and the indirect effects are $\sum_m E(Y_{1m}) * P(M_1 = m) - \sum_M E(Y_{1m}) * P(M_i = m)$ and $\sum_m E(Y_{0m}) * P(M_0 = m) - \sum_m E(Y_{0m}) * P(M_i = m)$ where M_i is the mediator distribution of the mediator intervention. There are indirect effects for the exposed and control groups. Their difference is the overall indirect effect which sums with the direct effect to the total effect. The direct effect measures the effect of A on Y not through M, whereas the overall indirect effect measures the effect of A on Y through M after mediation intervention. The two group-specific indirect effects compare the impact of intervening on M within each group. In contrast, the controlled indirect effect is usually not estimated, as its sum with the direct effect does not equal the total effect. Interaction of exposure with mediator on the outcome means the controlled direct effect can differ from the total effect, even when the exposure has no effect on the mediator.[4,5] In other words, the difference is owing to interaction and not mediation. From an interventional perspective, this is an important result as mediator interventions may benefit health even when there is no relationship between exposure and mediator.[6]

In social epidemiology, for example, there is debate about the relative impact of population and targeted health behavior (smoking in the example below) interventions on socioeconomic health inequalities.[7] Adapting a toy dataset,[8] three mediation intervention scenarios are shown in the Table. The first changes the smoking rate of those disadvantaged to that of those advantaged, the next decreases the rate in both groups to 20%, and the third eliminates smoking. The outcome is 10-year probability of death. The direct effects show that eliminating differences in smoking do not fully

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TABLE. Differing Interventions on Smoking and Direct and Indirect Effects on Socioeconomic Inequalities

	To That of Control Group		Lowered to Same Level		Smoke Free	
Trial arm	**Probability of death**	**Probability of smoking**	**Probability of death**	**Probability of smoking**	**Probability of death**	**Probability of smoking**
1) Advantage, no intervention on smoking	0.48	0.4	0.48	0.4	0.48	0.4
2) Disadvantage, no intervention on smoking	0.736	0.6	0.736	0.6	0.736	0.6
3) Advantage, intervention on smoking	0.48	0.4	0.34	0.2	0.2	0
4) Disadvantage, intervention on smoking	0.624	0.4	0.512	0.2	0.4	0
			Effects (probability of death)			
Total effect (=Arms 2–1)		0.256		0.256		0.256
Direct effect (=Arms 4–3)		0.144		0.172		0.2
Indirect effect, advantage (=Arms 3–1)		0		0.14		0.28
Indirect effect, disadvantage (=Arms 4–2)		0.112		0.224		0.336
Overall indirect effect (=IE,A1–IE, A0)		0.112		0.084		0.056

Not real data.

explain away the socioeconomic differences and that the more drastic cuts in smoking have less impact on inequality (at least on the difference scale), while decreasing the death risk the most. Why is this? Although intervention on smoking has a greater impact on the disadvantaged's death rate, the advantaged also see reductions as their smoking rate falls and so the disadvantaged's relative gain is lessened.

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