# Multiple mediators approach to study environmental chemicals as determinants of health disparities

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## Abstract

A major goal of health disparities research is to identify and intervene upon modifiable risk factors that help explain the observed associations between social factors and adverse health outcomes. To this end, statistical methods incorporating mediation analysis have shown promise, as they quantify the contribution of an intermediate variable in an exposure-outcome association.

A growing body of literature suggests that environmental chemicals can contribute to health disparities. However, evaluating environmental chemicals as an important component of health disparities introduces methodological complexities that may make standard mediation approaches inadequate. Specific to environmental health is the issue of evaluating both the source and biomarker of the environmental toxicant in order to calculate the proportion of the disparity that would remain had we intervened on the modifiable factors. Recent methodological developments on multiple mediators can improve efforts to integrate both source and biomarker of exposure into epidemiological studies of health disparities.

We illustrate a conceptual framework and present how mediation techniques can be used to address environmental health disparities questions. With this, we provide a methodological tool that has the potential to advance this growing field, while simultaneously informing public health prevention and policy surrounding the impact of environmental factors on health disparities.

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## Introduction

Health disparities are defined as differences that systematically have an adverse effect on the health of less-advantaged populations. Disadvantaged groups are generally defined in terms of sociological, economic or anthropological constructs, such as race/ethnicity; religion; socioeconomic status (SES); disability; sexual orientation; gender or gender identity. In addition, constructs such as age, mental health status, culture, as well as geographic locations, can define vulnerable populations. These factors are often immutable, which makes it possible to identify disadvantaged or vulnerable populations, but makes developing recommendations or interventions more challenging. To develop effective public health recommendations and interventions, identification of proximal risk factors that may help to explain why these groups show enhanced vulnerability to a specific set of diseases or health outcomes is critical.

A growing body of literature suggests that environmental factors may be important contributors to the biological pathways leading to disparities in health outcomes.⁻ However, little has been done to quantify the proportion of disparate conditions/diseases that may be attributed to a given environmental toxicants, such as environmental chemicals, where biomarker data exist. Part of this gap in the literature is due to the fact that this quantification would require not only a marker of the environmental toxicant, but also information on its modifiable sources and whether these differ between vulnerable and non-vulnerable populations. This information is crucial from a public health perspective as interventions or recommendations aimed at reducing the disparity would do better to target the modifiable factors (i.e. sources of environmental toxicants) rather than the non-modifiable factors (e.g. an individual's immutable characteristics, such as race/ethnicity).

Mediation analysis is an increasingly popular statistical method to investigate the contribution of third variables in explaining an exposure-outcome association. By providing insights into the pathway underlying statistical associations, this method has been useful for understanding health disparities;⁻ yet, it has been underutilized in environmental health disparities. Recent developments have extended the mediation analysis framework to incorporate several methodological complexities that may be present when investigating environmental factors. For example, methods for multiple mediators have been developed, and may be used to simultaneously incorporate in the same statistical framework environmental factors together with their modifiable sources.· The aim of this commentary is to illustrate how methods for mediation analysis, particularly the use of multiple mediation analysis, may aid in addressing environmental health disparities research questions. For this, we will conceptualize the model of interest in a non-technical review of the relevant regression-based statistical approaches for mediation analysis. In addition, we will provide

several relevant examples to conceptualize the use of this analytic technique to address current environmental health research questions.

## Conceptual model

The Figure presents a basic conceptual model to describe environmental health disparities, while the Table presents several examples of environmental health disparities research questions. Let $X$ be an immutable or difficult to modify social factor (e.g. race/ethnicity) and $Y$ be the health outcome unequally distributed across subgroups of $X$ (e.g. CVD). The goal in environmental health disparity research is to evaluate the contribution of environmental factors to this $X$-$Y$ association. This occurs if a potential environmental chemical $E$ (e.g. a phthalate metabolite)⋅ is both unequally distributed over levels of $X$ and is a risk factor of $Y$. When planning interventions to reduce the disparity (e.g. CVD having a higher prevalence among racial minorities), an additional step is to identify modifiable sources of $E$, in this case $B$ (e.g. diet, such as fast food consumption). Such sources, $B$, are also unequally distributed by $X$, and may be independent risk factors for $Y$. In the case of the present example, fast food consumption is likely unequally distributed by race/ethnicity and an independent risk factor of CVD.

