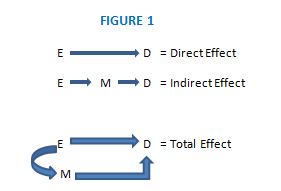
The concept of mediation, and methods for its assessment, entered mainstream epidemiologic literature less than 15 years ago. In that short time, a lively and contentious debate has developed. Some authors (e.g., Kaufman) contend that only controlled effects have utility in the context of epidemiology. Others (e.g., Vanderweele) contend that natural effects often have greater utility. Write an essay describing your position in this debate and how you will approach the assessment of mediation in your work. Make a principled argument to defend your position. In so doing be sure to address the following:

1. Define mediation and explain why epidemiologists might be interested in assessing mediation.
2. Explain the relationship between mediation and direct and indirect effects
3. Define controlled and natural effects and their relationship to the traditional Baron and Kenny method and the critiques of that method.
4. Compare and contrast the assumptions needed to estimate controlled and natural effects, and the interpretation of each
5. Clearly articulate and defend your approach to mediation.

The assessment of mediation has many benefits including but not limited to 1) determine targets for interventions 2) strengthen knowledge/confidence on main effect (exposure) 3) strengthen understanding of causal pathway (the process) 4) determine generalizability of results. In this essay, I will argue that both the controlled effect and natural effect are of value in the assessment of mediation and that selection of the best approach is contingent upon 1) determining the presence of interaction between the exposure and mediator 2) meeting the assumptions required for both approaches 3) research question and goal of the investigation. To support my contention, I will begin by defining mediation and explain why epidemiologists might be interested in assessing them. Second, I will explain the relationship between mediation and direct and indirect effects. Third, I will describe the traditional Baron and Kenny method for the assessment of mediation and its relationship to controlled, followed by the assumptions needed for both the controlled and natural effects.

A mediator variable (M) resides in the causal pathway between two variables (E->M-> D). Indirect effect is of interest when the investigator wants to assess the mediator(s) in the causal pathway between E and D (Figure 1). If M is controlled, the resulting relationship is considered the direct effect. When M is not controlled (M is unadjusted), the resulting relationship between E->D is an total effect. Mediation is of interest for the following reasons, 1) determines targets for interventions. For example, mammography plays a mediating role in the relation between hormone replacement therapy (HRT) and breast cancer (Hormone replacement therapy -> screenings -> breast cancer). The direct effect may conclude HRT-> Breast cancer, however, mediation analysis found that HRT strengthened detection of breast cancer due to increased mammography. Therefore, through well-defined interventions, the focus would be to strengthen screenings (and not HRT) for timely detection and intervention 2) strengthens knowledge/confidence on main effect (Exposure), for falsification and biologic plausibility. Using the HRT example, though the exposure is HRT, HRT led to increase detection of breast cancer and early intervention through increased mammography. Hormone replacement therapy does not decrease breast cancer, therefore, this direct effect is falsified through mediation analysis 3) Specifies the processes through which exposure causes disease. Mediation analysis strengthens knowledge of causal pathway (the process), by identifying an active ingredient which can further narrow the causal pathway. By better understanding the E->D relationships, the generalizability of results is strengthened.

**Presence of Interaction Between E & M Strengthen the Utility of Natural Effects**

Mediators can be assessed through controlled effect and natural effect. Controlled effects are considered to be prescriptive in nature. The effect of exposure is determined by setting the mediator to a particular value at a fix level. As a result, the relationship between exposure and mediator are not preserved. Instead, the value of the mediator is set according to a defined intervention. Barron and Kenny utilize a controlled effect in their traditional method of mediation analysis. The classic assessment of mediation by Barron and Kenny are as follows,

1) Demonstrate X (independent variable) is associated with Y (dependent variable)

2) Demonstrate X (independent variable) is associated with M (hypothesized mediator)

3) Demonstrate M is associated with Y conditional on X

4) Demonstrate X’s association with Y is diminished conditioned on M. [Decrease in the parameter estimate of X]

5) Demonstrate no interaction between X and M

Controlled effect cannot assess for mediation in situations when there is interaction between the exposure and mediator. Barron and Kenny, therefore, assume that there is no interaction between E and M (and there is no confounding (more on assumptions below)). This is a limitation of Barron and Kenny’s assessment of mediation and this is when natural effects is of higher utility.

