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Tutorial: A nontechnical explanation of the counterfactual definition of effect modification and interaction

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Abstract

Effect modification and interaction are important concepts for answering causal questions about interdependent effects of two (or more) exposures on some outcome of interest. Although conceptually alike and often mistakenly regarded as synonymous, effect modification and interaction actually refer to slightly different concepts when considered from a causal perspective. Their subtle yet relevant distinction lies in how the interplay between exposures is defined and the causal roles attributed to the exposures involved in the effect modification and interaction. To gain more insight into similarities and differences between the concepts of effect modification and interaction, the counterfactual theory of causation, albeit complicated, can be very helpful. Therefore, this article presents a nontechnical explanation of the counterfactual definition of effect modification and interaction. Essentially, effect modification and interaction are reflections of the reality and complexity of multicausality. The causal effect of an exposure of interest often depends on the levels of other exposures (effect modification) or causal effects of other exposures (interaction). Consequently, exposure effects should not be regarded in isolation but in combination. Understanding the underlying principles of effect modification and interaction on a conceptual level enables researchers to better anticipate, detect, and interpret these causal phenomena when setting up, analyzing, and reporting findings of (clinical) epidemiological studies. Effect modification and interaction are not biases to be avoided but properties of causal effects that ought to be unveiled. Hence, evidence for effect modification and interaction needs to be shown in order to delineate in whom and which instances causal effects occur.

Keywords: Effect modification; Interaction; Causal effects; Counterfactual theory; Additive and multiplicative models

1. Effect modification and interaction are natural aspects of causal effects, not bias

Causal questions addressed by (clinical) epidemiological studies usually focus on the causal effect of a single exposure on a certain outcome. For instance, whether and how exposure to a specific risk factor or medical treatment causes the occurrence or cure of some disease. It is well-recognized, however, that most outcomes are not caused by single exposures in *isolation* but by multiple exposures in *combination*. That is why experimental and observational studies frequently report results of subgroup or stratified analyses [4–12], to explore if the effect of the primary exposure under study depends on the level of another factor or on the effect of a secondary exposure. Indeed, it is often appropriate to investigate if the causal relation between an exposure and outcome under study is different for different types or groups of individuals [11–17]. In other words, to study for whom and in which situation(s) causal effects occur. Studying the combined influence of two (or more) exposures on some outcome constitutes a more elaborate and refined type of causal question that refers to the concepts of *effect modification* and *interaction* [18–24]. These concepts are very relevant for the practice of (clinical) epidemiological research and potentially have far-reaching implications for medical practice and public health, but can be difficult to fathom and

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may be poorly understood as a consequence. It is very easy to get lost in the literature and no longer see the forest for the trees because the terms effect modification and interaction are often used interchangeably, even though they refer to slightly different concepts from a causal viewpoint. What's more, effect modification and interaction may sometimes be confused with the concept of confounding. Confounding is concerned with separating causal from noncausal effects that cloud inferences about exposure-outcome relations [25–28]. Unlike confounding though, effect modification and interaction are not unwanted biases to be eliminated, but are part of causal reality to be elucidated. It is important that researchers and professionals from related disciplines (e.g., clinicians) have a proper understanding of what effect modification and interaction actually encapsulate. This will foster selection of appropriate design and analysis strategies in research practice, as well as adequate application of research findings in medical or public health practice.

The road to understanding starts with definitions. Effect modification and interaction have been defined as follows within the field of epidemiology [29]:

> *Effect modification:* Variation in the selected effect measure for the factor under study across levels of another factor.
>
> *Interaction:* The interdependent, reciprocal, or mutual operation, action, or effect of two or more factors to produce, prevent, control, mediate, or otherwise influence the occurrence of an event.

These are useful general definitions, but they do not clarify the *causal* connotation of the concepts of effect modification and interaction. Nor do they clearly designate the subtle differences between these concepts [21,23]. Because effect modification and interaction deal with causal effects, a theory of causation helps explaining and facilitates understanding of these concepts. For that purpose, counterfactual theory is useful [26,30–35].

1.1. The counterfactual framework is useful for explaining effect modification and interaction

Simply speaking, counterfactual theory deals with hypothetical scenarios about the occurrence of an outcome in contrasting states of exposure by posing "What if?" questions [26]. Counterfactual thinking basically amounts to imagining what might have been, a unique characteristic of human brainpower [36]. When thinking about the causal effect of an exposure on an outcome, an example of a counterfactual question is "Would the outcome have been different if exposed individuals had not been exposed in the first place?" For answering such a question, a mental picture of relevant contrasting situations and their potential outcomes needs to be drawn. It follows logically that the exposure causally affects the outcome in case the occurrence of the outcome would differ between contrasting situations (e.g., outcome occurs in exposed individuals but not if these individuals were unexposed, or vice versa). This is the counterfactual definition of a causal effect [26,30–35]. Clearly, only one situation is potentially observable in reality, whereas the hypothetical contrasting situation remains unobservable. Conceiving a relevant hypothetical contrast is crucial when sketching counterfactual scenarios. It is the truthmaker of causation since causal effects are context-dependent, meaning that an exposure may cause some outcome in one situation or target population but not in another [26,30,31]. Different causal contexts become particularly relevant when considering counterfactual questions regarding effect modification and interaction, which are more intricate because they deal with causal effects of a combination of exposures. Consequentially, more than one contrasting situation needs to be imagined for providing a counterfactual definition of these concepts. After all, the effect of a single exposure on some outcome is an incomplete picture of causality when there is effect modification or interaction [26,35].

