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Evaluation of Medication-mediated Effects in Pharmacoepidemiology

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Abstract: Medical conditions such as epilepsy or infection with human immunodeficiency virus (HIV) are known to be associated with a spectrum of adverse health outcomes if not appropriately managed by efficacious treatment and care. Medications for such conditions can be potent, and their use might sometimes have unintended health consequences. Prominent examples have emerged in HIV perinatal research in which use of antiretroviral treatment during pregnancy to treat maternal HIV infection and prevent transmission of the virus to the fetus have been shown to be associated with adverse birth outcomes. Likewise, use of antiepileptic drugs during pregnancy to treat maternal epilepsy has been shown to increase the risk of birth defects. Pharmacoepidemiology studies routinely aim to quantify the extent to which, in such settings, an observed association between an underlying medical condition and certain health outcomes can be attributed to the natural progression of the disease, and the extent to which it might be mediated by medication used to slow disease progression. We describe a simple yet principled methodology to quantify medication-mediated effects to address these types of queries. While methods for causal mediation analysis abound, there also has been much criticism of these methods as relying on untestable and sometimes unrealistic assumptions. In contrast, here we show that when the disease-free control group is also medication-free, mediated effects of the type described above are nonparametrically identified under standard no-unobserved confounding conditions, thus establishing that such effects are in a sense immune to recent criticism leveled at causal mediation methodology.

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There has recently been a surge of interest in epidemiologic methods for causal mediation analysis.[1–16] Such methods aim to quantify the extent to which the effects of a given exposure are mediated by an intermediate variable on the causal pathway to the outcome.[1,2] In pharmacoepidemiology, queries of this type arise routinely in the context of understanding the mediating role of exposure to medication prescribed to combat disease progression. Specifically, medications taken for serious health conditions such as infection with HIV or epilepsy can be potent, and their use to slow disease progression and improve the health of those living with the condition might sometimes have unintended health consequences.

Several prominent examples have recently emerged in perinatal epidemiology research, where the use of some medications during pregnancy has been associated with adverse birth outcomes. For instance in HIV research, several studies have shown evidence for an increased risk in stillbirths, preterm delivery, and small for gestational age among women who used combination antiretroviral treatment (ART) during pregnancy compared with those who did not[17–21]; yet the use of combination ART during pregnancy is the standard of care for HIV-infected pregnant women due to the remarkable efficacy of these medications to treat maternal HIV infection and simultaneously prevent transmission of the virus to the fetus.[22–24] Likewise in epilepsy research, a harmful association has been found between use of antiepileptic drugs during pregnancy and adverse birth outcomes, including birth defects, growth retardation, and cognitive function.[25–28]

In both settings described above, it is of interest to quantify the extent to which an existing association between an underlying medical condition and certain health outcomes can be attributed to the natural progression of the disease, and the extent to which such an association might be mostly mediated by medication used to slow disease progression. Recent literature on causal mediation analysis has made important contributions toward a formalization of causal and statistical conditions under which one might be able to decompose the total effect of an exposure into the effect not mediated by a specific intermediate variable (known as the direct effect) and the effect mediated by the intermediate variable (known as the indirect effect), accounting for pre-exposure confounding, interactions, and possible nonlinearities.[1,2,4] Henceforth, any mention of direct/indirect effects in this article will specifically be referring to the so-called natural direct/indirect effects of Robins–Greenland–Pearl[1,2] which are formally

