

# An Organizational Schema for Epidemiologic Causal Effects

Nicolle M. Gatto,<sup>a,b</sup> Ulka B. Campbell,<sup>a,b</sup> and Sharon Schwartz<sup>a</sup>

**Abstract:** Epidemiologic textbooks and methodological papers define multiple causal effects. These causal effects can differ substantially; yet, the causal effect of interest is rarely specified in published epidemiologic studies perhaps because their distinctions are underappreciated. Here, we provide an organizational schema that distinguishes causal effects based on six characteristics. We use simple numeric examples to demonstrate the variability across effects and show why specifying the causal effect is necessary for an accurate intervention interpretation even under the simplest scenarios. The objective of our schema was to illuminate the distinguishing characteristics of various causal effects and clarify their interpretation, thus guiding epidemiologists in choosing an appropriate causal effect to estimate.

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Epidemiologic textbooks and methodological papers define multiple causal effects.<sup>1–7</sup> These causal effects can differ substantially; yet, the causal effect of interest is rarely specified in published studies<sup>5,7</sup> perhaps because their distinctions are underappreciated.

Here, we provide an organizational schema that distinguishes average causal effects based on six characteristics, whether (1) the effect measures disease etiology or excess<sup>8–11</sup>; (2) the measure of disease occurrence is a risk or rate; (3) the measure of effect is absolute or relative; (4) the effects are hypothesized to be causal or preventive; (5) contrasts incorporate facts or only hypotheticals; and (6) the effects apply to the entire study population or only a subset of the study

population (eg, only those who are exposed). Using simple numeric examples, we demonstrate the variability across effects and show why specifying the causal effect is necessary for accurate intervention interpretations. The objective of our schema was to articulate the characteristics that differentiate causal effects to help epidemiologists identify and describe the effect of interest in their own studies.

## TERMINOLOGY AND SCOPE

In line with the potential outcomes framework, we use the term “exposure” to mean any exposure or treatment that can theoretically be manipulated.<sup>3,12–14</sup> We refer to an exposure hypothesized to cause more disease than it prevents as “causative” and an exposure hypothesized to prevent more disease than it causes as “preventive.” For simplicity, we describe average causal effects for dichotomous outcomes and dichotomous point treatments (ie, exposures measured at one time point). As noted by Hernán,<sup>3</sup> the term “causal effect” is redundant; thus, we use this term and “effect” interchangeably.

We discuss causal effects in a real-world population (called here, “study population”) consisting of people who are actually exposed or unexposed in nature (ie, not assigned by a study protocol). In this article, we are “all-knowing”; we know the (unobservable) potential outcomes of everyone in the study population and therefore can calculate causal effects even when there are violations of exchangeability between the exposed and the unexposed. Furthermore, there is no bias related to sampling because we see the entire population of interest.

In line with potential outcomes convention, we assume that the epidemiologist intends to estimate an intervention effect—the precise reduction in disease risk that would occur in an intervention target if a preventive exposure was given to all the unexposed or a causative exposure was removed from all the exposed in the study population, with all else equal. Accordingly, we address causal questions that ask about the impact of giving a beneficial exposure to all unexposed people or removing a harmful exposure from all exposed people (additional effects, mentioned in the discussion, may be of interest to researchers who intend to forecast potentially harmful interventions). Although in most real-world interventions it is unrealistic to expect an intervention to reach all intended people, this bound yields the maximal possible reduction in

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From the <sup>a</sup>Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY; and <sup>b</sup>Epidemiology, Worldwide Safety & Regulatory, Pfizer Inc., New York, NY.

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**Editors' note:** A commentary on this article appears on page 98.

Correspondence: Nicolle M. Gatto, WSR Epidemiology, Pfizer Inc., 235 East 42nd Street MS 219/9/1, New York, NY 10017. E-mail: [nicolle.gatto@pfizer.com](mailto:nicolle.gatto@pfizer.com).

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disease risk. Note that “all else equal” means the exposure can be given or removed without any other impact,<sup>15</sup> and the study result is fully transportable to the intervention population.<sup>13</sup> The requirements for “all else to be equal” are complex and restrictive, as discussed elsewhere.<sup>13,15–20</sup> Nonetheless, the potential outcomes literature (such as Hernán and Taubman<sup>12</sup> and Kaufman<sup>21</sup>) encourages epidemiologists to conduct studies such that their estimates can be interpreted as intervention effects. To do so requires this assumption.

## NOTATION

We use notation conventions of potential outcomes<sup>3,17</sup> and response types<sup>18</sup> reviewed briefly here. Let “Y” represent the dichotomous disease (1 = diseased, 0 = not diseased) and “A” the dichotomous exposure (1 = exposed, 0 = not exposed) of interest.  $\Pr(A = 1)$  represents the prevalence of exposure in the study population,  $\Pr(Y = 1)$  represents the risk of disease in the study population under actual exposure status,  $\Pr(Y = 1|A = 1)$  represents the risk of disease in those actually exposed from the study population, and  $\Pr(Y = 1|A = 0)$  represents the risk of disease in those actually unexposed from the study population.

Let “a” represent possible exposure status (for a given person, one state will be actual and the other counterfactual), such that  $Y_{a=1}$  is the outcome that would be observed if a person is exposed and  $Y_{a=0}$  is the outcome that would be observed if a person is unexposed. Thus,  $\Pr(Y_{a=1} = 1)$  represents the risk of disease in the study population had they all been exposed and  $\Pr(Y_{a=0} = 1)$  represents the risk of disease in the study population had they all been unexposed.

Response types provide a useful shorthand to describe these sets of potential outcomes.<sup>18</sup> Considering a dichotomous exposure and disease, a person could develop the disease by the end of the study period under both exposure conditions (doomed or “type 1”), only if exposed (susceptible-causative or “type 2”), only if unexposed (susceptible-preventive or “type 3”), or under neither exposure condition (immune or “type 4”). If a person’s potential outcomes by the end of the study period would be different under the two exposure conditions (ie, if the person is type 2 or 3), there is a causal effect of the exposure on the outcome. Epidemiologic studies estimate the average of these individual causal effects. If the proportion of type 2 people is greater than the proportion of type 3 people in the population, the average exposure effect will be causal. If the proportion of type 3 people is greater than the proportion of type 2 people, the average exposure effect will be preventive.