Understanding effect modification and interaction on a conceptual level according to counterfactual theory is not an easy task. The literature on this topic can be quite technical and intimidating. The main aim of this tutorial article, therefore, is to provide a nontechnical explanation of the counterfactual definition of effect modification and interaction. Thereby, it may pave the way towards the more advanced literature on these concepts. For ease of explanation, unless stated otherwise, it is assumed throughout this article that exposures and outcomes are dichotomous and positively related (e.g., exposure to a risk factor causes more disease or exposure to a treatment causes more cure of disease). Nevertheless, the underlying concepts of effect modification and interaction also apply to non-dichotomous or inversely related exposures and outcomes, even though specific analytic strategies may differ. In a previous tutorial article, the counterfactual definition of confounding was explained nontechnically [27].

2. Effect modification and interaction are similar but not identical from a counterfactual perspective

To define the concepts of effect modification and interaction within the counterfactual framework of causation, a number of thought experiments must be conducted to compare outcomes between contrasting exposure states that all but one are unobservable. Counterfactual thinking is like mental time traveling, so imagine having Doc Brown's DeLorean to travel back and forth through time. This would allow for comparing potential outcomes that occur, possibly contrary to the fact, in one and the same group of individuals at the same time and place but for different states of exposure. For each different exposure state, the occurrence of an outcome of interest could then in theory be determined by means of an incidence measure express-

ing the risk of the outcome in the group of individuals. To identify causal effects, these risks have to be compared between the different exposure conditions that are identical with regard to all other variables related to person, time, and place (i.e., the situation of exchangeable background risks). When effect modification and interaction refer to a combination of two dichotomous exposures in relation to one dichotomous outcome, four hypothetical scenarios with counterfactual risks of potential outcomes are of interest:

- R_{00}: risk if exposed to neither exposure (background risk, independent of either exposure);
- R_{10}: risk if exposed to only first exposure (background risk plus effect of first exposure);
- R_{01}: risk if exposed to only second exposure (background risk plus effect of second exposure);
- R_{11}: risk if exposed to both exposures (background risk plus joint effect of both exposures).

These four counterfactual risks essentially form the basis for delineating both effect modification and interaction from a counterfactual point of view, although the way they are compared differs somewhat for the concept of effect modification than for that of interaction [23,26].

2.1. Effect modification: the causal effect of one exposure differs across levels of a second exposure

When considering effect modification according to a counterfactual definition, the main concern is whether the causal effect of the primary exposure of interest differs across levels or categories of a secondary exposure [13,21,23,26,37]. Effect modification is an *asymmetric* concept. It is focused on variation in the causal effect of the primary exposure among subgroups based on the secondary exposure, but not on variation of the effect of the secondary exposure, if any, among subgroups based on the primary exposure [23,26,38]. Whether or not the secondary exposure (i.e., the effect modifier) itself influences the outcome is not of primary interest for causal questions about effect modification. Although a secondary exposure can have a (in)direct causal relation with the outcome under study, this is not a prerequisite for it to modify the causal effect of the primary exposure [26,37,38].

Causal effects of the primary exposure in subgroups based on the secondary exposure can be expressed on different scales using the aforementioned counterfactual risks. An *additive* scale based on risk differences (RD) expresses the absolute magnitude of a causal effect, while a *multiplicative* scale using risk ratios (RR) expresses the relative magnitude of a causal effect. Effect modification is present on an additive scale when the absolute causal effect of the primary exposure in the *absence* of the secondary exposure ($RD_{.0} = R_{10} - R_{00}$) differs from the absolute causal effect in the *presence* of the secondary exposure ($RD_{.1} = R_{11} - R_{01}$). On the other hand, there is multiplicative effect modification if the relative causal effect of the primary exposure in the *absence* of the secondary exposure ($RR_{.0} = R_{10} / R_{00}$) differs from the relative causal effect in the *presence* of the secondary exposure ($RR_{.1} = R_{11} / R_{01}$). For defining modification of the causal effect of the primary exposure, two reference conditions are thus required for assessing heterogeneity versus homogeneity of effects [21,39]; one in which the secondary exposure is absent (R_{00}) and one in which it is present (R_{01}). Causal effect modification will always be evident on an additive scale ($RD_{.0} \neq RD_{.1}$) but not necessarily on a multiplicative scale ($RR_{.0} \neq RR_{.1}$), depending on whether and how the effect modifier affects the outcome. Fig. 1 visualizes the counterfactual definition of effect modification.

Evaluation of effect modification is akin to assessing *effect heterogeneity* [12,13,17,26,35,39–41]. That is, assessing whether the causal effect of an exposure on an outcome is heterogeneous in different subgroups based on an effect modifier that alters the causal exposure effect of interest. Effect modifiers are mostly non-modifiable, intrinsic factors not amenable for intervention (e.g., personal characteristics like sex, genotype) [42,43]. Effect modification can come to expression as a different magnitude of causal effects (*quantitative effect modification*, e.g., no or weak versus strong effects) or an opposite direction of causal effects (*qualitative effect modification*, e.g., beneficial versus harmful effects).

2.2. Interaction: the joint causal effect of two exposures differs from their expected combined effect

According to its counterfactual definition, the concept of interaction is focused on how a particular outcome is causally affected by two exposures operating together [13,18,21,23,26,35,39]. Besides the causal effect of the exposure of primary interest, the secondary exposure now also has a causal effect on the outcome [23,35,39]. Contrary to effect modification, interaction is essentially a *symmetric* concept. It refers to whether the effect of one exposure on some outcome is affected by the effect of another exposure on the same outcome, and vice versa [23,26,35,39]. If there is interaction between two exposures, the causal effect of the first exposure varies across levels of the second exposure and, simultaneously, the effect of the second exposure varies across levels of the first exposure. Two interdependent exposures have an equal status in the definition of interaction. This differs from effect modification, where only the causal effect of one exposure but not the other is of interest [21,23,26,35,38,40].