defined in the next section. Natural direct/indirect effects are particularly relevant to our interest in medication-mediated effects as they sum-up to produce the total effect of exposure to the disease on birth outcome, and therefore quantify the extent that an effect might be operating through medication versus by another pathway. In contrast, so-called controlled direct effects are arguably not of primary interest in this article, as they quantify residual effects of the disease in question on birth outcome if one were to hypothetically intervene and say prevent all persons in the population from exposure to medication irrespective of disease status; thus controlled direct effect cannot generally be used to quantify indirect effects and henceforth are not further considered. Recent advances in identification and inference about natural direct/indirect effects have allowed for a better understanding of the strong assumptions needed for mediation analysis to have a compelling causal interpretation, of which some could never be enforced to hold even in experimental settings. In fact, a major limitation of mediation analysis (more specifically of natural direct and indirect effects) is that it is not generally possible to (nonparametrically) identify a mediated effect with a clear causal interpretation when the intermediate variable of interest is subject to exposure-induced confounding, even if all of the confounders are observed.[3,4,29] Because most examples of intermediate variables encountered in epidemiology, and certainly in pharmacoepidemiology applications mentioned above, are bound to be confounded by post exposure variables, existing identification assumptions for causal mediation analysis may be of limited relevance for modern epidemiologic practice. For instance, maternal use of ART during pregnancy is likely to be confounded with maternal immune status (e.g., CD4 cell count), an important correlate of birth outcomes, which is also influenced by maternal HIV status (i.e., the exposure). Therefore, CD4 cell count is likely an exposure-induced confounder of the effects of maternal ART use (the mediator) on birth outcomes, in which case, according to existing mediation theory, ART-mediated effects of HIV on birth outcomes would in principle not be identified empirically even if CD4 cell count were observed and there were no-unobserved confounders.

In this article, we exploit a particular feature shared by a large class of medication-mediated effects of interest in pharmacoepidemiology to show that despite the previous observation, nonparametric identification remains possible in such settings, even in the presence of exposure-induced confounding, under fairly straightforward no-unobserved confounding assumptions that could in principle be enforced under a simple experimental design. Specifically, as is typically the case for a number of diseases, healthy persons are a priori excluded from receiving medication for the disease in question. As we establish, this particular restriction allows one to identify the natural direct effect (and the natural indirect effect) of exposure to disease not mediated (mediated) by medication from observational data, provided there is no-unobserved confounding even if a confounder of the mediator–outcome relationship is directly affected by exposure to disease. Therefore as we elaborate below, the specific mediation setting described in this article is in a sense immune to the aforementioned limitations. Interestingly, we also establish that the proposed medication-mediated effect (i.e., the natural indirect effect) retains a causal interpretation even if there is an unmeasured common cause between the exposure (i.e., maternal disease status) and the outcome (i.e., birth outcome), provided that there is no unmeasured confounding of the effects of the mediator on the outcome, and of the effects of the exposure on the mediator. In other words, we formally show that medication-mediated effects may be causally interpreted even if effects of maternal disease status cannot be interpreted causally. Results regarding robustness to unobserved confounding of the exposure-mediator relationship, provided exposure-outcome and mediator-outcome relationships are unconfounded.

METHODS

We now introduce the notation, assumptions, and definitions we will use throughout.

Identification conditions

We will first discuss a simple setting without exposure-induced confounding of the mediator. Let A denote the exposure of interest, for example maternal epilepsy; let Y denote a post exposure outcome, such as a birth defect; and let M denote a post exposure intermediate variable to the outcome, such as use of antiepileptic drugs during pregnancy. Let C denote the value of a set of pre-exposure confounding variables of the effects of A and M on Y, for example age and race. Throughout, we will assume independent and identically distributed sampling of C, A, M, and Y. If there is no confounder of the mediator effect on the outcome that is affected by the exposure, then the relationships between these variables may be depicted in the causal diagram in Figure 1.

