Dear Editor,

Moreno-Betancur & Carlin contrast interventional with natural mediation excellently[1]. They did not discuss the policy relevant controlled mediation[2]. I illustrate how controlled is a generalisation of interventional mediation, at least in simple settings, using Moreno-Betancur & Carlin's 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 $\sum_m E(Y_{1m})*P(M_1=m) - \sum_m E(Y_{1m}) * P(M_0= m)$. 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 group. 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, while 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 is not 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 due 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 behaviour (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 explain away the socio-economic 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? While 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.

References

1. Moreno-Betancur M, Carlin JB. Understanding Interventional Effects: A More Natural Approach to Mediation Analysis? *Epidemiology* 2018;29(5):614-617.
2. Naimi AI, Kaufman JS, MacLehose RF. Mediation misgivings: ambiguous clinical and public health interpretations of natural direct and indirect effects. *International Journal of Epidemiology* 2014;43(5):1656-61.
3. Vansteelandt S, Daniel RM. Interventional Effects for Mediation Analysis with Multiple Mediators. *Epidemiology* 2017;28(2):258-265.
4. VanderWeele TJ. Controlled direct and mediated effects: definition, identification and bounds. *Scandinavian journal of statistics, theory and applications* 2011;38(3):551-563.
5. VanderWeele TJ. A Unification of Mediation and Interaction: A 4-Way Decomposition. Epidemiology 2014;25(5):749-761.
6. Kivimäki M, Shipley MJ, Ferrie JE, Singh-Manoux A, Batty GD, Chandola T, Marmot MG, Smith GD. Best-practice interventions to reduce socioeconomic inequalities of coronary heart disease mortality in UK: a prospective occupational cohort study. *Lancet* 2008;372(9650):1648-1654.
7. Capewell S, Graham H. Will Cardiovascular Disease Prevention Widen Health Inequalities? *PLoS Medicine* 2010;7(8):e1000320.
8. Pang M, Kaufman JS, Platt RW. Studying noncollapsibility of the odds ratio with marginal structural and logistic regression models. *Statistical Methods in Medical Research* 2016;25(5):1925-1937.

Table. Differing interventions on smoking and direct and indirect effects on socioeconomic inequalities. Not real data.

	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