Like effect modification, interaction can also be expressed and defined on different scales [18,23,26,35,39]. When considering an additive scale, interaction between two exposures is present if the *sum* of the absolute causal effects of each exposure in isolation (separate effects) is different from the absolute causal effect of both exposures

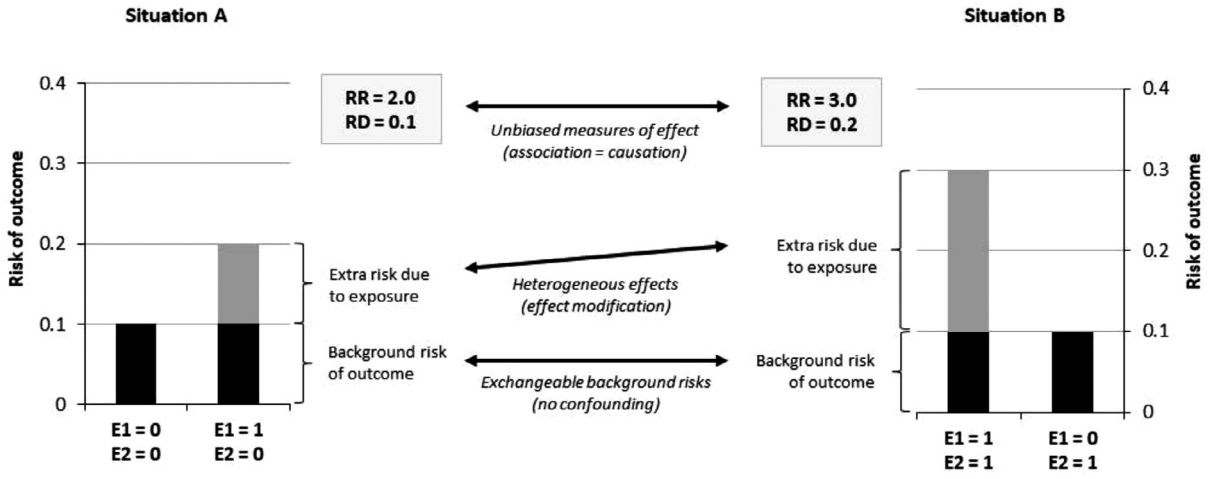

Fig. 1. The counterfactual definition of effect modification. The effect of an exposure E1 on the risk of an outcome in a single target population is shown in two contrasting exposure conditions: exposed (E1 = 1) and unexposed (E1 = 0). These conditions are depicted in two contrasting situations A and B based on the level of a second exposure variable E2, which is either absent (E2 = 0) or present (E2 = 1). In each situation, the absolute or relative difference in risks of the outcome between the exposed and unexposed conditions indicates the causal effect of exposure E1. The measures of effect (RD: risk difference, RR: risk ratio) are unconfounded due to exchangeability of background risks [27]. Effect modification by E2 is indicated by the different magnitudes of the extra risk of the outcome caused by E1, being smaller in situation A as compared to situation B. There are actually two causal effects of E1 that depend on the level of E2 and come to expression as heterogeneous measures of effects. Of note, the figure assumes that E2 has no causal effect on the outcome because the magnitude of the background risks is identical in situations A and B. When E2 would have a causal effect on the outcome, this effect would need to be incorporated in the background risk which would then be different (say 0.1 higher) in situation B than in situation A. Effect modification by E2 would still be present in case the absolute magnitude of the extra risk of the outcome caused by E1 remains different between situation A and B, which would then be reflected by heterogeneity of the RD but not necessarily of the RR.

in combination (joint effect). Translated into risk differences, the separate effects of two exposures are expressed as $RD_{10} = R_{10} - R_{00}$ and $RD_{01} = R_{01} - R_{00}$ for the first and second exposure, respectively. The joint effect of the combination of both exposures equals $RD_{11} = R_{11} - R_{00}$. To define interaction between exposures, one common reference condition is used for comparing separate with joint effects; the condition reflecting the background risk when both exposures are absent (R_{00}) [39]. There is no additive interaction if $RD_{11} = RD_{10} + RD_{01}$. Put differently, if two exposures affecting the occurrence of one and the same outcome do *not* interact, then the occurrence of the outcome in the presence of both exposures is merely the sum of their separate effects (e.g., effect of one risk factor plus effect of another risk factor). If this is not the case, however, then the absolute causal effects of the exposures depend on each other, that is, they interact ($RD_{11} \neq RD_{10} + RD_{01}$). The whole is then different from the sum of its parts. Additive interaction can be either *superadditive (synergism)* or *subadditive (antagonism)* in case the sum of the separate exposure effects is smaller or larger, respectively, than the joint effect of both exposures [39,44]. Fig. 2 visualizes the counterfactual definition of additive interaction.

Defining interaction on a multiplicative scale follows a similar logic as additive interaction, except that risk ratios are used instead of risk differences. Accordingly, multiplicative interaction between two exposures is present if the *product* of the relative causal effects of each exposure in isolation (separate effects) is different from the relative causal effect of both exposures in combination (joint effect). The separate exposure effects are now expressed as $RR_{10} = R_{10} / R_{00}$ and $RR_{01} = R_{01} / R_{00}$ for the first and second exposure, respectively, while their joint effect equals $RR_{11} = R_{11} / R_{00}$. Again, separate and joint effects are compared relative to a common reference condition (R_{00}, the background risk). There is no multiplicative interaction if $RR_{11} = RR_{10} \times RR_{01}$. In other words, if two exposures affecting the occurrence of one and the same outcome do *not* interact, then the occurrence of the outcome in the presence of both exposures is merely the product of their separate effects (e.g., effect of one risk factor multiplied by effect of another risk factor). If this is not the case, then the relative causal effects of the exposures are interdependent ($RR_{11} \neq RR_{10} \times RR_{01}$). Like additive interaction, interaction on a multiplicative scale can be *supermultiplicative (synergism)* or *submultiplicative (antagonism)* in case the product of the separate exposure effects is smaller or larger, respectively, than their joint effect (Fig. 3) [39,44].