We now consider counterfactuals or potential outcomes, under possible interventions on the variables. Let $Y(a)$ denote a subject's outcome if exposure A were set, possibly contrary to fact, to a. In the context of mediation there will also be potential outcomes for the intermediate variable. Let $M(a)$ denote a subject's counterfactual value of the intermediate M if exposure A were set to the value a. Finally, let $Y(a, m)$ denote a subject's counterfactual value for Y if A were set to a and M were set to

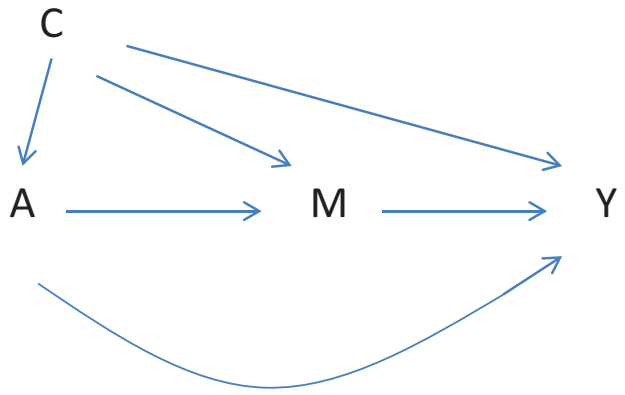

FIGURE 1. No confounder of M–Y relation is affected by A.

m. Robins and Greenland[1] and Pearl[2] considered the following decomposition of individual total effect of exposure A:

$$Y(a) - Y(a^*) = Y(a, M(a)) - Y(a^*, M(a^*)) \text{(total effect)} \quad (1)$$

$$= Y(a, M(a^*)) - Y(a^*, M(a^*)) \text{(natural direct effect)} \quad (2)$$

$$+ Y(a, M(a)) - Y(a, M(a^*)) \text{(natural indirect effect)} \quad (3)$$

where a^* indicates a reference or baseline value of A. For instance, it is common to choose $a^* = 0$ and $a = 1$ for binary A, where $a = 1$ indicates exposure to say, epilepsy. The contrast in (2) displayed above defines the natural direct effect of exposure A on outcome Y in a given person. The potential outcome $Y(a^*, M(a^*))$ captures the behavior of Y under the baseline exposure value, for example, the outcome under no epilepsy, while $Y(a, M(a^*))$ describes the behavior of Y under the active exposure value, in a hypothetical situation where the mediator behaves as if exposure were set to baseline. Conceptually, for $a = 1$ and $a^* = 0$, the potential outcome $Y(a, M(a^*))$ could be obtained if it were possible in an intervention to deactivate the component of the exposure that affects solely the mediator, so that the mediator would take the value $M(a^*)$, while at the same time leaving active the component of the exposure which affects only the outcome, so that we would observe $Y(1, M(0))$. Using our epilepsy example, this is the potential outcome if a person with epilepsy were to receive the treatment they would have received had they been epilepsy-free. The contrast in (3) of the display above corresponds to the natural indirect effect of exposure A on outcome Y. The potential outcome $Y(a, M(a))$ describes the behavior of Y under the active exposure value, while the second "subtracts off" the behavior of Y under the active exposure value in a hypothetical situation where the mediator behaves as if exposure were set to its baseline value. In graphical terms, the individual natural indirect effect quantifies the effect of A on Y along the indirect causal pathway $A \rightarrow M \rightarrow Y$, but not along the direct arrow from A to Y. Because potential outcomes under conflicting exposure status are never jointly observed, individual causal effects are generally not identified. However, one can hope that under certain assumptions, population average causal effects would become identified. Thus we shall consider estimation of the average total, natural direct, and natural indirect effects

$$\text{TE}(a, a^*) = E\{Y(a) - Y(a^*)\}$$
$$\text{NDE}(a, a^*) = E\{Y(a, M(a^*)) - Y(a^*, M(a^*))\}$$
$$\text{NIE}(a, a^*) = E\{Y(a, M(a)) - Y(a, M(a^*))\}$$

A conventional interpretation of the graph in Figure 1 implies the following no-unobserved confounding assumptions, for all a and m:

(a.1) A is independent of $\{Y(a), M(a)\}$ given C;

(a.2) A is independent of $Y(a, m)$ given C;

(a.3) $M(a)$ is independent of $Y(a, m)$ given C and $A = a$.

