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Assessing Natural Direct and Indirect Effects Through Multiple Pathways

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Within the fields of epidemiology, interventions research and social sciences researchers are often faced with the challenge of decomposing the effect of an exposure into different causal pathways working through defined mediator variables. The goal of such analyses is often to understand the mechanisms of the system or to suggest possible interventions. The case of a single mediator, thus implying only 2 causal pathways (direct and indirect) from exposure to outcome, has been extensively studied. By using the framework of counterfactual variables, researchers have established theoretical properties and developed powerful tools. However, in practical problems, it is not uncommon to have several distinct causal pathways from exposure to outcome operating through different mediators. In this article, we suggest a widely applicable approach to quantifying and ranking different causal pathways. The approach is an extension of the natural effect models proposed by Lange et al. (*Am J Epidemiol*. 2012;176(3):190–195). By allowing the analysis of distinct multiple pathways, the suggested approach adds to the capabilities of modern mediation techniques. Furthermore, the approach can be implemented using standard software, and we have included with this article implementation examples using R (R Foundation for Statistical Computing, Vienna, Austria) and Stata software (StataCorp LP, College Station, Texas).

causal inference; mediation; multiple mediators

Abbreviation: DAG, directed acyclic graph.

The purpose of this article is to provide a unified way of analyzing problems with multiple mediators. As a motivating example, consider the work by Hvidtfeldt et al. (1), in which the effect of lifestyle factors on the risk of breast cancer was studied. The authors considered 3 possible causal pathways from exposure (lifestyle factors), for example, alcohol intake, to breast cancer; the first is through estrogen levels, the second is through insulin levels, and the third is a direct effect (i.e., through other nonspecified mediators). The authors (1) argue that the 2 indirect paths correspond to distinct causal pathways, but nevertheless, the lack of tools to handle several causal pathways restricts the analysis to consideration of only 1 indirect path at a time. Each indirect pathway was analyzed using the technique of Lange and Hansen (2). However, this approach is mathematically consistent only in the absence of interactions. Furthermore, a hypothesis involving both indirect paths (i.e., that the remaining direct effect is 0) cannot be tested.

Consider briefly the situation of a single mediator in which the standard approach, inspired by Baron and Kenny (3), involves estimating the direct effect as the residual association between outcome and exposure after regression adjustment for the mediator(s) and the indirect effect by subtracting this from the total effect (on an appropriate scale). It has been shown that this approach works in the special case of linear models without interactions, but it is fundamentally flawed otherwise (4–6). A formal approach to mediation analysis has now been developed, building on the counterfactual framework of Pearl (7). Using ideas of Robins and Greenland (8), Pearl (9) showed that the total effect of an exposure can always be decomposed into "natural" direct and indirect effects, regardless of the underlying statistical model. In the last decade, conditions for identifying natural direct and indirect effects have been developed and refined (8–13). In practice, estimation of natural effects can be done through rather complex nonlinear functions of parameter estimates

from regression models for the mediator and the outcome (2, 6, 10, 12–16). Recently, methods focusing on either ease of implementation (17, 18) or robustness (19, 20) have been suggested. None of these methods, however, considers the case of multiple mediators working through different causal pathways.

In the special case of only linear models without interactions, the Baron and Kenny approach (3) can easily be adapted to accommodate multiple mediators, as also noted by MacKinnon (21). The present article suggests a unified approach applicable to any type of exposure, mediators, and outcome (Web Appendices 1 and 2, available at http://aje.oxfordjournals.org/). The method builds on the work in Lange et al. (17). Although the method can, in principle, be applied to any number of mediators and corresponding causal pathways, only few (say 5) causal pathways would seem reasonable in any practical application.