Unlike effect modification, a requirement for the counterfactual notion of causal interaction is that two interacting exposures both have causal effects on an outcome [13,26,35,39]. The nature of the causal effect of one exposure on some outcome thus depends on the causal effect of a second exposure on the same outcome. For instance, the

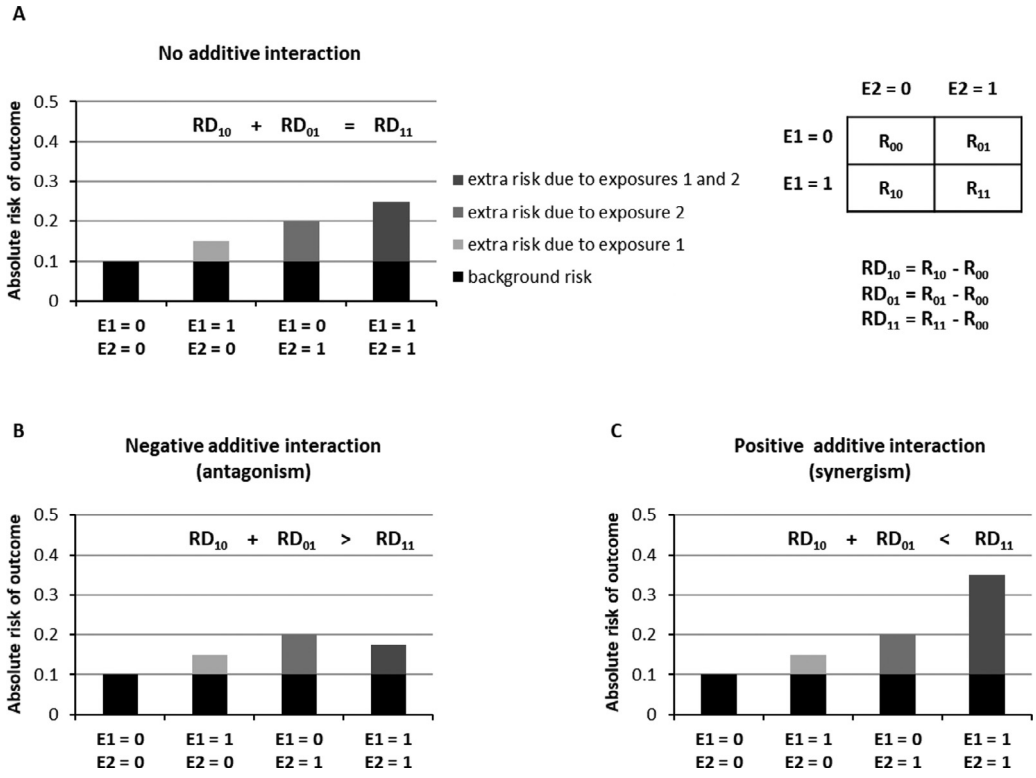

Fig. 2. The counterfactual definition of additive interaction. The absolute causal effects of two exposures E1 and E2 on the risk of an outcome in a single target population are shown in four contrasting conditions: exposed to neither (E1 = 0 & E2 = 0), either (E1 = 1 or E2 = 1), or both exposures (E1 = 1 & E2 = 1). The separate effects of each exposure in isolation and the joint effect of both exposures in combination are expressed by three risk differences (RD). All effects are unconfounded, and therefore causal, because the four conditions have exchangeable background risks equaling the risk of the outcome in the doubly unexposed condition [27]. A comparison of the *sum* of the risk differences for the singly exposed conditions (RD_{10} and RD_{01}) with the risk difference for the doubly exposed condition (RD_{11}) indicates whether interaction is absent (A), subadditive (B), or superadditive (C).

causal effect of one exposure can be enhanced, inhibited, or nullified by the effect of another exposure. A further difference between interaction and effect modification is that the secondary exposure usually is a modifiable factor (e.g., a treatment or lifestyle factor) that can potentially be intervened upon to influence the causal effect of the primary exposure [21,23,26,35,39,40,42,43]. Two exposures can interact in a variety of ways and, usually but not always, causal interaction will be present on both additive and multiplicative scales. Recently, an insightful overview of various types of interaction in the form of an interaction continuum was presented elsewhere [44]. A graphical presentation expressing interplay between two exposures on this continuum is included in Appendix A (see Supplementary material).

3. Evaluation, interpretation, and implication of effect modification and interaction

Reasons for evaluating effect modification and interaction are diverse [26,35,39]. Additionally, the proper way to present and interpret results of analyses of these concepts can be challenging [45–48]. Furthermore, it may be difficult to recognize what the implications of evidence regarding effect modification and interaction are for medical practice and public health [13,15,18].