It is well known that the average total effect TE(a, a^*) of A on Y is identified under assumption (a.1), and is given by the g-formula of Robins.[30] The assumption that there is no exposure-induced confounding of M may be unrealistic in many epidemiologic applications, particularly in pharmacoepidemiology settings where A indicates disease status, and the mediator M is medication taken to slow disease progression. Because the decision to initiate treatment is likely based on a patient's current health status, exposure-induced confounding of the mediator–outcome relation can seldom be ruled out. In the causal diagram depicted in Figure 2, N now encodes an exposure-induced confounder of M. Thus, in this graph, N is simultaneously a confounder of the effects of the mediator M on Y, and on the causal pathway from exposure to outcome. Going back to our maternal epilepsy example, the decision to initiate anticonvulsants might be based on the number of seizures a woman experiences, and her seizure status will likely be associated with birth defects. Seizure status is therefore simultaneously a confounder of the effect of antiepileptic drugs on birth defects and is also on the causal pathway of the effect of epilepsy on birth defects. While the total effect of A on Y remains identified in Figure 2 by Robins' g-formula, so that the presence of N presents no new difficulty, assumptions (a.1)–(a.3) do not suffice to identify NDE(a, a^*) and NIE(a, a^*).

We consider an alternative strategy for identification of NDE(a, a^*) and NIE(a, a^*) under the following conventional no-unobserved confounding assumptions encoded in the graph in Figure 2, (a.1), (a.2), and (b.3) given below

(b.3) $Y(a, m)$ is independent of $M(a)$ conditional on N, $A = a$ and C.

Although not explicitly shown in Figure 2, our approach does not technically require that there be no-unobserved confounding between (C, N, and Y) and therefore there may be unobserved common causes of these variables, although we shall continue to suppress such variables as done in the graph. Throughout, for simplicity we set $a = 1$ and $a^* = 0$,

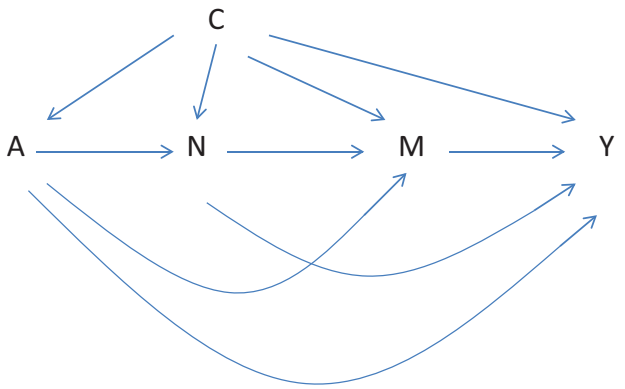

FIGURE 2. *N* is a confounder of *M*–*Y* relation that is affected by *A*.

so that we seek to identify NDE(1, 0) and NIE(1, 0). In this vein suppose that, as would usually be the case, the mediator indicates taking a particular medication (e.g., antiepileptic drugs) which may only be prescribed to a person with a specific disease ($A = 1$, e.g., epilepsy), and all disease-free persons ($A = 0$, e.g., no epilepsy) remain unexposed to this specific medication. Formally, this can be stated with counterfactuals as followed:

$$\text{(b.4)}\ M(0) = 0,$$

that is, a person is to remain medication-free if possibly contrary to fact the person were to be disease-free. It then follows that under (b.4),

$$E\{Y(1,M(0))\} = E\{Y(1,0)\},$$

and therefore,

$$\text{NDE}(1,0) = E\{Y(1,M(0)) - Y(0,M(0))\} = E\{Y(1,0)\} - E\{Y(0)\},$$
$$\text{NIE}(1,0) = E\{Y(1,M(1)) - Y(1,M(0))\} = E\{Y(1)\} - E\{Y(1,0)\}.$$

