Module 3

The investigations in Module 3 of the *Detectives in the Classroom* curriculum prepare students to answer the third of five Essential Questions:

> Is the association causal?

When students understand how to answer this question, they will be developing the third of five Enduring Understandings that provide the structural framework for the curriculum. The third Enduring Understanding is:

> Causation is only one explanation for finding an association between an exposure and an outcome. Because observational studies are flawed, other explanations must also be considered.

By completing the Module 1 investigations, students learned how health-related conditions and behaviors are not distributed uniformly in a population, that each has a unique descriptive epidemiology that can be discovered by identifying how it is distributed in a population in terms of person, place, and time. This descriptive epidemiology provides clues for formulating hypotheses. Students realized that descriptive epidemiology is only the first step and that formulating hypotheses is not the same as proving hypotheses.

By completing the Module 2 investigations, students learned that causal hypotheses could be tested by observing the exposures and diseases of people as they go about their daily lives. Testing is conducted by making and comparing risks and determining whether or not the exposure and the outcome turned up together, that is, whether or not the exposure and the outcome were associated with each other. This is called analytical epidemiology. Students learned about the methods used to test causal hypotheses and how the 2x2 table is used to numerically express the results of an analytical study.

The Module 3 investigations develop the ability of students to interpret the results of analytical epidemiological studies, namely, the ability to evaluate why an association between an exposure and an outcome has been found. An association means that things are linked in some way that makes them turn up together. When epidemiologists test hypotheses, they are interested in determining whether or not an exposure and an outcome turned up together.

A cause is something that produces an outcome and one reason why an exposure and an outcome turned up together could be because the exposure caused the outcome. But causation is only one of several possible explanations for why an exposure and an outcome would turn up together in an epidemiological study.

Why aren't associations necessarily causal? Epidemiological studies rely on observations of the exposures that free-living people encounter and the diseases they develop as they go about their daily lives. As such, observational studies of these "natural experiments" are not as precise and well controlled as actual experiments. Therefore, we are less certain of why an association was found in an observational epidemiological study of a "natural experiment" than in an actual experiment.

In **Investigation 3-1: In the News,** students interpret headlines and reports of epidemiological studies that have appeared in the popular press and uncover the tendency to interpret phrases, such as “linked with,” “tied to,” “related to,” and “associated with,” as being synonymous with cause. They then begin to appreciate the fundamental distinctions between an association and a cause and that association is not necessarily causation.

When an epidemiological study has found an association, explanations, other than causation, must also be considered. These alternative explanations include the possibility that the association was found due to chance or that the association is due to confounding by the effects of another risk factor that is the actual cause of the disease. In addition, associations are sometimes found because of the way the study sample was selected and at other times there may be uncertainty about the time order of the exposure and the outcome. The next few investigations teach students to consider these possible explanations for why an association was found in an epidemiological study. Finally, students learn how epidemiologists examine an accumulation of evidence for an association between an exposure and an outcome and make a judgment as to whether or not the association is causal based on specific criteria.

This is summarized in the table below:

Evidence for an Association	Considerations
Single Epidemiological Study	Causality Chance Confounding Selection Bias Reversed Time Order
Accumulation of Epidemiologic and Other Evidence	Answers to Causal Criteria Questions

In **Investigation 3-2: Cause,** students explore the first of several explanations for finding an association: causation. They learn how data can be distributed in a 2x2 table when an exposure is a cause of an outcome. A causal association between an exposure and an outcome can be found when there is a one-to-one relationship between the two. That is, the exposure by itself causes the disease, and the disease is caused only by that exposure. If this were the case, we would expect that everyone in the study would be in either cell a or cell d. In other words, everyone with the exposure had the disease and everyone without the exposure did not have the disease. See 2x2 table below:

	Disease	No Disease	
Exposure	a	b	
No Exposure	c	d	

Students will learn, however, that the situation is seldom this simple. Using the example of the association between smoking and lung cancer, students will realize they may know someone (like an uncle) who smokes but does not have lung cancer, who would be in cell b. This can happen because smoking may not always be enough to cause lung cancer or because it takes a long time to get lung cancer. In addition, students will uncover circumstances under which someone can be in cell c, such as when an exposure, other than smoking, may cause lung cancer (such as asbestos or radon).

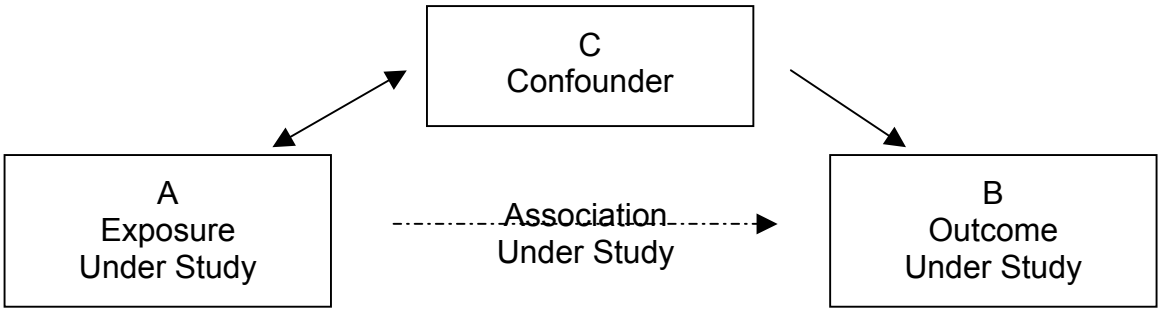
Students will appreciate that most diseases have multiple causes, that is, multiple exposures and susceptibility factors enter into virtually every exposure / outcome association. Rarely, if ever, do we find an "all or nothing" association between a given exposure and an outcome. Rather, most causal associations are "more likely - less likely" associations. When the exposure is present, the disease is "more likely" to occur and, when the exposure is absent, the disease is "less likely" to occur.