3.1. Evaluation of effect modification and interaction can provide evidence for targeted interventions and insight into mechanisms of causal effects

Two cardinal reasons for studying effect modification and interaction are to identify targets for intervention and to elucidate mechanisms of causal effects. First, evidence for effect modification and interaction can provide important insights for targeting preventive, curative, or palliative interventions [23,26,35,39]. According to abovementioned counterfactual definitions, effect modification focuses on subgroup-specific causal effects of single exposures, while interaction focuses on joint causal effects of multiple exposures [13,23,35]. Hence, effect modification is relevant when one wants to target an intervention to specific population subgroups, primarily to improve effectiveness but also in case of limited resources that prohibit treating the whole target population [21,23,26,35]. Evidence for effect modification helps to identify groups of individuals with certain intrinsic characteristics rendering them to experience stronger treatment effects than others, in whom

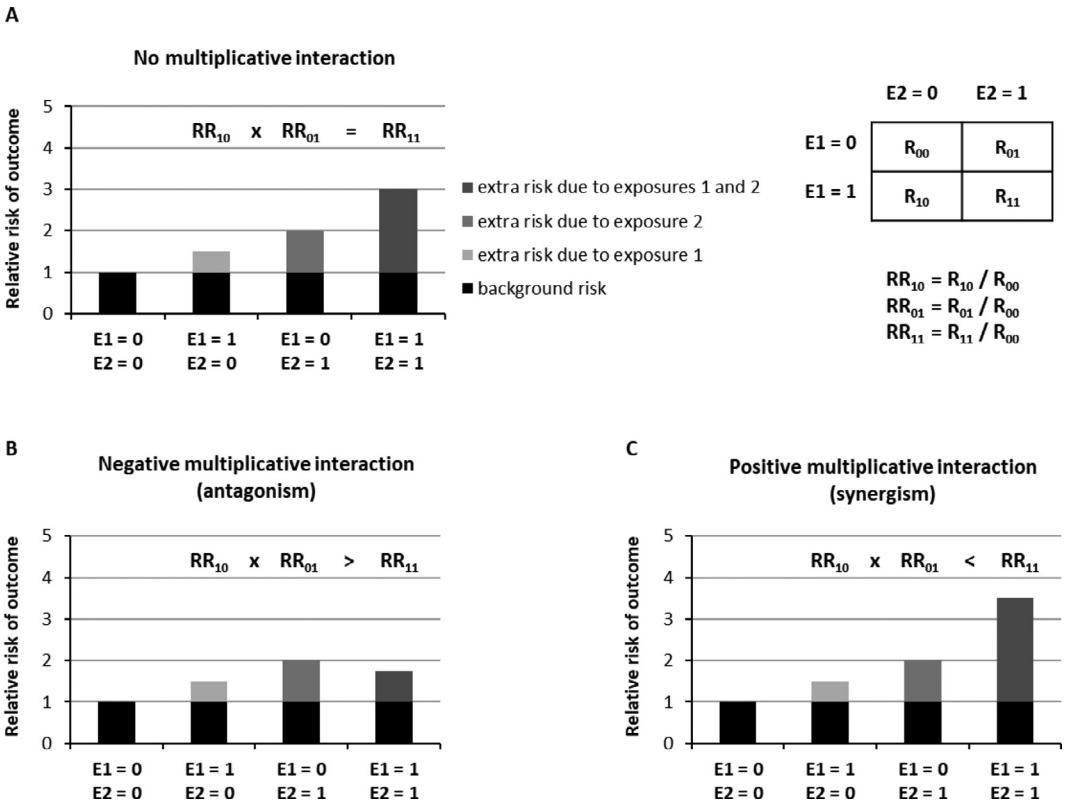

Fig. 3. The counterfactual definition of multiplicative interaction. The relative causal effects of two exposures E1 and E2 on the risk of an outcome in a single target population are shown in four contrasting conditions: exposed to neither (E1 = 0 & E2 = 0), either (E1 = 1 or E2 = 1), or both exposures (E1 = 1 & E2 = 1). The separate effects of each exposure in isolation and the joint effect of both exposures in combination are expressed by three risk ratios (RR). All effects are unconfounded, and therefore causal, because the four conditions have exchangeable background risks equaling the risk of the outcome in the doubly unexposed condition [27]. A comparison of the *product* of the risk ratios for the singly exposed conditions (RR_{10} and RR_{01}) with the risk ratio for the doubly exposed condition (RR_{11}) indicates whether interaction is absent (A), submultiplicative (B), or supermultiplicative (C).

treatment is less effective, ineffective, or even harmful [13,17,21,26,35]. Contrary to effect modification, the primary focus of interaction is on interventions and not on subpopulations. It provides insight into specific combinations of interventions that could be advantageous for a target population as a whole, not only for specific subgroups within that population [21,23,35,39]. Interaction is relevant when one wants to simultaneously intervene on more than one exposure, for instance by combining two medical treatments to optimize their effectiveness for improving patient outcomes (treatment-by-treatment interaction). Importantly, the additive rather than the multiplicative scale is most relevant for identifying targets for intervention [13,39]. This scale indicates which subgroup of individuals or which combination of interventions will generate the largest absolute benefit with regard to some outcome of interest. As the multiplicative scale does not indicate this absolute benefit, it is less useful and may even lead to opposite decisions regarding populations to target or interventions to combine [13,35,39,40]. Moreover, knowledge about effect modification and interaction allows for better judgment of how inferences about causal effects can be extrapolated beyond a target population under investigation [13,26,49,50]. If it is known that the effect of some intervention depends on the level or effect of another factor, then the average effect of the intervention will differ between populations with a different distribution of that other factor. Therefore, evidence for effect modification and interaction can provide relevant insights into (lack of) transportability [26,49,50] or transitivity [51,52] of intervention effects from one target population to another.