Because $E\{Y(1, 0)\}$, $E\{Y(0)\}$ and $E\{Y(1)\}$ are nonparametrically identified by Robins *g*-formula under assumptions (a.1), (a.2), and (b.3) encoded in the graph of Figure 2, it follows that NDE(1, 0) and NIE(1, 0) are therefore empirically identified under assumptions (a.1), (a.2), (b.3), and (b.4). Technically, identification of $E\{Y(1, 0)\}$ also requires the positivity assumptions $\Pr\{A = 1|c\} > 0$ and $\Pr\{M = 0|A = 1, c, n\} > 0$ for all c and n; and likewise identification of $E\{Y(a)\}$ requires that $\Pr\{A = 1|c\} > 0$ for all c. These identification results of NDE(1, 0) and NIE(1, 0) are quite remarkable and may seem somewhat surprising as previous literature has suggested that NDE(1, 0) and NIE(1, 0) are generally not identified in the setting of Figure 2, even under fairly stringent conditions.[4] In eAppendix 1 (http://links.lww.com/EDE/B152), we provide more extensive discussion about existing identification results in the literature, thus clarifying our previous claim that the proposed identification conditions are immune to well-known limitations of previous causal mediation methodology.

Instead of marginal effects, one may wish to estimate conditional effects such as say NDE(1, 0, c) = $E\{Y(1, M(0)) - Y(0, M(0))|c\}$. Then (b.4) likewise gives NDE(1, 0, c) = $E\{Y(1, 0)|c\} - E\{Y(0)|c\}$. For binary outcome, effect decomposition on the risk ratio scale is perhaps more relevant with

$$\text{TE}(1,0,c) = \Pr\{Y(1) = 1 \mid c\} / \Pr\{Y(0) = 1 \mid c\},$$
$$\text{NDE}(1,0,c) = \Pr\{Y(1,0) = 1 \mid c\} / \Pr\{Y(0) = 1 \mid c\},$$

and

$$\text{NIE}(1,0,c) = \Pr\{Y(1) = 1 \mid c\} / \Pr\{Y(1,0) = 1 \mid c\},$$

such that TE(1 ,0, c) decomposes on the multiplicative scale as

$$\text{TE}(1,0,c) = \text{NDE}(1,0,c) \times \text{NIE}(1,0,c).$$

It will also be of interest to quantify the proportion of the total effect that is mediated (known as proportion mediated), given by

$$\text{NIE}(1,0,c) / \text{TE}(1,0,c),$$

and

$$\log\text{NIE}(1,0,c) / \log\text{TE}(1,0,c),$$

for the additive and multiplicative scales, respectively.[31]

Robustness of Medication-mediated Effects to Unobserved Confounding of Disease Status

It is instructive to consider the empirical expression of NIE(1, 0 ,c) under assumptions (a.1), (a.2), (b.3), and (b.4) which follows from straightforward application of Robins' *g*-formula:

$$\text{NIE}(1,0,c) = E\{Y(1,M(1)) \mid c\} - E\{Y(1,M(0)) \mid c\}$$

$$= \sum_{m,n} E(Y \mid A = 1,m,n,c)\Pr(M = m,N = n \mid A = 1,c)$$

$$- \sum_{n} E(Y \mid A = 1,M = 0,n,c)\Pr(N = n \mid A = 1,c).$$

Interestingly, in eAppendix 1 (http://links.lww.com/EDE/B152), we show that the empirical expression in the above display can still be interpreted causally even if only assumptions (b.3) and (b.4) hold but either of assumptions (a.1) or (a.2) does not as long as the other assumption holds. That is either (1) the effect of A on Y may be subject to unobserved confounding but both the effects of A on M and the effects of M on Y are not; or (2) the effect of A on M is subject to unmeasured confounding however both the effects of A on Y and the effects of M on Y are not. Specifically, we show that

$$E\{Y(1,M(1)) \mid c\} - E\{Y(1,M(0)) \mid c\} = E(Y(M(1)) - Y(M(0)) \mid A = 1,c),$$

which defines the natural indirect effect of A on Y mediated by M among persons with $A = 1$ and $C = c$, that is, the conditional medication-mediated effect of exposure to disease among persons who have the disease, which we denote NIED(c). Therefore, we have successfully established that nonparametric identification of medication-mediated causal effects among diseased persons is possible even if the effects of disease status are subject to unobserved

confounding, provided that assumptions (b.3) and (b.4) hold. It is straightforward to show that the result also applies on the multiplicative scale. It is further possible to show that under (2) NDE(1,0,c) is infact nonparametrically identified. However, the result does not apply to either the total effect or the direct effect, and unobserved confounding of disease status A will in general result in biased inferences about these effects.