DEFINITIONS AND ASSUMPTIONS

The results of this article are based on the directed acyclic graph (DAG) depicted in Figure 1, in which A is the observed exposure of interest, $M^1, \ldots, M^K$ are the mediators, C is a set of baseline confounders, and Y is the outcome. Thus, it is assumed that there is no unmeasured confounding for the exposure-outcome relationship, exposure-mediator relationship, and mediator-outcome relationship. Variables are allowed to be of any type, for example, continuous, binary, categorical, or survival (the last only for the outcome). From Figure 1, it is evident that 1) there are no variables affected by the exposure that confound any of the mediator-outcome relationships, and 2) the mediators have no causal effect on each other; this property can also be described as the causal pathways being "nonintertwined," which is how the assumption will be referred to herein. This assumption is crucial for the suggested procedure. Indeed, there is no obvious way of defining a causal effect of a specific pathway if this pathway is intertwined with other causal pathways (22). In the case of a single mediator, this is referred to as the sequential ignorability assumption or the Pearl assumption (see VanderWeele and Vansteelandt (6) for a discussion). The precise mathematical formulation of the extended assumption of sequential ignorability (i.e., nonintertwined causal pathways) is presented in Web Appendix 3. If the causal pathways are intertwined, we have what is known as exposure-dependent confounding or time-dependent confounding, (see Martinussen et al. (23) for an in-depth discussion). Note that it is not necessary to include all mediators, as long as it is justified that these omitted mediators do not have a causal effect on any of the included mediators. This assumption is equivalent to the assumptions imposed in the single mediator case.

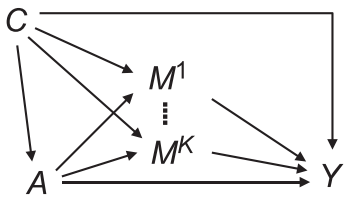

Figure 1. Direct acyclic graph of the causal structure assumed throughout the paper. Note that A is the exposure of interest, $M^1, \ldots, M^K$ the mediators, C a set of baseline confounders, and Y the outcome. The mediators $M^2, \ldots, M^{K-1}$ are not explicitly included on the graph, but are only represented by dots. The structure of the causal connections involving these omitted mediators must be the same as, for example, M^1. That is, M^2 can be affected by A and C and affects Y, but none of the other mediators.

In both the single and multiple mediator settings, the assumption of nonintertwined causal pathways is required to identify natural direct and indirect effects. If one is interested only in direct effects and is willing to accept a slight change of the definition of direct effects, so-called controlled direct effects can be identified without the assumption of nonintertwined causal pathways (14). It should be noted that, although natural direct and indirect effects provide a consistent way of performing effect separation, they can never be estimated directly in any randomized trial because it is impossible to have the exposure take on 2 different values for the same individual (see Imai et al. (24) for further discussion).

As in the DAG in Figure 1, we define the counterfactual variable $Y_{a,m^1,\ldots,m^K}$ as the outcome we would have observed, possibly contrary to the fact, had the exposure A been set to the value a and the mediators $M^1, \ldots, M^K$ set to $m^1, \ldots, m^K$. Similarly, for each mediator ($k = 1, \ldots, K$) the counterfactual variable M_a^k denotes the value of the kth mediator if, possibly contrary to the fact, the exposure A was set to a.

As elsewhere in the causal inference literature (11), we will describe direct and indirect effects using nested counterfactuals, $Y_{a*,M_a^1,\ldots,M_a^K}$, denoting the outcome that would have been observed if A were set to a* and the mediators were set to the values they would have taken if A were set to a. (In)direct effects can be obtained by changing the exposure from reference level at a single location in $Y_{a,M_a^1,\ldots,M_a^K}$; for example, the Kth indirect effect is obtained by comparing $Y_{a,M_a^1,\ldots,M_a^K}$ with $Y_{a,M_a^1,\ldots,M_{a*}^K}$. Such comparison can, for instance, be made in terms of an average difference within levels of covariates, $E[Y_{a,M_a^1,\ldots,M_a^K} - Y_{a,M_a^1,\ldots,M_{a*}^K}|C]$, marginally, $E[Y_{a,M_a^1,\ldots,M_a^K} - Y_{a,M_a^1,\ldots,M_{a*}^K}]$, or $P[Y_{a,M_a^1,\ldots,M_a^K} = 1]/P(Y_{a,M_a^1,\ldots,M_{a*}^K} = 1)$ as a risk ratio. The word "natural" refers to the fact that we let the mediators take the values they would take naturally when the exposure is set to some specific value.

