

# NUTRIENTS

## EPIDEMIOLOGY 101

### Introduction

Understanding the relationship between diet, lifestyle, genetics and chronic diseases or other aspects of health is challenging. The scientific community uses multiple types of studies, all with their own strengths and limitations, to shed light on these relationships.

Epidemiology is a branch of medical science that deals with the incidence, distribution and control of disease in a population. Basically, epidemiological studies look at populations to investigate potential associations between aspects of health (such as heart disease or cancer) and diet, lifestyle, genetics or other factors. Epidemiologic studies are observational in nature, and the outcomes need further study through other types of research such as clinical studies to be confirmed. Epidemiologic research provides information about the distribution and determinants of disease for further study, but *it does not establish cause and effect*.

A primary field within epidemiology is nutritional epidemiology – the study of the nutritional factors that influence disease frequency and distribution in human populations. Nutritional epidemiologists study the typical or usual eating patterns of individuals to assess long-term diets and measure levels of exposure to certain foods or nutrients. For example, a nutritional epidemiologist might compare the number of tomatoes eaten by each person in a group or within a total population to identify incidence of prostate cancer to determine if a relationship exists between lycopene intake (a carotenoid found in tomatoes) and a reduced risk of developing prostate cancer.

One of the primary challenges in epidemiology is that it does not prove cause and effect and can only draw associations for further research. Nutrition epidemiology is further complicated by poor methods for assessing dietary intake (see the sidebar on diet analysis).

### DIET ANALYSIS

There are many ways to document dietary intake. The three most common methods are through a 24-hour diet recall, food record and a food frequency questionnaire.

**24-hour diet recall:** A trained interviewer gathers information on what a subject has eaten in the past 24 hours, including a description of the food or drink and the estimated amount.

**Strengths:** 24-hour diet recalls are fast, inexpensive and easy to administer. This method can be used with illiterate individuals and on large populations and presents minimal burden for the respondent (no forms to fill out, etc.)

**Limitations:** 24-hour diet recall tends to underestimate the amount of food eaten because it is based on the subject's memory. Additionally, one day of dietary analysis is not a good representation of an individual's diet, and this method requires a trained interviewer to gather information from the subject in a non-judgmental manner.

**Food record:** A subject records what he or she ate for three days, ideally two weekdays and one weekend day. This is often referred to as a food diary, and can be kept for three days to one week.

**Strengths:** Food records are more accurate than a 24-hour diet recall, and they rely less on the subject's memory.

**Limitations:** This method of diet analysis requires significant commitment by the subject because of the time and labor involved. Literacy is also required.

**Food frequency questionnaire:** Subject records how often and in what quantity he or she generally eats specified foods over a specified time.

**Strengths:** Food frequency questionnaires are relatively reliable estimates of the subject's usual intake of foods. These questionnaires can be self-administered, are easy for subjects to complete and are inexpensive for large populations.

**Limitations:** The volume of food eaten is often overestimated or underestimated depending on the length of the questionnaire. Additionally, responses are dependent on which foods are prelisted. Subjects often have problems estimating portion sizes, remembering food preparation techniques and choosing how to classify mixtures of food.

## Hierarchy of Scientific Studies

The types of studies that can be used to evaluate the role of diet in various diseases are:

### ■ **Randomized controlled human clinical trial:**

In a randomized controlled human clinical trial, subjects are assigned randomly to one of two groups: one group that receives the treatment under investigation or the control group that receives either no treatment (placebo) or standard treatment. This type of study can prove cause and effect.

Randomized controlled trials are considered the gold standard in medical research. They lend themselves best to answering questions about the effectiveness of different therapies or interventions. However, randomized controlled human clinical trials cannot be done in certain situations for ethical reasons, for example, if subjects were asked to undertake harmful experiences or denied any treatment beyond a placebo when there are known effective treatments. These types of studies are often not practical for investigating diet and chronic diseases because of cost, ethics, complexities of diet and many other variables that are difficult to control.

### ■ **Animal model system:** Animal models are used to study the development and progression of diseases and to test new treatments before they are given to humans. They can also explore possible mechanisms. Animal laboratory studies can prove cause and effect in animals, but they can only support hypotheses or suggest possible effects in humans.

Although animal model system studies may allow for investigations not possible in an observational setting, the application of results from animal studies to human populations is often questionable. In most experimental animal studies, exposures are administered at higher doses and for shorter durations than those experienced by humans. Furthermore, findings from experimental animal studies are difficult to generalize to humans because of a variety of metabolic, physiologic and anatomic differences among species.