Natural effects are more descriptive in nature. While controlled effect hold the value of the mediator at a constant rate, natural effect allows for the mediator to vary. A major advantage of the natural effects is that effect decomposition works in the presence of interaction: both the direct and indirect estimates can be obtained. This allows for an estimation of the proportion mediated (the total effect due to the mediator) which is not feasible to estimate using controlled effects. Moreover, in a natural direct effect, only the effect of the exposure on the intermediate is blocked. Thus, a researcher would measure the effect of an exposure, blocking the exposure’s effect on the intermediate variable but allowing the intermediate to vary among individuals.

In brief, presence of interaction between E & M strengthens the utility of natural effects. Natural effects, however, add additional complexities with the requirement of strenuous assumptions.

**Strenuous Assumptions and Cross-world Counterfactual Decrease Utility of Natural Effect**

The following assumptions would need to be met for controlled and natural effects.

1. No measurement error
2. No unmeasured confounding of Yx (the exposure and the outcome). The absence of any unmeasured covariate that is a cause of both the exposure and outcome.
3. No unmeasured confounding of Ym (the intermediate variable (mediator) and the outcome).
4. No effect modification. Assume monotonicity. Therefore, X and M will need to be in different causal pies.

In addition, the following assumptions would need to be met for natural effects.

1. No unmeasured confounding between the exposure and the intermediate variable. Because the intermediate is not a “set value” for natural effect, we would like to ensure best estimates for the M value. We would need to assume no unmeasured confounding between the exposure and intermediate.
2. No unmeasured confounding between the mediator and the outcome that is caused by the exposure.

Meeting the assumptions for natural effects add additional nuances in identifying and adjusting for confounders that may bias the X-> M and M->Y by X relationships. Key experts debate the utility of natural effects and some say that the assumptions may be overly restrictive for many applications in the health sciences (i.e.Naimi and Kaufman). Composite counterfactuals are resultant of natural direct and indirect effects. Estimating them necessitates a union of two logically incompatible states[[1]](#footnote-1). Composite counterfactual requires information that can only exist in two separate ‘worlds’, since no individual can exist with exposure values x and x\*, this has been referred to as a cross-world counterfactual. Using the causal pathway HRT->Mammography-> breast cancer as an example, the experts argue that it is not feasible to define an intervention that results in unexposed women undergoing the mammography screening that they would have undergone had they been exposed to HRT (and vice versa). The additional nuances of assumptions to be met as well as cross-world counterfactuals may decrease the utility of natural effects. Consequently, its complexities may decrease its utility as a basis for policy and interventions.

**Research Question and Measurable Data can Help Inform Method of Assessment**

In the estimation of causal effect using mediation analysis, the choice of method (controlled vs. natural) should also be driven by the research question and availability of information. Controlled effect are useful when the goal is to determine the effect of exposure on outcome while universally blocking or assigning a mediator. In this scenario, the goal is to estimate the causal effect of an exposure (holding the level of the intermediate variable at a controlled level and set value). Moreover, controlled effect have less strenuous assumptions, if the research findings is unable to measure confounders for adjustment for assumptions #5 and 6, then a controlled effect is of higher utility. On the other hand, natural effects are of higher utility when there is presence of interaction between the exposure and mediator. Therefore, if the goal of the research is to preserve this interaction, natural effect is of higher utility. Moreover, natural effect preserves the relationship between the exposure and mediator and thus is of value if the investigator wants to explore the role of individual causal pathways (as well as sufficient causes) in an observed relationship. This allows the intermediate variable to flow the course it would have taken setting the exposure at the reference level.

In conclusion, both the controlled effect and natural effect are of value in the assessment of mediation and that selection of the best approach is contingent upon 1) when there is presence of interaction, natural effects are of higher utility. 2) When the additional assumptions for natural effects (No unmeasured X-> M confounding and No M->Y confounder that is caused by X) are not met, controlled effects are of higher utility. 3) Use of controlled effects or natural effects should also be informed by the research question and availability of information

1. Naimi and Kaufman describe the two states as the outcome under exposure x with the mediator set to what it would have been under x\* [↑](#footnote-ref-1)