Before one can decompose the total effect of changing exposure (e.g., alcohol intake) from a to a*, one must decide on the order in which the exposure is changed from reference level a. In the breast cancer example, this could be done by first comparing the risk of breast cancer when both the direct path and all indirect paths are kept at the reference level to the risk when only the mediators are kept at the value they naturally take when alcohol intake is at the reference level; this will be the natural direct effect. Second, the risk when only the mediators are kept at the value they naturally take when exposure is at the reference level is compared with the risk when insulin levels also take the value they naturally take when exposure is not at the reference level; this will then be the natural indirect effect through insulin levels. Finally, estrogen is also set to the value it naturally takes when

exposure is not at the reference level; this is the natural indirect effect through estrogen. Mathematically, this corresponds to the following definitions:

- Natural direct effect, $E[Y_{a*,M_a^1,M_a^2}] - E[Y_{a,M_a^1,M_a^2}]$
- Natural indirect effect through mediator 1, $E[Y_{a*,M_{a*}^1,M_a^2}] - E[Y_{a*,M_a^1,M_a^2}]$
- Natural indirect effect through mediator 2, $E[Y_{a*,M_{a*}^1,M_{a*}^2}] - E[Y_{a*,M_{a*}^1,M_a^2}]$.

Clearly, we could have interchanged the order of, for example, insulin and estrogen (mediators 1 and 2), which could have changed the size of these indirect effects. Only in the absence of interactions are both direct and all indirect effects unaffected by the order of the (hypothetical) interventions (see Hafeman and Schwartz (11) for an in-depth discussion).

THE PROPOSED PROCEDURE

Marginal structural models are designed for the marginal expectation (or distribution) of a counterfactual outcome (25). They have become popular for nonnested counterfactuals such as Y_a. For instance, the total causal effect of the exposure A on the outcome Y can be modeled in terms of a marginal structural model of the form $E[Y_a] = b_0 + b_1 a$, where b_1 then captures the average causal effect of the exposure. In the single mediator case, Lange et al. (17, 18) considered generalized marginal structural models for nested counterfactuals, so-called natural effects models, which directly parameterized natural direct and indirect effects as follows:

$$g(E[Y_{a^0,M_{a^1}}]) = \alpha + \beta_0 a^0 + \beta_1 a^1 + \beta_2 a^0 \times a^1.$$

Here, the exposure is included twice (a^0 and a^1) to accommodate that it essentially works through 2 distinct causal pathways. The function g is a link function specifying the requested model for the outcome (e.g., the logistic model), and β_2 is an interaction term, which can be included if required. In the work by Lange et al. (17), survival outcomes are also considered, and an estimation procedure based on weighting is suggested.

The direct parametrization of natural effects can be generalized to the multiple mediator case by a natural effects model for $Y_{a^0,M_{a^1}^1,\ldots,M_{a^K}^K}$, given as

$$g(E[Y_{a^0,M_{a^1}^1,\ldots,M_{a^K}^K}]) = \alpha + \beta_0 a^0 + \sum_{k=1}^{K} \beta_k a^k + \text{“possible interaction”}, \quad (1)$$

where $a^0, \ldots, a^K$ are values of the exposure relative to each of the causal pathways.

If the outcome is survival time, one would often use either Cox or Aalen models (26), but these are not included in the model class given by equation 1. Cox and Aalen models assume that the hazard function corresponding to the counterfactual survival time $Y_{a^0,M_{a^1}^1,\ldots,M_{a^K}^K}$ can be expressed as

$$\lambda_0(t)\exp\left(\alpha + \beta_0 a^0 + \sum_{k=1}^{K} \beta_k a^k + \text{“possible interaction”}\right) \text{or} \quad (2)$$

$$\gamma_0(t) + \alpha + \beta_0 a^0 + \sum_{k=1}^{K} \beta_k a^k + \text{“possible interaction,”} \quad (3)$$

where $\lambda_0(t)$ and $\gamma_0(t)$ are unspecified baseline hazards. Whenever the outcome is a survival time, we will additionally assume that censoring satisfies the usual assumptions (i.e., that censoring is independent of event time (27)). The rest of this article is devoted to estimating natural effects models that can be written as in equations 1–3.