Following the convention used by Greenland and Robins,<sup>18</sup> let “p” represent those in the study population who are exposed. The proportions of exposed people who are type 1, type 2, type 3, and type 4 are labeled  $p_1$ ,  $p_2$ ,  $p_3$ , and  $p_4$ , respectively. Let “q” represent those in the study population who are unexposed. The proportions of unexposed people who are type 1, type 2, type 3, and type 4 are labeled  $q_1$ ,  $q_2$ ,  $q_3$ , and  $q_4$ ,

respectively. In the entire population, the proportion of people who are type 1 is  $[p_1 \times \Pr(A = 1) + q_1 \times \Pr(A = 0)]$ , and the proportion of people who are type 2 is  $[p_2 \times \Pr(A = 1) + q_2 \times \Pr(A = 0)]$ , so on.

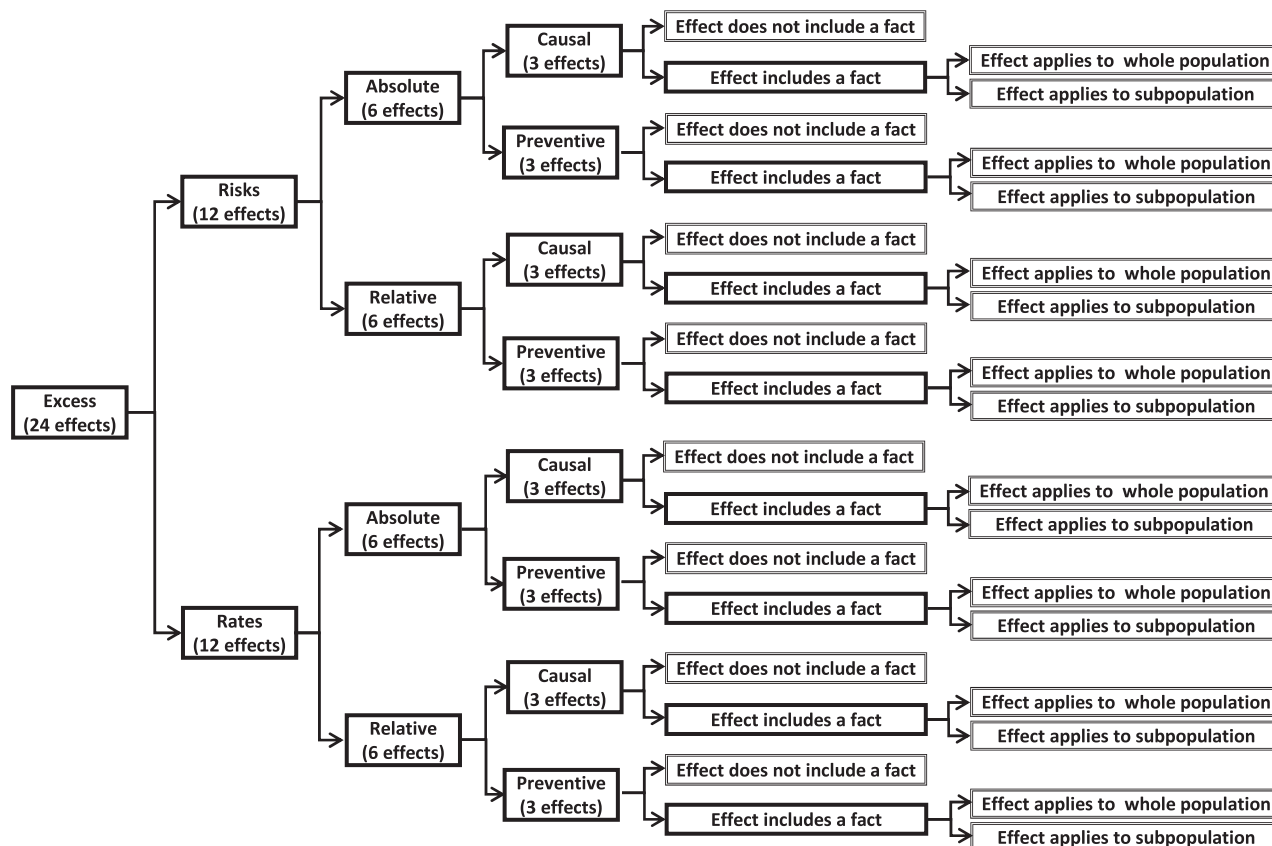
## AN ORGANIZATIONAL SCHEMA FOR CAUSAL EFFECTS

The organizational schema that arises from characteristics (1)–(6) yields 48 causal effects. There are 24 excess effects and 24 etiologic effects; “excess” effects refer to effects measuring the impact of the exposure by the end of some defined study period, and “etiologic” effects refer to effects measuring the impact of the exposure on the disease at the moment disease occurs.<sup>8–11</sup> Figure 1 depicts the organization of the 24 excess effects. These effects are divided into 12 risk-based and 12 rate-based effects. The effects are then subdivided into six absolute effects and six relative effects, and again into three causal effects and three preventive effects. Within the causal and preventive effect categories, the effects are subdivided into those that only include hypotheticals versus those that incorporate a fact. Finally, for the effects that incorporate a fact, the effects are subdivided by whether the effect applies to the entire study population or only a subset of the study population. This organizational structure for the 24 excess effects (Figure 1) is also applicable to the 24 etiologic effects.

In this article, we describe in detail the six excess risk-based absolute causal effects (ie, causal risk differences) and show the six excess risk-based relative causal effects (ie, causal risk ratios) in the eAppendix (<http://links.lww.com/EDE/A725>). Our focus is intended to provide detailed description of characteristics (4), (5) and (6) (ie, causal vs. preventive, incorporates a fact vs. only has hypotheticals, and entire study population vs. a subset of the study population, respectively) because these characteristics are not clearly described in epidemiology. Thus, rate-based effects are not described here but can be easily extrapolated from the risk-based effects. While important, the estimation of etiologic effects requires strong and generally untenable assumptions.<sup>9–11,22</sup> Nonetheless, the defining characteristics and labeling conventions easily accommodate all 48 causal effects. Therefore, we distinguish the six risk-based absolute causal effects (indicated on the top of Figure 1), based on characteristics (4)–(6).