In **Investigation 3-3: Chance,** students uncover how an epidemiologist can find an association between an exposure and an outcome by chance. Students are given a deck of 100 cards (25 labeled a, 25 labeled b, 25 labeled c, and 25 labeled d) that represent the way an exposure (eating M&M's) and an outcome (flu) could be distributed in the population. Students then calculate the relative risk for this distribution and find that it is a risk of 1, that is, there is no association between eating M&M's and getting the flu in the entire population. Then each Epi Team picks a sample of 20 cards from the 100 by chance, and calculates the relative risk for the sample. Despite the population risk of 1, some teams will find relative risks above 1 and others will find relative risks below 1 in the samples they picked by chance. From this exercise, students will learn that even though there may be no real association between eating M&M's and flu, an association can be found in a single study due to chance.

In **Investigation 3-4: Confounding,** students explore the possibility that an association has been found because of a confounder. A confounder is another exposure that is associated with the exposure under study and is also a cause of the outcome under study.

So it looks like the association is between the exposure and disease under study, but the causal association is actually between the confounder and the disease under study.

This is illustrated below:



In other words, the association between A and B is only seen because of the bridge formed by C (which is an actual cause of B and has made A look guilty because of its association with C).

In **Investigation 3-5: Reversed Time Order,** students learn about how an association in a study may be found because of reversed time order. In other words, instead of the exposure causing the outcome, the outcome may be causing the exposure. For example, a study may suggest that boys who play violent video games are more likely to engage in violent behavior, but it is also possible that the association was found because boys who engage in violent behavior are more likely to play violent video games.

In **Investigation 3-6: Selection Bias,** students learn how selection bias can be an alternate explanation for an association. Using an example of a study that examines the relationship between carrying a heavy backpack and back pain, students learn how the selection of a sample of subjects can produce an association that does not hold true for the overall population.

In **Investigation 3-7: Weighing the Evidence,** students evaluate an accumulation of epidemiologic and other evidence about a certain exposure / outcome association and realize that what may appear to be a solid case for causality often falls apart when it is properly critiqued. Epidemiologists have a systematic way of critiquing a body of evidence about a particular association. In fact, epidemiologists use a term similar to one used in a court of law – a "weight of evidence" review. This review uses a set of "causal criteria questions," the answers to which provide a basis for making a judgment about whether or not the association is causal. These questions include:

1. Is the evidence consistent? Causality is more likely if the association has been found in many studies done by a variety of researchers, using a variety of study designs, and a variety of study samples. Variety is important because a group of similar studies, done by the same researchers, using the same study design, and similar study samples could all be finding the association because of the same flaw in conducting the study. Replication of results is an essential part of scientific inquiry.

2. How strong is the association? Causality is more likely if the risk of the outcome is 5 or 10 times more likely in the exposed than in the unexposed, than if the risk of the outcome is only 1.2 or 2 times more likely in the exposed. The greater the strength of association, the less likely that difference is due to chance and the more likely the association is causal.

3. Is there a dose-response relationship? Causality is more likely if studies show that as the dose of the exposure increases, so does the occurrence of the outcome under study. For example, if low exposure to a chemical (dose) is associated with a slight skin rash (response) and a high exposure to the same chemical is associated with a severe allergic reaction, we tend to think that the chemical is causing the condition.

4. Is the epidemiologic evidence coherent with what was previously known? Causality is more likely if the association makes sense considering what was known before analytical epidemiologic studies were done. In other words, does the association make sense in terms of the descriptive epidemiology, time trends, geographic variation, and anecdotal knowledge? For example, the association between smoking and lung cancer was supported by increasing trends in lung cancer as smoking habits increased, different trends of lung cancer in males and females over time, higher rates of lung cancer in countries where tobacco use is more common, and anecdotal reports from doctors that most of their lung cancer patients had been smokers.

5. Experimental evidence: Causality is more likely if the association is seen in animal experiments or perhaps in trials in humans. This kind of evidence is not always available, but when it is, it can help make a causality judgment. For example, trials helped prove that lowering cholesterol reduces the risk of heart disease. Animal experiments demonstrated that certain exposures such as vinyl chloride and radium can cause cancer in animals, and thus, may cause cancer in humans as well.

In **Investigation 3-8: Concept Connections,** students identify the important concepts that need to be understood in order to answer the third Essential Question: "Is the association causal?" Each Epi Team then draws a Concept Map that depicts and explains how the concepts connect to each other. At the conclusion of this investigation, students will realize that they have developed the third Enduring Understanding of *Detectives in the Classroom*: "Causation is only one explanation for finding an association between an exposure and an outcome. Because observational studies are flawed, other explanations must also be considered."