Inverse Probability Weighting Estimation of Medication-mediated Effects

Both simple parametric and semiparametric methods are well developed to estimate Robins' g-formula for $E\{Y(a, m)|c\}$ and, therefore, statistical inference does not present any new difficulty that is not easily addressed with existing methodology. Here we shall only consider a simple weighted strategy which is perhaps most relevant for routine application.[32] Suppose that Y is a rare, binary outcome, such that a standard logistic regression may be used to estimate the total effect of A conditional on C on the risk ratio scale, that is,

$$\text{Logit}\Pr(Y = 1 \mid A,C) = b_0 + b_1 \times A + b_2' C$$

Then under assumption (a.1), $\text{TE}(1, 0, c) \approx \exp(b_1)$. To estimate the direct effect, one may simply run a weighted version of the above logistic regression, $\text{Logit Pr}(Y = 1|A, C) = B_0 + B_1 \times A + B_2'C$, restricted to the sample of observations with $M = 0$, with individual weight $\widehat{\Pr}\{M = 0 \mid A,C,N\}^{-A}$, where $\widehat{\Pr}\{M = 0 \mid A,C,N\}$ is the maximum likelihood estimator of $\text{Logit}\Pr\{M = 0 \mid A,C,N\} = d_0 + d_1 \times A + d_2'C + d_3'N$, the probability of remaining free of the mediator. Under assumptions (a.1), (a.2), (b.3), (b.4), the positivity assumption, and in the absence of model misspecification, this procedure will produce a consistent estimate of $\text{NDE}(1, 0, c) = \exp(B_1)$. Intuitively, the direct effect of A can be evaluated among persons without the mediator, by comparing what their potential outcome would be if possibly contrary to fact they were disease free (therefore also without the mediator by (b.4)) to what it would be if they had the disease (and remained without the mediator). Therefore a change in the outcome resulting from this contrast can only be attributed to an effect of the exposure not through the mediator. The weights are needed to account for post exposure confounding by N, which is only active for persons with the disease, because disease-free persons are also free of the mediator by (b.4) and therefore are not susceptible to confounding of the mediator.

To estimate the indirect effect, one can evaluate the following ratio:

$$\text{NIE}(1,0,c) = \text{TE}(1,0,c) / \text{NDE}(1,0,c)] = \exp(b_1 - B_1),$$

on estimating the total and direct effects as described above. Conservative Wald-type confidence intervals can be obtained for $\text{NDE}(1, 0, c)$ using the standard sandwich variance estimator,[32] or alternatively, more accurate confidence intervals are available with the nonparametric bootstrap which may be used for inference about both $\text{NDE}(1, 0, c)$ and $\text{NIE}(1, 0, c)$. Analogous steps can be followed for a nonrare binary outcome, on substituting the log-link for the logit link in all outcome regressions. Likewise, continuous outcomes can be handled by simply replacing logistic regression with linear regression in all outcome models.

Data Application

In this section, we illustrate the mediation analysis techniques described above to quantify the AED-mediated effect of maternal epilepsy on birth outcomes (specifically, growth retardation, microcephaly, and hypoplasia of the fingers). To accomplish this, we decompose the total effect into two different pathways: (1) the effect of epilepsy on birth outcomes through a pathway mediated by use of antiepileptic drugs during pregnancy, that is, the natural indirect effect, and 2) the effect of epilepsy on birth outcomes through a pathway that is not mediated by AED use, that is, the natural direct effect. For each birth outcome, we then estimate the proportion of the total effect of epilepsy that is mediated by antiepileptic drug use.