## Components of the Causal Effects

The risks that comprise the causal risk differences include factual risks, counterfactual risks, and hypothetical risks. Factual risks represent the actual proportion of the diseased people in the study population—the risk in those actually exposed ( $\Pr(Y = 1|A = 1)$ ) or  $[p_1 + p_2]$ , the risk in those actually unexposed ( $\Pr(Y = 1|A = 0)$ ) or  $[q_1 + q_3]$ , and the risk in the entire study population composed of the actually exposed and actually unexposed ( $\Pr(Y = 1)$  or  $[p_1 \times \Pr(A = 1) + p_2 \times \Pr(A = 1) + q_1 \times \Pr(A = 0) + q_3 \times \Pr(A = 0)]$ ). Crude



**FIGURE 1.** An organizational schema for excess causal effects. (The schema for the 24 excess causal effects shown here also applies to the 24 etiologic causal effects.)

estimates are comparisons between factual risks. The crude estimate is  $([p_1 + p_2] - [q_1 + q_3])$  for a causative exposure and  $([q_1 + q_3] - [p_1 + p_2])$  for a preventive exposure.

Counterfactual risks represent the proportion of diseased people there would have been in the study population under conditions counter to the actual exposure condition—the risk in those actually exposed had they been unexposed ( $\text{pr}(Y_{a=0} = 1|A = 1)$  or  $[p_1 + p_3]$ ) and the risk in those actually unexposed had they been exposed ( $\text{pr}(Y_{a=1} = 1|A = 0)$  or  $[q_1 + q_2]$ ).

We refer to the remaining risks as “hypotheticals”; a hypothetical risk represents the proportion of diseased people there would have been in the study population of exposed and unexposed if the individuals had all been exposed or if they had all been unexposed. Although often referred to as counterfactual risks, they are not completely counter-to-fact; hypothetical risks combine facts and counterfactuals.<sup>20,23</sup> While this distinction was noted by Rubin,<sup>23</sup> Morgan and Winship,<sup>20</sup> and Williamson et al,<sup>24</sup> “counterfactuals” and “hypotheticals” are often used interchangeably within epidemiology. The hypothetical risks in the study population are the risk in exposed and unexposed people if all were unexposed ( $\text{pr}(Y_{a=0} = 1)$  or  $[p_1 \times \text{pr}(A = 1) + p_3 \times \text{pr}(A = 1) + q_1 \times \text{pr}(A = 0) + q_3 \times \text{pr}(A = 0)]$ ) and the risk in exposed and unexposed people

if all were exposed ( $\text{pr}(Y_{a=1} = 1)$  or  $[p_1 \times \text{pr}(A = 1) + p_2 \times \text{pr}(A = 1) + q_1 \times \text{pr}(A = 0) + q_2 \times \text{pr}(A = 0)]$ ). In the former, the risk in those actually exposed is counter-to-fact and the risk in those actually unexposed is fact. In the latter, the risk in those actually exposed is fact and the risk in those actually unexposed is counter-to-fact.

## Causal Effects

The causal risk differences (RD) shown in Table 1 are labeled (in column 1) in the form of  $\text{RD}_{X,Z}$ . First, each effect is either causative or preventive, depending on the hypothesized exposure effect ( $\text{RD}_{\text{CAUS},Z}$  or  $\text{RD}_{\text{PREV},Z}$ ). Second, borrowing terminology from the literature on mediation, each effect is then labeled either “controlled” or “natural.”<sup>25</sup> Controlled effects do not include facts, whereas natural effects do. Third, each effect is labeled to indicate its applicability to the entire population, only the exposed or only the unexposed. Controlled effects apply only to the entire study population ( $\text{RD}_{X,\text{CONPOP}}$ ). Natural effects can apply to the entire study population ( $\text{RD}_{X,\text{NATPOP}}$ ), to those actually exposed ( $\text{RD}_{X,\text{EXP}}$ ), or to those actually unexposed ( $\text{RD}_{X,\text{UNX}}$ ). These characteristics yield three effects for causative exposures ( $\text{RD}_{\text{CAUS},\text{CONPOP}}$ ,  $\text{RD}_{\text{CAUS},\text{NATPOP}}$ , and  $\text{RD}_{\text{CAUS},\text{EXP}}$ ) and three effects for preventive exposures ( $\text{RD}_{\text{PREV},\text{CONPOP}}$ ,  $\text{RD}_{\text{PREV},\text{NATPOP}}$ , and  $\text{RD}_{\text{PREV},\text{UNX}}$ ). Note that the labels for the six relative causal effects

TABLE 1. Causal Effects in Potential Outcomes and Response Type Notation, with Description, Interpretation, and Requirements for Validity