A second reason for evaluating effect modification and interaction is to help uncover mechanisms of causal effects [35,39], for instance biological or psychosocial mechanisms underlying disease causation or treatment effectiveness. Especially interaction is relevant for elucidating causal mechanisms, because it provides mechanistic insight into how a particular outcome is produced by multiple interdependent causes, as described within the sufficient-cause model of causation [53,54]. This model emphasizes multicausality by describing how individual factors (component causes) will inevitably produce an outcome when combined in the right way. A sufficient cause represents a unique combination of component causes (i.e.,

a causal mechanism) leading to an outcome. Rather than the counterfactual model which focuses on "the effects of causes," the sufficient-cause model focuses on "the causes of effects" [55–58]. According to this model, causal effects of two exposures are interdependent when at least one sufficient cause for an outcome exists that includes both exposures as components. The exposures then interact in causing the outcome, which is called *sufficient-cause interaction* [18,26,35,39,59,60] or *biological interaction* when it involves causal co-action between exposures on a biological level (e.g., cellular factors cooperating in pathogenic mechanisms of disease) [18,19,60–64]. The sufficient-cause model is also very insightful for explaining synergism and antagonism [53,65]. Two exposures within a sufficient cause are said to interact synergistically when the presence of both exposures is required for an outcome to occur. On the other hand, exposures interact antagonistically when the presence of one but the absence of the other exposure is required for the outcome to occur. A more detailed discussion of links between sufficient-cause and counterfactual models can be found elsewhere [26,65–70].

At this point, it is important to realize that the evaluation of effect modification and interaction using statistical (e.g., regression-based) models is scale-dependent [13,16,17,39,44,71,72]. The type of model determines on which scale effect modification or interaction is expressed statistically, that is, on an additive or multiplicative scale (e.g., linear versus logistic models) [17,72]. As a consequence, conclusions about the presence and direction of effect modification and interaction can differ depending on the analytic scale. Additionally, the exact properties of the variables involved in the interaction and effect modification (e.g., categorical versus continuous exposures and/or outcomes) has important implications for the type of analytic models and strategies. Presentation of effect modification or interaction analyses should ideally include information for interpreting results on both the additive and multiplicative scale [5,7,13,39,45,48], as well as specific statistical measures for quantifying the presence and nature of effect modification and interaction on these scales (Appendix B; see Supplementary material) [17,35,39,72–75]. Practical examples of the presentation and interpretation of analyses of effect modification and interaction are presented in Boxes 1 and 2.

3.2. Confounding needs to be considered differently when evaluating effect modification or interaction

Because analyses of effect modification and interaction focus on causal effects, careful consideration of confounding is important. Causal interpretation of the presence and nature of effect modification and interaction can be seriously biased by confounding due to nonexchangeability of background risks of the outcome under study [27,76–79]. When comparing exposure conditions between distinct groups of individuals in research practice, the groups need to have comparable (exchangeable) background risks in order to enable valid inferences about interdependent causal effects [27,80]. Therefore, an analysis of effect modification and interaction must adequately control for relevant confounders to create conditional exchangeability (e.g., by multivariable regression modeling). This is especially relevant in observational studies, where absence of confounding is a crucial yet difficult if not impossible to verify assumption for allowing a causal interpretation of observed findings regarding effect modification or interaction. In this regard, the idea of target trial emulation can be relevant [81–84]. Thinking of design and analytic principles of a randomized trial that could in theory be used for answering observational questions can help to better deal with confounding and approach observational analyses from a causal perspective.

Because effect modification and interaction are not identical concepts, counterfactually speaking, the consideration of confounding should differ accordingly. Only one set of confounders is relevant for assessing effect modification, whereas two sets of confounders are relevant for assessing interaction [23,35,39,40]. An analysis of effect modification is focused on the causal (unconfounded) relation between an exposure and outcome across levels of another factor that somehow modifies this relation. Therefore, only confounders of the exposure-outcome relationship under study need to be considered in the analysis for drawing valid conclusions about heterogeneous causal exposure effects. The causal relation (if any) of the effect modifier with the outcome is not of primary interest, so confounding of this relation is a nonissue [23,35,39,40]. However, it has been noted that the interpretation of results of effect modification (subgroup) analyses can be misleading if interrelations between subgrouping variables are not accounted for, and techniques for confounder adjustment in subgroup analysis (e.g., standardization) are available [85]. From a counterfactual perspective, the co-occurrence of confounding and effect modification implies that both nonexchangeability (different background risks) and effect heterogeneity (different causal effects) are at play (Fig. 4). Contrary to effect modification, interaction analyses focus on combined causal effects of two exposures on an outcome. Consequently, these analyses should account for two sets of confounders, one for each of the exposures involved in the interaction [35,39,40]. The confounder sets may be the same, but not necessarily. If confounders for only one of the interacting exposures are accounted for, then inferences regarding causal interaction are potentially biased by confounding of the causal effect of the disregarded exposure.

4. Summary

Effect modification and interaction are causal concepts with subtle differences regarding their counterfactual def-

Box. 1 Practical example of effect modification

Effects of targeted immunotherapy in metastatic colorectal cancer depend on oncogenic mutation status
A randomized controlled trial was conducted in 427 metastatic colorectal cancer patients to study if mutations in the oncogene *KRAS* affected the effect of panitumumab monotherapy on progression-free survival [1]. Panitumumab is a human monoclonal antibody that targets the epidermal growth factor receptor (EGFR), thereby inhibiting cell growth and angiogenesis and inducing apoptosis [3]. Patients were randomly allocated to receive either best supportive care (control group, n = 219) or biweekly panitumumab monotherapy next to best supportive care (treatment group, n = 208). *KRAS* mutations were found in 43% of patients. The effect of panitumumab therapy on progression-free survival in the first 6 months after randomization was modified by *KRAS* status (Table 1).