We used data from a study by Holmes et al.[25] conducted between 1986 and 1993 at five maternity hospitals in the Boston area (Brigham and Women's Hospital, Beth Israel Hospital, St. Margaret's Hospital, St. Elizabeth Hospital, and Newton-Wellesley Hospital). The goal of the study was to assess whether the increased risk of abnormalities in infants exposed to anticonvulsant drugs in utero are caused by the maternal epilepsy itself or whether it is due to exposure to anticonvulsant drugs. Briefly, the study screened a total of 128,049 pregnant women at delivery to identify three groups of infants who were then examined for the presence of malformations: those whose mothers had epilepsy and were exposed to anticonvulsant drugs in utero (N = 316), those whose mothers had epilepsy but were unexposed to anticonvulsant drugs in utero (N = 98), and those unexposed to anticonvulsant drugs in utero with no maternal history of seizures (i.e., controls, N = 508). In the original article, standard multivariate logistic regression analyses were performed to assess the association between each exposure group and each of the outcomes adjusting for other risk factors; however, the study did not formally quantify the proportion of the total effect of maternal epilepsy that is mediated by anticonvulsant use. The original study protocol was reviewed and approved annually by the institutional review board at each participating hospital. Additional details regarding the study sample, data extraction and analysis are available in the original article.[25]

Using SAS statistical analysis software (Version 9.4, SAS Institute, Cary NC), we evaluated the total effect by regressing each outcome on maternal epilepsy status using multivariate logistic regression to obtain risk ratio estimates,[33]

adjusting for risk factors that were available in our data source (maternal age and race). To estimate the natural direct effect of maternal epilepsy, we regressed each outcome on maternal epilepsy status using a weighted multivariate logistic regression and adjusting for the same risk factors as in the model for the total effect (maternal age and race); this analysis was restricted to the subsample of antiepileptic drug-naïve women (with or without epilepsy). Restricting the analysis to antiepileptic drug-naïve women ensured that we isolated the effect of epilepsy that is not mediated by use of these drugs during pregnancy (i.e., direct effect). The weights for women with epilepsy were defined as the inverse probability of remaining antiepileptic drug-naïve conditional on the woman having epilepsy, her baseline risk factors (alcohol use, cigarette smoking, and substance abuse), and the severity of her seizures during pregnancy (no seizures, no loss of consciousness, or loss of consciousness). Because seizure status is both an important confounder of antiepileptic drug use and a mediator of the effect of epilepsy on growth retardation and malformations, it is not appropriate to adjust for it directly in the regression model and a weighted analysis is typically recommended as previously discussed.[32] The weights were set to 1 for women who did not have epilepsy reflecting the fact that none of these women received antiepileptic drugs during pregnancy by study design (although in practice, some women with no epilepsy may receive these drugs for other medical reasons). Finally, we estimated the natural indirect effect by calculating the ratio of the total effect and direct effect risk ratios,[31,34] and the proportion mediated as the ratio of the log indirect effect and the log total effect. Sample SAS code illustrating our analyses is provided in eAppendix 2 (http://links.lww.com/EDE/B152).

Our results showed evidence of significant mediation of the effect of maternal epilepsy through a pathway involving antiepileptic drug use during pregnancy for microcephaly, growth retardation, and hypoplasia of the fingers (Table). The largest indirect effect was for microcephaly (proportion mediated = 87%), followed by growth retardation (proportion mediated = 79%), while for hypoplasia of the fingers only 42% of the total effect of maternal epilepsy is through a pathway involving antiepileptic drug use during pregnancy. We therefore conclude, based on these results, that use of antiepileptic drugs mediates the majority of the effect of maternal epilepsy on microcephaly and growth retardation, while another pathway (not involving these drugs) possibly accounts for the majority of the effect of maternal epilepsy on hypoplasia of the fingers.