Label	Type of Effect and Definition	Potential Outcomes Notation	Response Type Notation	Conditions for Valid Estimation of (a Non-Null) Effect <sup>a</sup>	Intervention Target and Interpretation <sup>b</sup>	References for Effect <sup>c</sup>
RD <sub>CAUS_CONPOP</sub>	<ul style="list-style-type: none"><li>• Causative, controlled, population</li><li>• Risk in the study population if all exposed (hypothetical) - risk in the study population if all unexposed (hypothetical)</li></ul>	$\begin{aligned} &\text{pr}(Y_{a=1} = 1) - \text{pr}(Y_{a=0} = 1) \\ &= [p_1 \times \text{pr}(A = 1) + p_2 \times \text{pr}(A = 0)] - [q_1 \times \text{pr}(A = 0) + q_2 \times \text{pr}(A = 1)] \\ &= [p_1 \times \text{pr}(A = 1) + p_3 \times \text{pr}(A = 0)] - [q_1 \times \text{pr}(A = 0) + q_3 \times \text{pr}(A = 1)] \\ &= [p_2 \times \text{pr}(A = 1) + q_2 \times \text{pr}(A = 0)] - [p_3 \times \text{pr}(A = 1) + q_3 \times \text{pr}(A = 0)] \\ &= \text{pr}(A = 1)[p_2 - p_3] + \text{pr}(A = 0)[q_2 - q_3] \end{aligned}$	<ul style="list-style-type: none"><li>▪ <math>p_1 = q_1</math> and <math>p_2 = q_2</math> and <math>p_3 = q_3</math> (stronger)</li><li>▪ <math>(p_1 + p_2) = (q_1 + q_2)</math> and <math>(p_1 + p_3) = (q_1 + q_3)</math> (weaker)</li></ul>	<ul style="list-style-type: none"><li>• Entirely exposed population</li><li>• Reduction in population disease risk if causative exposure removed from entirely exposed population</li></ul>	Explicit 3,6,13,15,24,26-36,43,47-52	
RD <sub>PREV_CONPOP</sub>	<ul style="list-style-type: none"><li>• Preventive, controlled, population</li><li>• Risk in the study population if all unexposed (hypothetical) - risk in the study population if all exposed (hypothetical)</li></ul>	$\begin{aligned} &\text{pr}(Y_{a=0} = 1) - \text{pr}(Y_{a=1} = 1) \\ &= [p_1 \times \text{pr}(A = 1) + p_3 \times \text{pr}(A = 0)] - [q_1 \times \text{pr}(A = 0) + q_3 \times \text{pr}(A = 1)] \\ &= [p_1 \times \text{pr}(A = 1) + p_2 \times \text{pr}(A = 0)] - [q_1 \times \text{pr}(A = 0) + q_2 \times \text{pr}(A = 1)] \\ &= [p_3 \times \text{pr}(A = 1) + q_3 \times \text{pr}(A = 0)] - [p_2 \times \text{pr}(A = 1) + q_2 \times \text{pr}(A = 0)] \\ &= \text{pr}(A = 1)[p_3 - p_2] + \text{pr}(A = 0)[q_3 - q_2] \end{aligned}$	<ul style="list-style-type: none"><li>▪ <math>p_1 = q_1</math> and <math>p_2 = q_2</math> and <math>p_3 = q_3</math> (stronger)</li><li>▪ <math>(p_1 + p_2) = (q_1 + q_2)</math> and <math>(p_1 + p_3) = (q_1 + q_3)</math> (weaker)</li></ul>	<ul style="list-style-type: none"><li>• Entirely unexposed population</li><li>• Reduction in population disease risk if preventive exposure given to entirely unexposed population</li></ul>	NA	
RD <sub>CAUS_NATPOP</sub>	<ul style="list-style-type: none"><li>• Causative, natural, population</li><li>• Risk in the study population under actual exposure status (fact) - risk in the study population if all unexposed (hypothetical)</li></ul>	$\begin{aligned} &\text{pr}(Y = 1) - \text{pr}(Y_{a=0} = 1) \\ &= [p_1 \times \text{pr}(A = 1) + p_2 \times \text{pr}(A = 0)] - [p_1 \times \text{pr}(A = 0) + q_3 \times \text{pr}(A = 1)] \\ &= [p_1 \times \text{pr}(A = 1) + p_3 \times \text{pr}(A = 0)] - [q_1 \times \text{pr}(A = 0) + q_3 \times \text{pr}(A = 1)] \\ &= p_2 \times \text{pr}(A = 1) - p_3 \times \text{pr}(A = 1) \\ &= \text{pr}(A = 1)[p_2 - p_3] \end{aligned}$	No conditions, however, if $p_1 = q_1$ and $p_3 = q_3$ can multiply crude by $p(A = 1)$	<ul style="list-style-type: none"><li>• Partially exposed population</li><li>• Reduction in population disease risk if causative exposure removed from exposed in a partially exposed population</li></ul>	Explicit 37-39	
RD <sub>PREV_NATPOP</sub>	<ul style="list-style-type: none"><li>• Preventive, natural, population</li><li>• Risk in the study population under actual exposure status (fact) - risk in the study population if all exposed (hypothetical)</li></ul>	$\begin{aligned} &\text{pr}(Y = 1) - \text{pr}(Y_{a=1} = 1) \\ &= [p_1 \times \text{pr}(A = 1) + p_2 \times \text{pr}(A = 0)] - [q_1 \times \text{pr}(A = 0) + q_3 \times \text{pr}(A = 1)] \\ &= [p_1 \times \text{pr}(A = 1) + p_3 \times \text{pr}(A = 0)] - [q_1 \times \text{pr}(A = 0) + q_2 \times \text{pr}(A = 1)] \\ &= q_3 \times \text{pr}(A = 0) - q_2 \times \text{pr}(A = 0) \\ &= \text{pr}(A = 0)[q_3 - q_2] \end{aligned}$	No conditions, however, if $p_1 = q_1$ and $p_2 = q_2$ can multiply crude by $p(A = 0)$	<ul style="list-style-type: none"><li>• Partially exposed population</li><li>• Reduction in population disease risk if preventive exposure given to unexposed in a partially exposed population</li></ul>	NA	
RD <sub>CAUS_EXP</sub>	<ul style="list-style-type: none"><li>• Causative, natural, exposed subpopulation</li><li>• Risk in actually exposed from the study population (fact) - risk in actually exposed from the study population if unexposed (counterfactual)</li></ul>	$\begin{aligned} &\text{pr}(Y = 1 A = 1) - \text{pr}(Y_{a=0} = 1 A = 1) \\ &= [p_1 \times \text{pr}(A = 1) + p_2 \times \text{pr}(A = 0)] - [p_1 \times \text{pr}(A = 0) + q_3 \times \text{pr}(A = 1)] \\ &= [p_1 \times \text{pr}(A = 1) + p_3 \times \text{pr}(A = 0)] - [q_1 \times \text{pr}(A = 0) + q_2 \times \text{pr}(A = 1)] \\ &= p_2 \times \text{pr}(A = 1) - p_3 \times \text{pr}(A = 1) \\ &= \text{pr}(A = 1)[p_2 - p_3] \end{aligned}$	<ul style="list-style-type: none"><li>▪ <math>p_1 = q_1</math> and <math>p_3 = q_3</math> (stronger)</li><li>▪ <math>(p_1 + p_3) = (q_1 + q_3)</math> (weaker)</li></ul>	<ul style="list-style-type: none"><li>• Exposed in partially exposed population</li><li>• Reduction in subpopulation disease risk if causative exposure removed from exposed in a partially exposed population</li></ul>	Explicit 3,6,18,24,37-41,43,45-52	