Relative to patients with *KRAS* mutations in the control group, panitumumab monotherapy increased the chance (risk) of progression-free survival by only 1% in patients with mutated *KRAS* but by 16% in patients with nonmutated (wild-type) *KRAS*. This was indicative of positive effect modification by *KRAS* status that led to a 14% extra increase in effectiveness above and beyond what was expected if panitumumab was independent of *KRAS* status. That is, the observed absolute survival benefit by panitumumab therapy (16%) was 8-fold higher than the expected survival benefit (2%). In panitumumab-treated patients with wild-type *KRAS*, 70% (14/20) of the total 6-month progression-free survival and 88% (14/16) of the extra survival benefit from panitumumab therapy could be attributed to the influence of *KRAS* status on panitumumab effectiveness. Patients with nonmutated *KRAS* receiving panitumumab therapy had a 5-fold higher chance of progression-free survival in 6 months compared to patients with mutated *KRAS* not receiving panitumumab. The relative effect of panitumumab in patients without *KRAS* mutations was 3.2-fold (4.00/1.25) higher than in patients with *KRAS* mutations.

Table 1. Effects of panitumumab therapy on 6-month progression-free survival in patients (n = 427) with metastatic colorectal cancer, differing by *KRAS* status

	Control group[I]			Treatment group[II]			Treatment regimen stratified for *KRAS* status	
	R	RD	RR	R	RD	RR	RD	RR
***KRAS* mutations**	0.04	0.00	1.00	0.05	0.01	1.25	0.01	1.25
No *KRAS* mutations	0.05	0.01	1.25	0.20	0.16	5.00	0.15	4.00

Measures of effect modification on additive scale: IC = 0.20−0.05−0.05+0.04 = 0.14 (14%); RERI = 5.00−1.25−1.25+1.00 = 3.50; S = (5.00−1) / [(1.25−1)+(1.25−1)] = 8.0; AP = 3.50 / 5.00 = 0.70 (70%); AP* = 3.50 / (5.00−1) = 0.88 (88%).
Measures of effect modification on multiplicative scale: IR = 5.0 / (1.25×1.25) = 4.00 / 1.25 = 3.2.
R, risk (measure of incidence), expressed as proportion of patients still alive 6 months after randomization; RD, risk difference; RR, risk ratio; IC, interaction contrast; RERI, relative excess risk due to interaction; S, synergy index; AP, attributable proportion; IR, interaction ratio.
[I] BSC (best supportive care) alone.
[II] BSC + panitumumab monotherapy.

In conclusion, the results demonstrate that patients with metastatic colorectal cancer harboring *KRAS* mutations do not show a clinically relevant benefit from anti-EGFR therapy by panitumumab. Gain-of-function mutations in the *KRAS* oncogene, which is involved in EGFR downstream signaling, induce resistance to panitumumab [3]. The evidence for effect modification can be leveraged to identify specific patient subgroups eligible for panitumumab therapy based on their *KRAS* status. Patients with nonmutated *KRAS* should be selected for panitumumab therapy.

initions and practical implications. Whereas effect modification is centered upon heterogeneous causal effects of one modifiable exposure (e.g., a treatment) across levels of a second, nonmodifiable exposure (e.g., an intrinsic, personal characteristic), interaction centers on the interdependent causal effects of two modifiable exposures (e.g., two treatments or lifestyle factors). Effect modification thus refers to the situation where intervening on only one factor in specific population subgroups is of interest, while interaction refers to the situation where two factors may potentially be intervened upon in an entire population. All in all, medical or public health interventions can thus be better targeted by leveraging effect modification and interaction. It either helps determining which

Box. 2 Practical example of interaction

Drinking tea at high temperatures augments the carcinogenic effects of alcohol on the esophagus

To study how alcohol use and high-temperature tea consumption affect the risk of esophageal cancer, a prospective cohort study was conducted in 456,155 Chinese adults 30–79 years of age followed up for a median period of 9.2 years [2]. A positive interaction was observed between daily alcohol use and daily burning hot tea consumption (Table 2).

Alcohol use elevated the risk of esophageal cancer independent of tea consumption, with an additional 78 new cases of esophageal cancer per 100,000 persons per year, which was 2.9 times higher than the yearly incidence in persons with no or low alcohol use. Independent of alcohol use, regular consumption of tea at burning hot temperatures led to a negligible increase in the yearly risk of esophageal cancer (3 extra cases per 100,000 persons per year), which was 1.1-fold increased relative to persons not drinking high-temperature tea. However, in persons who regularly drank alcohol and burning hot tea, 131 new cases of esophageal cancer per 100,000 persons were diagnosed each year in comparison with persons not regularly drinking alcohol and hot tea. This was 50 extra cases per 100,000 person-years above and beyond what was expected if alcohol and tea consumption had independent (additive) effects, i.e., a 1.6-fold (131/81) higher than expected excess risk. Persons who regularly consumed alcohol and high-temperature tea had a 4.2-fold elevated yearly risk of esophageal cancer relative to persons not regularly drinking alcohol and not drinking tea at high temperatures. On a yearly basis, this was a 1.3-fold higher relative risk than expected based on independent (multiplicative) effects of alcohol and high-temperature tea.