Although our analyses accounted for age and race as potential confounders, one cannot rule out with certainty the presence of unmeasured confounding. Fortunately, as previously shown, our estimates of indirect effects are robust to unmeasured confounding of maternal epilepsy, and may alternatively be interpreted as quantifying medication-mediated effects of maternal epilepsy on birth outcomes among mothers with epilepsy, even if maternal epilepsy itself is confounded, provided there is no-unobserved confounding of the effects of antiepileptic drugs on birth outcomes. However, both direct and total effects of maternal epilepsy may be biased if the latter is confounded, in which case, the proportion mediated may be difficult to interpret. Unfortunately, information identifying participant's study center was unavailable in our data source; therefore, unobserved confounding of the effects of antiepileptic drugs on birth outcomes by study center cannot be ruled out, and clustering of birth outcomes by study center may likewise impact the coverage of reported confidence intervals.

DISCUSSION

We have proposed straightforward conditions for identification of a large class of medication-mediated effects that may be of particular interest in pharmacoepidemiologic research. The proposed conditions combine conventional assumptions of no-unobserved confounding about the effects of exposure on the mediator and outcome variables, as well as about the effects of the mediator on the outcome (assumptions (a.1), (a.2), and (a.3)), with a condition that disease-free persons in the target population cannot be exposed to medication (assumption b.4). Under these assumptions, we have shown that direct and indirect effects can be evaluated empirically with careful use of Robins *g*-formula, which we implemented via standard inverse

TABLE. Adjusted RRs and 95% CIs for the Total Effect, Natural Direct Effect, and Natural Indirect Effect of Epilepsy on Birth Outcomes

Birth Outcome	Total Effect-adjusted RR (95% CI)[a]	Direct Effect-adjusted RR (95% CI)[b]	Indirect Effect-adjusted RR (95% CI)	Proportion Mediated (%)
Growth retardation	3.6 (1.4, 9.5)	1.3 (0.5, 3.4)	2.7 (1.4, 5.3)	78
Microcephaly	2.0 (0.8, 5.0)	1.1 (0.5, 2.4)	1.9 (1.0, 3.6)	88
Hypoplasia of the fingers	2.4 (1.1, 5.2)	1.7 (0.8, 3.4)	1.4 (0.8, 2.5)	40

Mediator = any AED use during pregnancy versus no AED use during pregnancy.
[a]Multivariate logistic model adjusted for maternal age and maternal race (Black, White, and Other).
[b]Weighted logistic model adjusted for same variables as in the total effect model. Weights for women with epilepsy were computed using the predicted probability from a logistic regression of AED use during pregnancy on risk factors (alcohol use, cigarette smoking, and substance abuse) and whether or not the woman had seizures during pregnancy; weights for women without epilepsy were set to 1.
AED indicates antiepileptic drug; CI, confidence interval; RR, risk ratio.

probability weighting. The methodology presented in this work could also potentially be of use in other settings not directly considered in our article. For instance, the methods could be used in analyses of randomized clinical trials where patients on the treatment arm have access to rescue medication; however, patients on the control arm do not. In such settings, one may use our proposed approach to tease apart the indirect effects of the randomized medication attributed to rescue medication from the direct effects not through rescue medication.

We note in closing that, while assumption (b.4) is expected to hold for a large class of medical conditions, the assumption may be violated in settings where medication may be taken by disease-free persons as a preventive measure. For example, treatment as prevention has recently emerged as an effective intervention to prevent HIV infection in certain high risk populations; an example of such a population is uninfected persons with HIV-infected sexual partners (i.e., discordant couples).[35,36] Likewise, antiepileptic drugs are sometimes prescribed for other conditions such as certain psychiatric disorders and pain syndromes.[37] In such settings, assumption (b.4) clearly cannot hold, and therefore the methods described herein may not apply, although other existing causal mediation methods mentioned in eAppendix 1 (http://links.lww.com/EDE/B152) that rely on stronger identifying assumptions may potentially apply.

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