(Continued)



TABLE 1. (Continued)

Label	Type of Effect and Definition	Potential Outcomes Notation	Response Type Notation	Conditions for Valid Estimation of (a Non-Null) Effect <sup>a</sup>	Intervention Target and Interpretation <sup>b</sup>	References for Effect <sup>c</sup>
RD <sub>PREV_UNX</sub>	<ul style="list-style-type: none"> <li>Preventive, natural, unexposed subpopulation</li> <li>Risk in actually unexposed from the study population (fact) - risk in actually unexposed from the study population if exposed (counterfactual)</li> </ul>	$\text{pr}(Y = 1 A=0) - \text{pr}(Y_{a=1} = 1 A = 0)$	$(q_1 + q_3) - (q_1 + q_2) = q_3 - q_2$	<ul style="list-style-type: none"> <li><math>p_1 = q_1</math> and <math>p_2 = q_2</math> (stronger)</li> <li><math>(p_1 + p_2) = (q_1 + q_2)</math> (weaker)</li> </ul>	<ul style="list-style-type: none"> <li>Unexposed in partially exposed population</li> <li>Reduction in subpopulation disease risk if preventive exposure given to unexposed in a partially exposed population</li> </ul>	Indirect <sup>42</sup>

<sup>a</sup>Such that the crude risk difference—an observed quantity—estimates the effect, and assuming for causative effects exposed are compared with unexposed (ie, relevant crude risk difference =  $[p_1 + p_2] - [q_1 + q_3]$ ) and for preventive effects unexposed are compared with exposed (ie, relevant crude risk difference =  $[q_1 + q_3] - [p_1 + p_2]$ ), and  $0\% < \text{Pr}(A = 1) < 100\%$ .

<sup>b</sup>Relevant to appropriate intervention target with all else equal.

<sup>c</sup>References categorized as those defined explicitly or indirectly. Most explicit reference(s) available in general epidemiology textbooks or published papers provided.

(eAppendix, <http://links.lww.com/EDE/A725>) are in the form  $RR_{X,Z}$ . Following convention in epidemiology (eg, Rothman et al<sup>16</sup>), we recommend  $ID_{X,Z}$  (“ID” represents incidence density) for rate differences and  $IR_{X,Z}$  for rate ratios. Finally, for etiologic effects,<sup>9–11,22</sup> we recommend  $RD_{ETIOL,X,Z}$  (and  $RR_{ETIOL,X,Z}$ ).

The type of effect and definition are provided in column 2; potential outcomes and response type notation are shown in columns 3 and 4, respectively. Column 5 shows conditions under which these effects could be validly estimated in the absence of our all-knowing perspective by the observable crude risk difference  $(p_1 + p_2) - (q_1 + q_3)$  for causative effects, or  $(q_1 + q_3) - (p_1 + p_2)$  for preventive effects. These are conditions in which the causal effect is equal to the crude risk difference. Each effect has a corresponding intervention target and intervention interpretation (column 6), as will be described later.

We searched general epidemiologic texts and papers oriented to epidemiology published in English since 1980. Papers with terms for “causal effect” and “epidemiology” in the title, abstract, or keyword were included. We supplemented this search with the forthcoming text by Hernán and Robins<sup>43</sup> and other important methods papers that were not initially found.

The last column of Table 1 lists citations that describe the contrast of interest (eg, all exposed versus all unexposed), regardless of whether described in terms of relative or absolute risks. If the contrast was described as causal (eg, the denominator represents a potential outcome, counterfactual or hypothetical comparison, or the effect is specifically referred to as a causal effect), we labeled the citation as “explicit.” If the contrast was described as an association in which the comparison could be imagined as counterfactual/hypothetical rather than observed, we labeled the citation as “indirect.” We also considered a category for effects not meeting these criteria but mentioned by name or deducible from an attributable fraction. However, no effects belonged to this category. When there are multiple citations for the same effect, we provide citations only for the most explicit definitions. Two of these effects do not appear at all in the reviewed literature:  $RD_{PREV\_CONPOP}$  and  $RD_{PREV\_NATPOP}$ . Note that Maldonado and Greenland<sup>5</sup> provide a general formula that can be used to describe the 24 excess effects discussed here. However, this article is not referenced in Table 1 because these authors do not define specific effects. Our literature search also led us to several descriptions of various causal effects in other fields, most notably in econometrics. For a thorough overview of causal effects from the econometrics perspective, see Heckman.<sup>44</sup> Econometrics publications are not referenced in Table 1 because they are not oriented to an epidemiologic audience.

### Controlled (Population) Effects

$RD_{CAUS\_CONPOP}$  the causal effect described in the first row of Table 1, is a controlled population effect that compares the risk in the study population if everyone had been exposed (hypothetical) with the risk in the study population if

everyone had been unexposed (hypothetical).  $RD_{PREV\_CONPOP}$  (second row of Table 1) compares the risk in the study population if everyone had been unexposed (hypothetical) with the risk in the study population if everyone had been exposed (hypothetical).

For both controlled effects, the response type notation makes clear the elements that affect the magnitude of A's effect on Y: the proportions of type 2 and type 3 people in the entire population. In addition, the requirements for valid estimation of these effects are the same for both effects. The crude risk difference comparing actually exposed with actually unexposed people (or vice versa) would be a valid estimate of  $RD_{CAUS\_CONPOP}$  (or  $RD_{PREV\_CONPOP}$ ) if the proportions of type 1, type 2, and type 3 (and thus, type 4) people in those actually exposed were equal to these proportions in those actually unexposed (a stronger condition) or if the sum of the proportions of type 1 and type 2 people in those actually exposed was equal to the sum of these proportions in those actually unexposed and the sum of the proportions of type 1 and type 3 people in those actually exposed was equal to the sum of these proportions in those actually unexposed (a weaker condition).