In statistical terms, both $B$ and $E$ can be seen as potential mediators of the $X$-$Y$ association. Specifically, there are four possible pathways through which the health disparity $X$-$Y$ (in the present example race/ethnicity and CVD) is generated: i) over-exposure to the modifiable factor $B$ in the disadvantaged group leading to higher levels of the harmful environmental factor $E$ ($X{\rightarrow}B{\rightarrow}E{\rightarrow}Y$ or, in this example, race/ethnicity$\rightarrow$ fast food consumption$\rightarrow$phthalates$\rightarrow$CVD); ii) over-exposure to $E$ due to other non-identified factors independent of $B$ ($X{\rightarrow}E{\rightarrow}Y$ or race/ethnicity$\rightarrow$phthalates$\rightarrow$CVD); iii) over-exposure to $B$ which affects the outcome through other pathways not including $E$ ($X{\rightarrow}B{\rightarrow}Y$ or race/ethnicity$\rightarrow$fast food consumption$\rightarrow$CVD); iv) other pathways that are independent to both $B$ and $E$. In the next sections, we present and illustrate how mediation techniques involving multiple mediators can be adopted to statistically evaluate environmental health disparities, and to what extent these pathways can be identified. In the Supplemental Content we also provide an illustration of such methods in a simulated dataset, together with guided Stata code for their implementation.

## Mediation analysis with a single mediator

Mediation models with a single mediator could be used to evaluate the contribution of the biomarker $E$ alone, for example the contribution of phthalates in explaining racial/ethnic disparities in CVD. In brief, mediation analysis allows decomposing the total effect of an *exposure X* on a given *outcome Y* into a *direct effect* of the exposure and an *indirect effect* that acts through a *mediator E*. Results from mediation analysis are often presented in terms of *proportion mediated*, calculated as the ratio between the indirect and the total effect. In the context of health disparity research, the proportion mediated may be interpreted as the extent to which the disparity can be attributed to the specific mediator of interest. Direct and indirect effect can also be defined in terms of potential outcomes (counterfactual approach). Of particular interest are the effect of $X$ on $Y$ after fixing the mediator to a predefined value

(*controlled direct effect*: CDE); and the effect of $X$ on $Y$ that only operates by changing $E$ (*natural indirect effect*: NIE). Controlled effects are useful to retrieve information about the result of potential interventions, while natural effects provide information on the pathway through which the disparity is generated. In the context of health disparities, the CDE represents the proportion of disparity that would remain if we were to intervene on the mediator, and can be referred to as *counterfactual disparity measure* (CDM), or residual disparity. In the context of our example, the CDM will provide a quantifiable estimate of the proportion of the disparity that would remain between race/ethnicity and CVD if we intervened on phthalates. Both parametric and non-parametric methods to estimate direct and indirect effects within the standard and counterfactual approaches have been presented, and are available in all major statistical software. Conditions and assumptions for the identification of such effects are reviewed in the Supplemental Content.

## Mediation analysis with multiple mediators

In practical situations (see the Table for examples), a model to describe environmental health disparities should also include upstream sources or factors to which interventions could be developed. For example, if we identified phthalates as a contributor to racial/ethnic disparities in CVD, we could target their modifiable sources such as fast-food consumption in potential interventions or recommendations. Ideally, we would like to quantify the effect of intervening on $B$ in reducing the disparity of interest.

Parametric frameworks to estimate multiple mediation models can be used. These frameworks can also be extended to include exposure-mediator interactions as well as to allow situations in which one of the two mediators is expected to be sequential to the other (e.g. $B$ and $E$ in Figure). Introducing multiple and possibly sequential mediators, however, makes identification and interpretation of effects more challenging. The CDE (i.e. the direct arrow from $X$ to $Y$ in Figure, not going through $B$ or $E$) can be estimated and identified under the same assumptions presented in the context of a single mediator (Supplemental Content) and retains its interpretation as the effect when both $B$ and $E$ are set to a referent value. In disparity terms, the CDE represents the proportion of disparity that would remain if we were to intervene on both mediators by fixing them to a specific arbitrary value. When mediators are sequential, the CDE represents the proportion that would remain after a hypothetical intervention on $B$ and all other non-identified sources of $E$. In our example, this would represent the CVD disparity that would remain after intervening on fast-food consumption and other unknown sources to reduce phthalate exposure.