The following procedure is a generalization of the work of Lange et al. (17), which, in turn, builds on ideas from Hong (28). We first describe the procedure for dichotomous exposure (assumed to be coded as 0 and 1) and afterward discuss more general exposures. The procedure is performed as follows:

1. Estimate a suitable model for the exposure conditional on confounders using the original data set.
2. Estimate a suitable model for each of the mediators conditional on exposure and baseline variables using the original data set.
3. Test that each of the mediators is independent of the others conditional on exposure and confounders. In practice, this can be done by including the other mediators in the mediator models in the last step and subsequently testing that their effects are insignificant. If 1 of the other mediators is significant, it indicates that either an important confounder is missing or the assumption of nonintertwined causal pathways is not met. For this reason, one can proceed to the next step only if the other mediators have insignificant effects.
4. Construct a new data set by repeating each observation in the original data set 2^K times and include new variables $A^1, \ldots, A^K$. The new variables are auxiliary exposure variables and therefore take the value 0 or 1 in all combinations of these. Thus, in the 2-mediator case with a binary exposure, each observation is repeated $2^2 = 4$ times. In practice, this is most easily done by first repeating the observations twice, letting A^1 first take the value 1 and then the value 0. Next, the resulting data set is again repeated twice, this time letting A^2 first take the value 1 and then the value 0. This procedure is repeated as many times as there are mediators. Table 1 below illustrates how to construct the extended data from the original data set.
5. Compute weights given by

$$W_i = \frac{1}{P(A = A_i | C = C_i)} \prod_{k=1}^{K} \frac{P(M^k = M_i^k | A = A_i^k, C = C_i)}{P(M^k = M_i^k | A = A_i, C = C_i)}, \quad (4)$$

Table 1. Illustration of How the First 2 Rows of the Original Data Set Appear in the Extended Data

Original Data Set[a]					Extended Data Set[a,b]					
Identification No.	Exposure (A)	Mediator (M)	Outcome (Y)	Confounders (C)	Identification No.	Exposure (A)	New Auxiliary Exposure (A^1)	New Auxiliary Exposure (A^2)	Mediator (M)	Outcome (Y)	Confounders (C)
101	1	1	0	1	101	1	0	0	1	0	1
102	0	1	1	0	101	1	1	0	1	0	1
Repeat[c]	Repeat	Repeat	Repeat	Repeat	101	1	0	1	1	0	1
					101	1	1	1	1	0	1
					102	0	0	0	1	1	0
					102	0	1	0	1	1	0
					102	0	0	1	1	1	0
					102	0	1	1	1	1	0
					Repeat	Repeat	Repeat	Repeat	Repeat	Repeat	Repeat

[a] For simplicity, all variables are assumed to be binary.
[b] Because the exposure is binary and there are 2 mediators, the extended data set will have $2^2 = 4$ rows for each row in the original data set.
[c] Indicates that the sketched process should be repeated for all observations in the original data set.

where subscript i refers to row i in the extended data set constructed in step 4. Thus, M_i and C_i are the values of the mediator and baseline variables, respectively, in row i. In most software packages, this can be done by using predict functionality and the fitted models from steps 1 and 2 on the data set constructed in the previous step.

6. Fit a suitable model (e.g., logistic, Cox) to the outcome including only A and $A^1, \ldots, A^K$ (and perhaps interactions) as covariates and weighted by the weights from the previous step. It can be shown that, provided the mediator models are sufficiently rich so as not to contradict the restrictions imposed by the chosen natural effects model, conservative confidence intervals can be obtained as the estimate of the natural direct or indirect ±1.96 times a robust standard error. These robust standard errors can be obtained from most statistical programs. However, we do suggest obtaining confidence intervals using bootstrapping as a precaution.

If one is instead interested in conditional effects, step 1 (and the first fraction in the weights) can be skipped and C included instead as additional covariates in the model in the last step. Indeed, this is what is done in the implementation examples presented in Web Appendices 1 and 2.

The intuitive content of the weight formula is that the first fraction ensures that the exposure-outcome association is adjusted for confounding by C. Indeed, the impact of upweighting observations with a rare combination of exposures and confounders is to create a pseudopopulation in which the exposure is no longer associated with C and, thus, there is no residual confounding by C (i.e., mimicking a randomized trial). The second fraction of the weights serves to distinguish between the direct and indirect paths by upweighting observations where the observed mediator value (M_i^k) would have been more likely to occur under a different exposure value (A_i^k) than the one actually observed (A_i).