### Natural Population Effects

There are four natural effects; all include a fact. The natural population effects compare a fact with a hypothetical.  $RD_{CAUS\_NATPOP}$  (third row of Table 1) compares the risk in the study population under actual exposure status (fact) with the risk in the study population had everyone been unexposed (hypothetical). The elements that affect the magnitude of A's effect on Y are the prevalence of exposure and the proportions of type 2 and type 3 people within those actually exposed.  $RD_{PREV\_NATPOP}$  (fourth row of Table 1) compares the risk in the study population under actual exposure status (fact) with the risk in the study population had everyone been exposed (hypothetical). The elements that affect the magnitude of A's effect on Y are the prevalence of exposure and the proportions of type 2 and type 3 people within those actually unexposed.

The natural population effects cannot be directly estimated (eg, with a crude RD). However, if the proportions of type 1 and type 3 people are equal across the exposed and unexposed (as expected in a randomized controlled trial),  $RD_{CAUS\_NATPOP}$  can be estimated by multiplying the crude (contrasting exposed to unexposed) by  $pr(A = 1)$ . Similarly, if the proportions of type 1 and type 2 people are equal across the exposed and unexposed,  $RD_{PREV\_NATPOP}$  can be estimated by multiplying the crude (contrasting unexposed to exposed) by  $pr(A = 0)$ .

### Natural Subpopulation Effects

The natural subpopulation effects compare a fact with a counterfactual.  $RD_{CAUS\_EXP}$  (fifth row of Table 1) compares the risk in the actually exposed (fact) with the risk in the actually exposed had they been unexposed (counterfactual). The elements that affect the magnitude of A's effect on Y are the proportions of type 2 and type 3 people within the exposed.  $RD_{PREV\_UNX}$  (sixth row of Table 1) compares the risk in the

actually unexposed (fact) with the risk in the actually unexposed had they been exposed (counterfactual). The elements that affect the magnitude of A's effect on Y are the proportions of type 2 and type 3 people within the unexposed.

The crude risk difference (contrasting exposed to unexposed) would be a valid estimate of  $RD_{CAUS\_EXP}$  if the proportions of type 1 and type 3 people were equal across the exposed and unexposed (a stronger condition) or if the sum of these proportions was equal across the exposed and unexposed (a weaker condition). The crude risk difference (contrasting unexposed to exposed) would be a valid estimate of  $RD_{PREV\_UNX}$  if the proportions of type 1 and type 2 people were equal across the exposed and unexposed (a stronger condition) or if the sum of these proportions was equal across the exposed and unexposed (a weaker condition).

## NONEQUIVALENCE OF THE CAUSAL RISK DIFFERENCES

Under many conditions, the effects shown in Table 1 would differ. The four rows in Table 2 represent four hypothetical nonrandomized studies. In row 1 where the exposure is causative (and  $p_2 \neq q_2$ ,  $p_3 = q_3$ , and the prevalence of A is 30%), the causative effects are not equal (and vary from 0.119 to 0.398). Likewise, in row 4 where the exposure is preventive (and  $p_2 = q_2$  but  $p_3 \neq q_3$  and the prevalence of A is 60%), the preventive effects are not equal (and vary from 0.159 to 0.398). In both examples, the discrepancies among the relevant effects are notable. eFigure 1 (<http://links.lww.com/EDE/A725>) further illustrates the impact of the prevalence of the exposure and proportions of types 2 and 3 in the exposed and unexposed.

The conditions under which the risk-based causal effects would be the same are also described in the eAppendix (<http://links.lww.com/EDE/A725>). However, these circumstances may rarely hold. In nonrandomized studies, confounding (eg, in the causative subpopulation effect when  $[p_1 + p_3] \neq [q_1 + q_3]$ )<sup>18</sup> is assumed to be ubiquitous because causes of disease (exposure of interest and other causes) tend to co-occur within people. This co-occurrence likely leads to differential distribution not only of doomed and preventive types but also of all response types across exposed and unexposed in naturally occurring populations. Thus, differences among these causal effects are likely.

## SPECIFYING THE APPROPRIATE CAUSAL EFFECT FOR THE INTERVENTION EFFECT OF INTEREST

Assuming an epidemiologist decided to estimate a risk difference, specifying the causal effect appropriate for a specific intervention effect depends on the answers to the following three questions: (1) Is the exposure hypothesized to be causal or preventive? (2) Is the intervention target entirely exposed, entirely unexposed, or composed of exposed and unexposed people? (3) If the intervention target is partially exposed, is the intent to estimate the potential reduction in the

**TABLE 2.** Numeric Example: Exposure A Is Causative, with More Type 2 Among Exposed People (Rows 1–2); Exposure A Is Preventive, with More Type 3 Among Unexposed People (Rows 3–4)

Row	pr(A = 1)	Distribution of Types in Exposed				Distribution of Types in Unexposed				Causal Effect					
		P <sub>1</sub>	P <sub>2</sub>	P <sub>3</sub>	P <sub>4</sub>	q <sub>1</sub>	q <sub>2</sub>	q <sub>3</sub>	q <sub>4</sub>	RD <sub>CAUS_CONPOP</sub>	RD <sub>PREV_CONPOP</sub>	RD <sub>CAUS_NATPOP</sub>	RD <sub>PREV_NATPOP</sub>	RD <sub>CAUS_EXP</sub>	RD <sub>PREV_UNX</sub>
1	0.3	0.050	0.400	0.002	0.548	0.050	0.200	0.002	0.748	0.258	-0.258	0.119	-0.139	0.398	-0.198
2	0.6	0.050	0.400	0.002	0.548	0.050	0.200	0.002	0.748	0.318	-0.318	0.239	-0.079	0.398	-0.198
3	0.3	0.050	0.002	0.200	0.748	0.050	0.002	0.400	0.548	-0.338	0.338	-0.059	0.279	-0.198	0.398
4	0.6	0.050	0.002	0.200	0.748	0.050	0.002	0.400	0.548	-0.278	0.278	-0.119	0.159	-0.198	0.398

population risk or in the subpopulation risk? Figure 2 aligns the responses to these three questions with each of the six causal RDs shown in Table 1. Recall the assumption needed for an intervention interpretation—that all else is equal.