The total NIE, representing the proportion of disparity that is jointly due to any pathway including $B$, $E$, or both, can be identified and estimated under the classical assumptions (Supplemental Content). This joint effect can be further decomposed into the sum of three path-specific NIE, capturing the effect of different mechanisms contributing to the disparity: i) the effect going through $E$, but not $B$ ($NIE_E$); ii) the effect going through $B$, but not $E$ ($NIE_B$); iii) the effect going through both $B$ and $E$ ($NIE_{EB}$). In the model presented in Figure (sequential mediators), $B$ also acts as a confounder of the mediator-outcome association, thus making the identification of path-specific effects more challenging. In such setting it is only possible to identify the joint NIE (e.g. the effect due to fast-food consumption on

phthalate exposure), the $\text{NIE}_B$ (e.g. the proportion due to fast-food consumption alone), and the $\text{NIE}_E$ (e.g. the proportion due to phthalate exposure alone). Identification and estimation of path-specific effects such as $\text{NIE}_{EB}$ (e.g., the proportion of effect due to phthalate exposure that would be reduced by intervening on fast-food consumption), on the other hand, are not straightforward and may require defining effects in terms of randomized-interventional analogues, involving advanced estimation techniques such as g-formulas and marginal structural models.[ ] We refer to previous publications for these and other identification and estimation procedures of all possible direct and indirect effects in the context of multiple mediators.[ ]

## Final remarks

In this commentary, we presented and illustrated classical and novel methods for mediation analysis as a possible quantitative approach to evaluate environmental health disparities specific to situations where source information and biomarker data are available. We discussed how methods for mediation can help to quantify the proportion of disparity due to a specific environmental factor (*natural indirect effect*) and the proportion of disparity that would remain by interventions aimed at reducing the environmental toxicant (*controlled direct effect*). We have discussed how extensions to incorporate multiple sequential mediators can prove useful when interventions target modifiable sources of the environmental toxicant rather than the biomarkers alone. Further, we discussed the conditions under which the estimated effects maintain their policy-oriented relevance.

Environmental health disparities have been relatively understudied in the context of chemical exposures, and a methodological framework to address how environmental chemicals could impact health disparities has not been well-established. One of the reasons for of this gap is that a conceptual model for environmental health disparities requires the simultaneous inclusion of biomarkers of environmental toxicants and their modifiable sources, thus making standard mediation techniques, commonly used in health disparities research, inadequate. Here, we have discussed how recent developments of methods for multiple mediators can be used to incorporate some of these additional complexities, and the extent to which measures of interest can be estimated. While we primarily focused this commentary on the simultaneous evaluation of environmental chemicals and their sources, there are several additional features that recent methodological developments allow us to take into account. For example, in the Supplemental Content, we briefly review how non-linearities, repeated measurements, and multiple independent mediators can also be included in the conceptual model presented. Future work should incorporate additional topics, including joint disparities.

To evaluate all factors involved in a conceptual model for environmental health disparities, it is important that questions of mediation are addressed in diverse study populations, as either primary or secondary analyses. As such, these factors should be taken into account from the initial phases of study design. For instance, evaluating mediated effects requires estimating a larger number of parameters, and a power calculation based on the estimation of a total effect does not generally extend to the estimation of direct, indirect, and interactive effects.[ ] Moreover, the sample size required to detect significant associations may rapidly grow as

multiple interactions or mediators are simultaneously taken into account. Studies aimed at investigating mediation should be designed in order to assure a temporal sequence in exposure, mediators, and outcomes. While studies of diverse populations are not easily accessible, particularly in environmental health research, we encourage an increased focus on these topics.

