Confounders and Effect Modifiers

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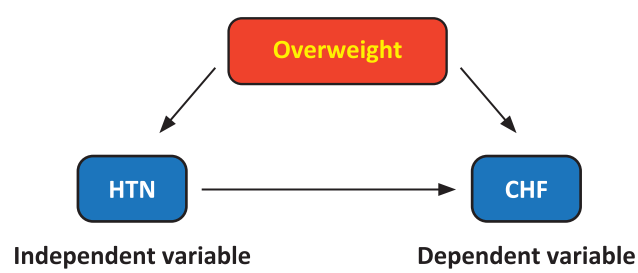
According to the classic definition, **a confounder is a variable that is associated with both the exposure and the outcome, although it is not on the causal pathway**. This could generate spurious associations or obscure existing ones. For instance, a study investigating the association between hypertension and heart failure risk should consider overweight participants, an independent predictor of heart failure (HF) that is likely associated with high blood pressure. (Figure 1)

Ideally, confounding factors are controlled during the design of the study. In a randomized clinical trial (RCT), for instance, randomization aims to prevent third variables of interest from being unbalanced by treatment assignment, thereby reducing potential confounding. **In population-based studies or clinical settings where randomization is not feasible or ethical, confounding can be mitigated through multivariable adjustment in regression models or alternative modern approaches to causal inference (e.g., propensity score methods).**

Figure 1. *The relationship between hypertension (exposure) and the risk of congestive heart failure (outcome variable) may be confounded by overweight (confounder), which is a risk factor for developing heart failure and is possibly associated with hypertension*



It is necessary to distinguish the concept of a confounder, as previously explained, from the concept of effect modifier.

An effect modifier is a third variable whose presence modifies the strength of the association between the exposure of interest and the outcome. Unlike confounding, effect modifiers should not be adjusted or eliminated, but described.

In the previous example, diabetes may modify the effect of the relationship between hypertension (HTN) and congestive heart failure (CHF), as it may

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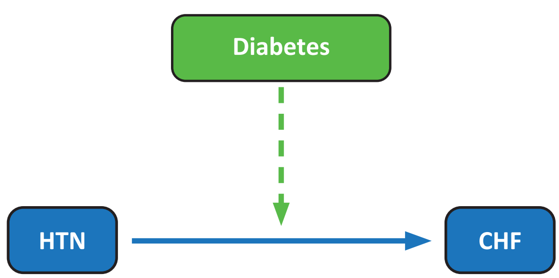
be different in those with and without diabetes. From an analytical point of view, effect modification can be detected by presenting results that are stratified by the level of the effect modifier variable (e.g., hypertension × diabetes) or by including an interaction term in the regression model. This is achieved by including the product of the effect modifier and the main exposure variable (in this example, HT x diabetes), which will have a statistically significant *p* - value. (Figure 2)

Figure 2. *Diabetes can act as an effect modifier in the relationship between hypertension and congestive heart failure; if we stratify it and there are differences between individuals with and without diabetes, we are dealing with an effect modifier of this relationship*



This can be exemplified as follows:

Univariate analysis of the relationship between hypertension and the risk of congestive heart failure

Dependent variable (CHF)	*Hazard Ratio*	Confidence Interval CI 95%
HTN	**2.1**	**(1.3 - 3.4)**

We include the overweight variable (univariate analysis)

Dependent variable (CHF)	*Hazard Ratio*	Confidence Interval CI 95%
Overweight	**1.7**	**(1.2 – 2.8)**

Dependent variable (CHF)	*Hazard Ratio*	Confidence Interval CI 95%
HTN	**1.2**	**(0.9 – 3.6)**
Overweight	**1.5**	**(1.2 – 3.3)**

The relationship between hypertension and the risk of congestive heart failure is altered by to the presence of a second variable (overweight). The *hazard ratio* of the univariate relationship is attenuated when adjusting for overweight (2.1 to 1.2), and the confidence interval is less than 1, which is not statistically significant). Therefore, overweight is a confounder of the relationship between hypertension and congestive heart failure.

If we stratify by the presence or absence of diabetes: Patients with diabetes

Dependent variable (CHF)	*Hazard Ratio*	Confidence Interval CI 95%
HTN	**2.5**	**(1.3 - 3.4)**

Patients without diabetes

Dependent variable (CHF)	*Hazard Ratio*	Confidence Interval CI 95%
HTN	**1.3**	**(0.97 - 3.8)**

As we can see, the relationship between hypertension and congestive heart failure differs depending on whether we stratify by the presence or absence of diabetes (effect modifier); we can also include the product of the interaction of Diabetes × Hypertension in the multivariable model of heart failure.

The concept of a confounder is key in observational studies in which the aim is to assess causality, since the baseline characteristics of the participants are not balanced between groups (i.e., not randomized), and must be adjusted for.

In observational studies, confounding is a source of bias that must be controlled through design or analysis, whereas effect modification represents real heterogeneity of effect between subgroups and must be described. Distinguishing confounding factors from effect modification is a prerequisite for proper causal interpretation.

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