The causative effects compare people under (factual or hypothetical) exposed status to (counterfactual or hypothetical) unexposed status. These effects will be positive when the exposure was in fact causative in the study population and can be generally interpreted as the reduction in disease risk associated with removing the exposure from exposed people. RD<sub>CAUS\_CONPOP</sub> applies when the intervention target is entirely exposed because it tells us the reduction in disease risk the target would have if the exposure was removed from everyone. For example, estimation of RD<sub>CAUS\_CONPOP</sub> would be appropriate when considering a potential toxin in the water supply for some defined population. The intervention question could be “What is the expected reduction in mortality if the toxin were removed from the water supply for the entire population?” RD<sub>CAUS\_NATPOP</sub> applies when the intervention target is partially exposed and we want to estimate the reduction in the population disease risk the target would have if the exposure was removed from the exposed. RD<sub>CAUS\_EXP</sub> applies when the intervention target is partially exposed and we want to estimate the reduction in the exposed disease risk the target would have if the exposure was removed from the exposed. Estimation of RD<sub>CAUS\_NATPOP</sub> and RD<sub>CAUS\_EXP</sub> would be appropriate when considering a marketed drug with a risk of myocardial infarction. Here the intervention question could be “What is the expected reduction in the risk of fatal myocardial infarction if this drug was removed from the market?” The choice of one natural causative effect over the other depends on whether the reduction in risk in the whole population (RD<sub>CAUS\_NATPOP</sub>) or in the exposed subpopulation (RD<sub>CAUS\_EXP</sub>) is of interest (Figure 2).

The preventive effects compare people under (factual or hypothetical) unexposed status with (counterfactual or hypothetical) exposed status. These effects will be positive when the exposure was in fact preventive in the study population and can be generally interpreted as the reduction in disease risk associated with giving the exposure to unexposed people. RD<sub>PREV\_CONPOP</sub> applies when the intervention target is entirely unexposed because it tells us the reduction in disease risk the target would have if the exposure was given to everyone. For example, estimation of RD<sub>PREV\_CONPOP</sub> would have been appropriate when AZT was in development (ie, before marketing). In phase 2 and 3 clinical trials, the intervention question might have been “What is the expected reduction in mortality if all people newly diagnosed with HIV in the US were to take AZT?”

RD<sub>PREV\_NATPOP</sub> applies when the intervention target is partially exposed and we want to estimate the reduction in the population disease risk the target would have if the exposure was given to the unexposed. RD<sub>PREV\_UNX</sub> applies when the intervention target is partially exposed and we want to

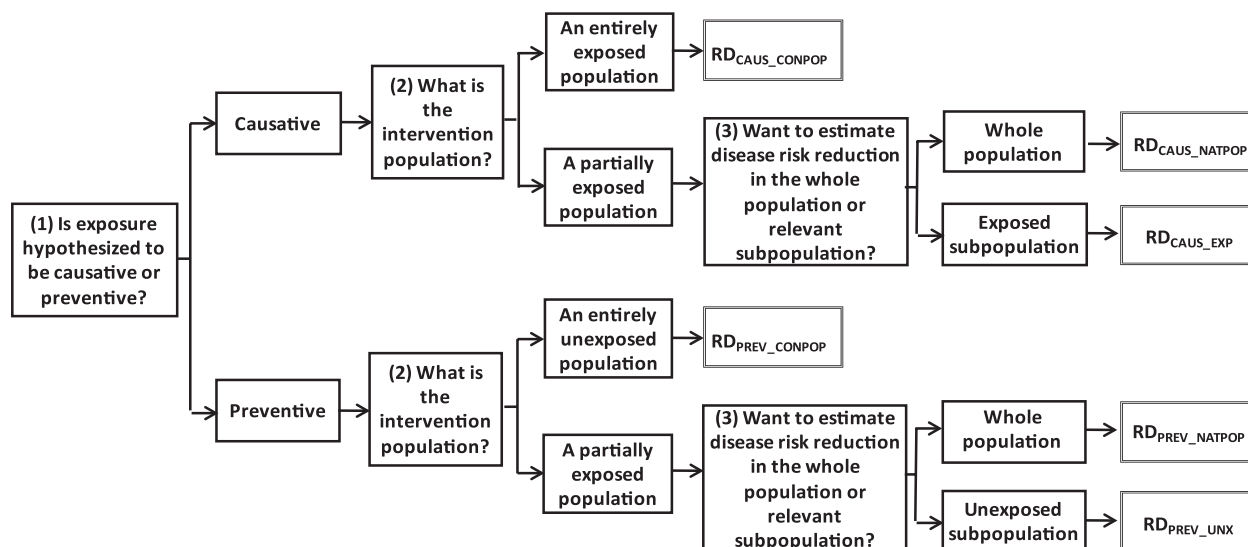


FIGURE 2. Considering the intervention population to identify the causal effect of interest.

estimate the reduction in the exposed disease risk the target would have if the exposure was given to the unexposed. Estimation of  $RD_{PREV\_NATPOP}$  and  $RD_{PREV\_EXP}$  would be appropriate if a policy maker is considering a program to provide free AZT (which is already marketed) for patients with HIV in New York City who do not have access to the drug. The choice of one natural preventive effect over the other depends on whether the reduction in risk in the whole population ( $RD_{PREV\_NATPOP}$ ) or in the unexposed subpopulation ( $RD_{PREV\_UNX}$ ) is of interest (Figure 2).