Step 3 serves to justify the assumption of nonintertwined causal pathways. However, it must be stressed that an insignificant P value in this step does not guarantee that the causal pathways are indeed nonintertwined. An insignificant P value could just be the result of large statistical uncertainty. Ideally, the nonsignificant P value should be combined with a narrow confidence interval, but even this cannot replace subject matter–based (i.e., nonstatistical) arguments further justifying the assumption of nonintertwined causal pathways.

Although the proposed method used some of the same tools (in particular, the creation of artificial exposure values and subsequent weighting) as the parametric g-formula (29, 30), the 2 approaches are not closely linked because their end goals are different (effect separation vs. estimating the effect of a time-varying exposure).

The proposed procedure is widely applicable; however, it may lend itself less ideally to the analysis of continuous mediators, because this requires substituting the probabilities $P(M^k = M_i^k | A = A_i, C = C_i)$ in the weights by probability densities, which, in turn, may yield unstable weights. For categorical exposures A, a minor modification is required in that one must repeat the original data set as many times as needed to ensure that, for each subject, A^k takes on all possible values. For continuous exposures, we recommend fitting natural

effects models conditional on covariates to avoid instability due to inverse weighting by the exposure distribution. Here, the user is advised to follow the procedure prescribed for categorical exposures but to replace A^k in row i by randomly drawn exposures from the observed exposures (i.e., resampling). For continuous exposures, one must draw so many samples for each original observation that the final estimates are not affected by the precise random draw; in our experience, approximately 5 draws are adequate.

Web Appendix 3 contains a mathematical validation of the procedure. In addition, Web Appendices 1 and 2 present implementations of this procedure in R (R Foundation for Statistical Computing, Vienna, Austria) and Stata software (StataCorp, LP, College Station, Texas), respectively.

DISCUSSION AND CONCLUSION

We have suggested a generally applicable method (in which all types of mediators and most types of outcomes are allowed) to estimate natural direct and indirect effects through multiple mediators by extending the natural effects models suggested by Lange et al. (17). The method can be used in standard statistical software, and implementation examples are presented in Web Appendices 1 and 2.

The method requires that the individual pathways defined by the chosen mediators correspond to distinct, nonintertwined causal pathways. Our suggested 6-step procedure includes assessing whether the assumption of nonintertwined causal pathways appears to be satisfied. As with the original proposal of the estimation procedure in the single mediator case presented by Lange et al. (17), the simplicity of the proposed procedure comes at the price of not exploiting all available information in the data; thus, more efficient estimators can, in principle, be obtained. In addition, the models used for exposure, mediators, and outcome must be reasonable descriptions of the true distributions. The advice, therefore, is to conduct a thorough misspecification analysis for all the models used and to evaluate the stability of the weights (e.g., by using histograms). In the case of a single mediator, Tchetgen and Shpitser (19) and subsequently Zheng and van der Laan (20) proposed estimators that are efficient and multiply robust in the sense that they merely require the correctness of 2 out of 3 models (the 3 models being those for the exposure, the mediator, and the outcome) regardless of which 2 are correct. However, these suggestions have not been generalized to multiple meditators, and the implementation of these estimators is more demanding at present.

Compared with the single mediator case, the method suggested for the multiple mediator case explicitly states that the different causal pathway must not be intertwined. However, in the single mediator case, the usual assumption ensuring identifiability of natural direct and indirect effects (i.e., sequential ignorability) also implies that the indirect causal path must not be intertwined with paths through other mediators (measured or unmeasured) not included in the analysis. Naturally, when considering a richer DAG with more mediators, this assumption appears more restrictive. These restrictions are, however, an unavoidable consequence of that particular causal structure (manifested through the DAG) and not a consequence of using the suggested approach to deal with multiple mediators, per se. Finally, we note that DAGs with multiple mediators, which do not satisfy the assumptions discussed above, can rarely be analyzed by reduction to a single mediator problem because of likely exposure-dependent confounding.

In summary, we have suggested a unified procedure for estimating natural direct and indirect effects through multiple mediators. The procedure can be applied to almost any combination of variable types and can be conducted in standard software. Web Appendices 1 and 2 provide implementation examples in R and Stata software, respectively.

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