### ■ **Observational human epidemiological studies:** Observational human epidemiological studies look at human populations to investigate how, when and where diseases occur. This type of research provides information about the distribution and determinants of disease for further study, but does not establish cause and effect.

The vast majority of data linking diet to various types of chronic disease such as heart disease or cancer is the result of observational human epidemiological studies.

## Types of Human Epidemiologic Studies

Following are some of the more commonly used human epidemiologic studies, listed in order of strongest to weakest evidence when properly performed.

### ■ **Prospective cohort:** A research study that follows over time a group of individuals (cohort) who do not yet have a disease and collects specific information regarding diet and other factors related to the development of the disease. The common association measure for a prospective cohort study is relative risk.

For example, a prospective cohort study recruits subjects, follows them over a period of time and analyzes their diets. If any of the subjects develop cancer, researchers analyze differences in dietary patterns.

### ■ **Retrospective case-control:** Subjects who already have a certain condition are compared with those who do not. Information bias can be a problem in these studies, as people with a disease are likely to report dietary intake differently than those without the disease. The common association measure for a case-control study is the odds ratio.

For example, in a case-control study researchers compare the diets of people with cancer (case) to those of people without cancer (control).

### ■ **Cross-sectional:** A cross-sectional study compares groups in terms of their current health and exposure status and assesses their similarities. An important limitation of this approach is that it does not allow for changes over time, and thus cannot accommodate diseases that take time to develop.

For example, in a cross-sectional study, the same survey asks people about prostate cancer diagnosed in the past year and their current tomato intake (rather than their tomato intake over time).

### ■ **Ecologic:** Ecologic studies compare the frequency of events or disease rates in different populations with per capita consumption of certain dietary factors.

For example, an ecologic study compares per capita lycopene intake amounts and prostate cancer rates in the United States to those in Europe.

Original data from any of the above types of human epidemiologic studies can be used to conduct a pooled analysis or a meta analysis.

■ **Pooled analysis:** Pooled analysis involves the simple pooling of data (data are combined without being weighted) to provide an overall summary from a number of related studies. This type of analysis combines data sets (not necessarily published data) from similar studies. The decision to include or exclude individual studies is a potential confounding variable with pooled analysis.

For example, a pooled analysis evaluates original data sets from several different prostate cancer study cohorts.

■ **Meta analysis:** A meta analysis uses quantitative methods to merge the results of valid studies. This type of analysis summarizes published data to derive effect estimates. In meta analysis, the decision to include or exclude individual studies is a potential confounding variable (an uncontrolled outside variable).

For example, a meta analysis analyzes the results from several published research studies on diet and prostate cancer. This type of analysis would weigh each study, considering aspects such as study size and study variance.

### Bradford-Hill Criteria

No matter what type of human epidemiologic study is done, Bradford-Hill criteria should be used as a systematic approach for using scientific judgment to infer causation from statistical associations observed in epidemiologic data. These nine criteria, proposed by Sir Austin Bradford Hill and subsequently refined and expanded by other epidemiologists, include strength of association, temporality, consistency, theoretical plausibility, coherence, specificity in the causes, dose response relationship, experimental evidence and analogy. Each criterion is defined below, followed by an example to further explain the concept.

- **Strength of association:** The stronger the relationship between the independent variable and the dependent variable, the less likely it is that the relationship is due to an extraneous variable (a confounder).
  - Very early on, the lung cancer rate for smokers was quite a bit higher than for nonsmokers.
- **Temporality:** It is logically necessary for a cause to precede an effect in time.
  - Smoking in the vast majority of cases preceded the onset of lung cancer.

- **Consistency:** Multiple observations, of an association, with different people under different circumstances and with different measurement instruments increase the credibility of a finding.
  - Different methods (e.g. prospective and retrospective studies) produced the same result for smokers. The relationship also appeared for different kinds of people (e.g. males and females).
- **Theoretical plausibility:** It is easier to accept an association as causal when there is a rational and theoretical basis for such a conclusion.
  - The biological theory of smoking causing tissue damage, which over time results in cancer in the cells, was a highly plausible explanation.
- **Coherence:** A cause-and-effect interpretation for an association is clearest when it *does not conflict* with what is known about the variables under study and when there are no plausible competing theories or rival hypotheses. In other words, the association must be coherent with other knowledge.
  - The conclusion (that smoking causes lung cancer) made sense given the then current knowledge about the biology and history of the disease.
- **Specificity in the causes:** In the ideal situation, the effect has only one cause. In other words, showing that an outcome is best predicted by one primary factor adds credibility to a causal claim.
  - Lung cancer is best predicted from the incidence of smoking.
- **Dose response relationship:** There should be a direct relationship between the risk factor (i.e. the independent variable) and people's status on the disease variable (i.e., the dependent variable).
  - Data showed a positive, linear relationship between the number of cigarettes smoked and the incidence of lung cancer.
- **Experimental evidence:** Any related research that is based on experiments will make a causal inference more plausible.
  - Tar painted on laboratory rabbits' ears was shown to produce cancer in the ear tissue over time. Hence, it was clear that carcinogens were present in tobacco tar.
- **Analogy:** Sometimes a commonly accepted phenomenon in one area can be applied to another area.
  - Induced smoking with laboratory rats showed a causal relationship. With the totality of other evidence, it, therefore, was not a great jump for scientists to apply this to humans.