Researchers commonly estimate a causative effect and interpret a positive risk difference (or risk ratio  $>1$ ) as causative and a negative risk difference (or risk ratio  $<1$ ) as preventive. Assuming exchangeability, this is acceptable when the interpretation is qualitative (eg, the exposure has a preventive effect on the outcome) or the preventive controlled effect is of interest (and the causative controlled effect was estimated). To estimate a precise natural causal effect, however, it is generally inappropriate to interpret a causative effect for a preventive exposure (eg, see Table 2, row 1). As expected, the causative effects are all positive and the preventive effects are all negative. While any of these measures could be used to confirm the hypothesized direction of the effect, we need to specify the causative effect of interest to estimate a precise effect from our study population.

Using the study population in row 2,  $RD_{CAUS\_CONPOP}$  indicates that there would be a 31.8% decrease in the population disease risk if exposure A was removed from everyone in an entirely exposed population.  $RD_{CAUS\_NATPOP}$  indicates that there would be a 23.9% decrease in the population disease risk if exposure A was removed from the exposed in a partially exposed population. While the controlled population effects,  $RD_{CAUS\_CONPOP}$  and  $RD_{PREV\_CONPOP}$  have the same absolute value of 31.8%, this is not the case for the natural effects. It would be incorrect to interpret the absolute value

of  $RD_{PREV\_NATPOP}$  (7.9%) as the reduction in the population disease risk if the exposure was removed from the exposed. This requires interpretation of  $RD_{CAUS\_NATPOP}$  (23.9%). Similarly, it would be incorrect to interpret the absolute value of  $RD_{PREV\_UNX}$  (19.8%) as the reduction in the exposed disease risk if the exposure was removed from the exposed. This requires interpretation of  $RD_{CAUS\_EXP}$  (39.8%). In these examples, the discrepancy between the absolute value of the causative effect (ie, the exposed to unexposed comparison) versus the preventive effect (ie, the unexposed to exposed comparison) is quite large. In rows 3 and 4, where exposure A is preventive, similar principles hold.

## DISCUSSION

We provided an organizational schema that distinguishes 48 causal effects based on six characteristics, whether the effect: (1) measures disease etiology or excess, (2) uses risks or rates, (3) uses an absolute or relative comparison, (4) uses an exposure hypothesized to be causative or preventive, (5) incorporates facts or only hypotheticals, and (6) applies to the entire study population or only a subset of the study population. We focused the main text on excess causal risk differences; excess causal risk ratios are shown in eTable 1 (<http://links.lww.com/EDE/A725>). Our schema also incorporates 12 rate-based excess effects and 24 etiologic effects and uses labeling that can be applied to all 48 effects. For instance, if rate ratios were of interest (using "ID" to represent incidence density<sup>6</sup>), the causal effects in Figure 2 could be replaced with  $ID_{CAUS\_CONPOP}$ ,  $ID_{CAUS\_NATPOP}$  and so on. While our schema incorporates etiologic effects, additional notation is needed to define these effects in potential outcomes or response type notation. We also provided a decision tree that allows an epidemiologist to specify and correctly interpret the causal effect appropriate for a specific intervention target. This tree corresponds to



characteristics (4)–(6) [assuming a decision has already been made regarding characteristics (1)–(3)] and also translates to the other 42 causal effects (risk ratios, rate differences, etiologic effects, etc.). Also note that risk differences could be used to estimate effects of continuously distributed exposures.

This schema led to the identification of two population-preventive causal effects not described in epidemiology (the preventive controlled population and natural population effects), which would be of interest when estimating the effect of common interventions, such as new drug approvals, and public health educational programs. In fact, none of the preventive causal effects were explicitly defined in the epidemiology literature; the other preventive effect (the preventive unexposed subpopulation effect) has been described only indirectly as an associational measure.

Our schema was limited to full causal effects (ie, the intended intervention was to give a preventive exposure to all unexposed people or remove a causative exposure from all exposed). However, in most cases, it is unrealistic to expect an intervention to accomplish this intended result. Therefore, an epidemiologist might be interested in the impact of giving an exposure to (or removing one from) some proportion of the study population.<sup>5</sup> Our schema and corresponding labeling convention can be extended to these “partial” causal effects by (1) specifying the exposure proportion given to unexposed or removed from exposed and (2) assuming that the exposure addition or removal is unassociated with other factors that cause disease (ie, the exposure is randomly given to unexposed or removed from exposed). However, this assumption is also unrealistic and likely unpredictable. Nonetheless, if an epidemiologist was interested in the reduction in population disease risk that would occur if the exposure was removed from (a randomly selected) 50% of the exposed,<sup>5</sup> then the label could be  $RD_{CAUS\_NATPOP\_50\%REM}$ .

Similarly, although we focused on risk reduction as the intervention goal, there may be circumstances in which researchers are interested in forecasting the effects of exposing populations to factors that cause disease or removing preventive exposures from those who are exposed. In fact, several publications describe the causative effect in the unexposed subpopulation,<sup>24,45–47</sup> which we would label  $RD_{CAUS\_UNX}$ . Our schema could also be extended to accommodate the preventive effect in the exposed subpopulation:  $RD_{PREV\_EXP}$ .

Differences between exposed and unexposed people can lead to substantial variability across causal effects under the same causal scenario. This natural variability is likely ubiquitous. Just as epidemiologists expect confounding in real-world populations, we should assume that the causal effects in Table 1 will differ within a study population. To ensure our estimates address our intended questions, we must first specify the causal effect of interest and then use appropriate methodology to estimate that causal effect (eg, standardization, inverse probability weighting). We have provided the requirements for validly estimating these effects (ie, conditions for

no confounding). Although several articles demonstrate that  $RD_{CAUS\_CONPOP}$  and  $RD_{CAUS\_EXP}$  can be estimated with various methods of confounding control,<sup>48–52</sup> an important next step is to align study designs and analytic techniques with more of the effects in our organizational schema. Furthermore, we reiterate that any interpretation of a causal effect as an intervention effect also requires the strict and likely unrealistic assumptions encapsulated within “all else being equal.” Indeed, it is difficult to imagine scenarios in which the causal effect estimated in a study could be fully transportable with no unintended consequences.<sup>53</sup>

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