Table 2. Interdependent effects of alcohol use and high-temperature tea consumption on esophageal cancer risk in Chinese adults (n = 456,155)

	Less than weekly burning hot tea			Daily burning hot tea			Tea consumption stratified for alcohol use	
	R	RD	RR	R	RD	RR	RD	RR
Alcohol use <15 g/d	41	0	1.0	44	3	1.1	3	1.1
Alcohol use ≥15 g/d	119	78	2.9	172	131	4.2	53	1.4
Alcohol use stratified for tea consumption		78	2.9		128	3.9		

Measures of interaction on additive scale: IC = 172−119−44+41 = 50 cases/100,000/year; RERI = 4.2−2.9−1.1+1.0 = 1.2; S = (4.2−1) / [(2.9−1)+(1.1−1)] = 1.6; AP = 1.2 / 4.2 = 0.29 (29%); AP* = 1.2 / (4.2−1) = 0.38 (38%).

Measures of interaction on multiplicative scale: IR = 4.2 / (2.9×1.1) = 3.9 / 2.9 = 1.4 / 1.1 = 1.3.

R, risk (measure of incidence), expressed as number of cases per 100,000 persons per year; RD, risk difference; RR, risk ratio; IC, interaction contrast; RERI, relative excess risk due to interaction; S, synergy index; AP, attributable proportion; IR, interaction ratio.

In conclusion, daily tea consumption at burning hot temperatures augments the risk-increasing effect of daily alcohol use on esophageal cancer. The proposed working mechanism is that burning hot tea induces damage to the epithelial cells lining the esophagus, which thereby becomes more susceptible to the carcinogenic effect of alcohol. Drinking tea at burning hot temperatures thus has a synergistic influence on the effect of alcohol on esophageal cancer, that is, there is a positive interaction between alcohol and high-temperature tea use. Interventions on both risk factors are possible to lower esophageal cancer risk, leveraging the interaction between alcohol and hot tea whose interdependent effects are responsible for 38% (50/131) of the extra esophageal cancer cases each year and 29% (50/172) of all new cases of esophageal cancer. Advising individuals to drink their tea at lower temperatures, in addition to the recommendation to limit alcohol use, can potentially prevent a considerable number of additional esophageal cancer cases each year.

subpopulation(s) to target (effect modification) or which combination(s) of interventions to target (interaction). A summary of different types and definitions of effect modification and interaction is provided in Appendix C (see Supplementary material). The concepts of effect modification and interaction are reflections of a complex multicausal world, like the multifaceted nature underlying disease etiology or progression [86,87]. Causal reality is not made up of isolated causes that are independent, but of multiple causes that are interdependent and context-specific

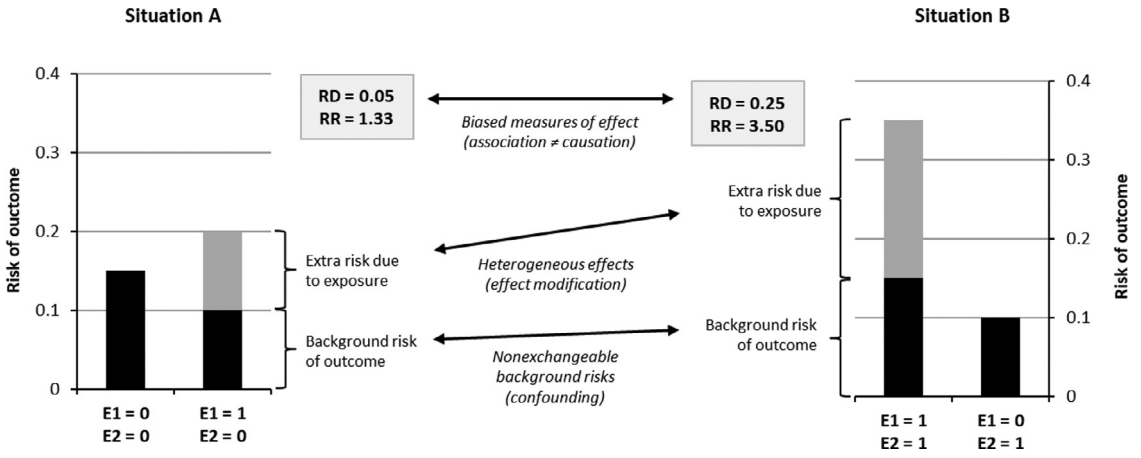

Fig. 4. Co-occurrence of confounding and effect modification. Evaluation of effect modification is confounded in case of nonexchangeable background risks between exposure groups. The effect of an exposure E1 on the risk of an outcome is shown in two contrasting exposure conditions: exposed (E1 = 1) and unexposed (E1 = 0). These conditions are depicted in two contrasting situations A and B based on the level of a second exposure variable E2, which is either absent (E2 = 0) or present (E2 = 1). In case the background risks of the outcome under study differ depending on whether individuals are exposed or unexposed to E1, then the heterogeneous effects of exposure E1 across levels of exposure E2 are confounded due to nonexchangeability of background risks [27]. The risk difference (RD) and risk ratio (RR) in both situations are confounded by factors responsible for the difference in background risks between exposure groups. Causal inference about effect modification is biased, unless factors confounding the heterogeneous effect of exposure E1 are accounted for by design or in the (subgroup) analysis.

(e.g., population-/time-dependent). Effect modification and interaction are therefore not biases to be eradicated, but a natural part of causal exposure effects to be detected and presented. In fact, bias would result when evidence for effect modification or interaction would be kept hidden from view.

In conclusion, a conceptual understanding of counterfactual principles underlying effect modification and interaction can be useful for guiding design and analyses of studies aiming to uncover these causal phenomena. It will also facilitate appropriate interpretation, reporting, and communication of study findings. To increase understanding, this tutorial article has provided a nontechnical explanation of the counterfactual definition of effect modification and interaction. Together with a previous tutorial article on confounding [27], the present article may be useful as teaching tool for introducing these extremely relevant causal concepts for research and medical or public health practice.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jclinepi.2021.01.022.

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