The ultimate goal of health disparities research is to identify causal effects in order to develop interventions aimed at reducing the disparity. In recent years, approaches based on counterfactuals of potential outcomes have been the most widely used and developed methods for causal inference in observational studies, especially in the context of mediation analysis. However, applying the counterfactual approach in the context of health disparities research may not be straightforward as causal effects are defined in terms of hypothetical interventions. This has brought some discussion as to whether it is reasonable to speak of a causal effect of non-modifiable factors such as race or gender. In addition, it has been shown that, when mediation analysis is used with non-modifiable exposures such as the social/ anthropological constructs, it is not straightforward to justify the assumptions required for the causal interpretation of effects. Despite recent studies discussing the analytical and conceptual issues that are required to interpret the direct effect as the magnitude of disparity that would remain if a mediator were changed, our general recommendation is that causal interpretation of statistical results--even in the most ideal situation--should always be taken with caution.

In conclusion, our work provides a conceptual framework and illustrates the methodological tools for future research in environmental health disparities. Utilizing a multiple mediation approach to address these questions has the potential to advance this growing field, while simultaneously informing public health prevention and policy.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

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**What this study adds:**

A growing body of literature suggests that environmental factors may contribute to the biological pathways leading to disparities in health outcomes, but statistical frameworks for environmental health disparities are not well-established. In this commentary we conceptualize a model of interest in environmental health disparities and present how mediation analytic techniques can be used to simultaneously evaluate biomarkers of environmental toxicants, as well as their modifiable sources. The potential impact of this information would inform public health prevention and policy. As such, this commentary provides a methodological tool for future research that could advance the growing field of environmental health disparities.
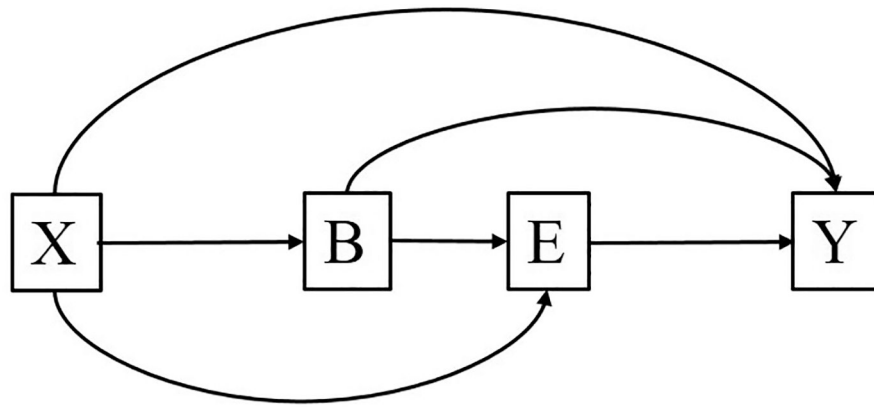
**Figure.**

Conceptual model to describe environmental health disparities.

The figure describes the contribution of an environmental factor (E) and its modifiable source (B) in the health disparity X-Y, where X is an immutable or difficult to modify social factor (e.g. race/ethnicity, gender, SES) and Y the health outcome known to be unequally distributed across subgroups of X.

**Table.**

Examples of health disparities (X–Y) where the joint contribution of environmental factors (E) and their modifiable sources (B) might be hypothesized from the literature.

| Disparity of interest | Social/anthropological construct (X) | Modifiable sources of environmental factors (B) | Biomarkers of environmental toxicants (E) | Health Outcomes (Y) |
|---|---|---|---|---|
| 1. African American race is associated with higher prevalence of cardiovascular disease* | Race/ethnicity | Fast food consumption | Phthalates | Cardiovascular disease |
| 2. Living longer in the U.S. is associated with higher risk of GDM in Asian immigrants | Acculturation | Occupational exposures (e.g. nail salons) | Toluene Formaldehyde | Gestational diabetes |
| 3. African-American race is associated with higher risk of premature puberty | Race/ethnicity | Hair product use | Environmental phenols | Age at menarche |
| 4. Poverty is associated with reduced IQ | Socioeconomic status | Housing and household factors (e.g furniture) | PBDEs | Neurodevelopment |
| 5. Women have higher prevalence of asthma | Gender | Cleaning products | Volatile organic compounds | Asthma |

*
Illustrative examples provided in the manuscript refer to the first line of this Table. These can be extended to any other environmental health disparity in which modifiable sources and biomarker of environmental exposures can be identified.