Hill is cited in the 1991 *British Medical Journal* as saying, “None of these nine viewpoints can bring indisputable evidence for or against a cause and effect hypothesis...What they can do, with greater or less strength, is to help answer the fundamental question — is there any other way of explaining the set of facts before us, is there any other answer equally, or more, likely than cause and effect?”

### Interpreting Results of Epidemiologic Studies

Alone, epidemiological studies do not prove causality; they express possible risk. The results of epidemiologic studies are expressed in terms of relative risk (RR) or odds ratio (OR).

The first step to interpreting the results of an epidemiologic study is to determine the absolute risk for the outcome being studied. For example, the absolute risk for males in the United States to develop prostate cancer could be about 17 percent, or 17 out of every 100 males. Absolute risk defines how likely the outcome is to happen overall.

The next statistical value, RR, puts risk in comparative terms, i.e. the outcome rate for people exposed to the factor in question compared with the outcome rate for those not exposed to the factor. RR greater than 1 indicates an increased risk of the outcome under investigation (but not necessarily a causal association); RR less than 1 indicates a decreased risk of the outcome (but not necessarily a protective association). For RR values close to 1.0 (often referred to as the null value), there is likely no increased or decreased risk. It is important to consider RR in the context of absolute risk – if the absolute risk is negligible, then RR may be irrelevant (see sidebar Understanding Absolute and Relative Risk).

#### UNDERSTANDING ABSOLUTE AND RELATIVE RISK

A news report claiming people who consume Product X are 75 percent more likely to suffer from Chronic Disease Y than those who don't consume it may seem convincing. This type of statement is an expression of RR.

In the same example, the absolute risk of someone in the study suffering from Chronic Disease Y may only be 0.001 percent or 1 person out of 100,000 people. In this case, the absolute risk is the more meaningful result; as it states only 0.001 percent of people suffer from Chronic Disease Y anyway. In this example, expressing results as RR made the problem seem more important than it was. Therefore, it is important to consider both RR and absolute risk when evaluating research results

The results of case-control epidemiologic studies are most often reported as OR, but OR and RR are interpreted the same.

If an epidemiologic study produces an association, the strength of this association can be evaluated by looking at RR. Most nutrition epidemiologists agree that RR *less than 2.0 is not considered strong*.

To explain further, the RR for lung cancer in smokers vs. non-smokers is approximately 10.0 (smokers have a 900 percent increased risk for developing lung cancer when compared to non-smokers). This would be considered a strong association.

Epidemiologists use a statistical value called the confidence interval (CI) to determine whether the obtained RR values are due to chance or whether they indeed reflect an association. The CI is a range of values that has a specified probability of including the true value. In the example above for which RR was 10, a CI could be 8.3-11.7. If the CI includes 1 (for example, a CI of 0.5-2.5), the results of the study are likely due to chance. If the CI does not include 1, the results of the study are likely not due to chance. Additionally, a wide or broad CI implies a greater uncertainty in the value of the true RR estimate.

### Considerations for Diet-related Epidemiologic Studies

Diet-related epidemiologic studies contain many interwoven, complex diet-related variables that must be considered when interpreting these types of studies. Following are a few examples to highlight the complexity of factors associated with the diet.

- Is the type of food clearly defined in the research methodology? For example, when determining if an association exists between tomato consumption and rate of prostate cancer, does the study include whole tomatoes (cherry tomatoes, specific varieties of tomatoes) or are tomato products such as pasta sauce, salsa and tomato juice included?
- Does the study define the preparation/cooking methods of the food involved? In the example above, are the tomatoes raw, cooked, canned or sun-dried?
- Are the levels of intake by participants in the study realistic? Relating to the tomato example, are participants consuming levels of fruits and vegetables consistent with the recommended intake?
- Do intake levels represent actual intake or perceived intake? What method was used to document dietary intake, and what are the limitations of this method?

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