**Teacher Notes for Vitamins and Health – Why Experts Disagree**[[1]](#footnote-1)

In this discussion/worksheet activity, research concerning the health effects of vitamin E is used as a case study to help students understand why different research studies may find seemingly opposite results. Students learn useful approaches for evaluating and synthesizing conflicting research results, with a major focus on understanding the strengths and weaknesses of different types of studies (laboratory experiments, observational studies, and clinical trials). Students also learn that the results of any single study should be interpreted with caution, since results of similar studies vary (due to random variation and differences in factors such as the population studied).

**Learning Goals**

* Even experts who are factually accurate can arrive at opposite conclusions and write persuasive arguments based on selective citation of only the evidence that supports their opinions.
* In an observational study, researchers observe people or nature as they are without any intervention. In observational studies, confounding factors may be responsible for observed correlations or associations, so correlation does *not* necessarily imply causation.
* In an experimental study, researchers control the conditions for two or more groups of subjects so that all variables are the same for these groups, except for one experimental variable which differs between the groups. In this way, the experimenter can test the causal effect of the experimental variable.
* A clinical trial is an experiment in which people are randomly assigned to two groups; participants in one group receive the treatment (e.g. vitamin supplements) and participants in the other group receive a placebo (a pill that does not contain the vitamin but cannot be distinguished from the vitamin supplement pill). Due to random assignment, the participants in the two groups will have the same characteristics on average, with the exception of treatment vs. placebo. Therefore, a clinical trial (like other experiments) can evaluate the causal effect of the treatment.
* Different studies with a similar research design typically yield variable results, e.g. due to random variation (especially if sample size is small) or differences in the population studied. This is one reason we need to be cautious in interpreting the results of any single study. Meta-analysis is a statistical technique for systematically evaluating the combined results from multiple studies.
* Evidence that supports a hypothesis under one condition or in one population should be extrapolated with caution, since the same hypothesis may not hold under different conditions or for a different population. For example, low-dose vitamin E supplements may decrease mortality for people who have low intake of vitamin E in their diets, but vitamin E supplements may increase mortality for people who have adequate diets.
* Laboratory studies provide useful information about molecular and cellular effects. Laboratory studies typically find multiple effects, some of which may be beneficial and others may be harmful. Thus, it is difficult or impossible to extrapolate from the findings of laboratory studies to the overall effect of a vitamin supplement or other treatment on human health.
* The scientific method is a complex process that requires multiple studies to evaluate a hypothesis. Often, new research evidence requires modification of the original hypothesis.

**Suggestions for Implementation and Background and Additional Information**

This activity is designed for high school students or for college students in an introductory non-majors biology course or an introductory nutrition course. To maximize student participation and learning, I suggest that you have students complete the questions in each section individually or in pairs, followed by a class discussion.

For many students, it will be helpful to precede this relatively challenging activity on vitamins and health with our more introductory activity, **"Carbohydrate Consumption, Athletic Performance and Health – Using Science Process Skills to Understand the Evidence" (available at http://serendipstudio.org/exchange/bioactivities/sciproc). In this discussion/worksheet activity on the effects of carbohydrate consumption, students design an investigation, compare their experimental design with the design of a research study that tested the same hypothesis, evaluate research evidence concerning two hypothesized effects of carbohydrate consumption,** evaluate the pros and cons of experimental vs. observational research studies, **and revise a standard diagram of the scientific method to make it more accurate, complete and realistic.**

Vitamins are molecules that we need to get from our food because:

* our bodies cannot make these molecules;
* we need small amounts (milligrams or micrograms) of these molecules to allow important chemical reactions to happen or to slow down harmful chemical reactions.

The second website in the box refers to a "small but statistically significant increase in mortality". The Student Handout does not attempt to explain the concept of statistical significance, but a good brief explanation is that a result that is statistically significant is unlikely to be due to random variation or chance. (However, a small percentage of statistically significant results are due to random variation, as illustrated by the results discussed near the bottom of page 3 of the Student Handout.)

Observational studies do not meet the criterion given in question 1 for an experiment because people's characteristics are correlated (e.g. diet and supplement use is correlated with education and general health habits). Therefore, in an observational study, two groups that differ in one characteristic will also differ in other correlated characteristics.

When researchers analyze the results of observational studies, they try to control statistically for confounding factors (also known as confounding variables). However, it is impossible to fully control for all possible confounding factors. Statistical procedures to control for confounding factors are not fully effective, especially because, in most cases, measurements of confounding factors are not sufficiently precise and some confounding factors have not been measured at all (sometimes because important confounding factors have not yet been identified). Therefore, correlation does *not* necessarily imply causation. The example of confounding factors illustrates the important general point that, when scientists interpret their findings, they need to consider the whole range of possible alternative interpretations, not just their preferred interpretation.[[2]](#footnote-2)

It should be noted that when observational studies find an extremely strong association (e.g. the roughly ten-fold greater risk of lung cancer among cigarette smokers), it becomes highly unlikely that any confounding factors that have not been controlled for will have a strong enough effect to account for this very strong association. Furthermore, reverse causation can be ruled out since cigarette smoking precedes lung cancer by decades. Thus, a causal effect of cigarette smoking on lung cancer risk is the only plausible interpretation of the extremely strong correlation between cigarette smoking and lung cancer risk in observational studies.

A clinical trial can meet the criterion for an experiment because randomization and placebo controls result in two groups that are the same except for the effect of the treatment (see explanation in the Student Handout). Researchers usually test the expectation that the characteristics of the treatment and placebo groups in a clinical trial are the same and they typically confirm the expectation of no significant differences between the treatment and placebo groups in any of the characteristics that have been measured. If a researcher assigns participants to the treatment and placebo groups by any method other than randomization, the two groups will probably or certainly differ in one or more of the confounding factors, so the causal effects of the treatment cannot be evaluated. Obviously, the dim-witted researcher and grossly biased clinical trial described in question 2 are purely hypothetical, invented for the purposes of getting the students to think. The Student Handout does not mention that clinical trials should also be double-blind. Double-blind means that neither the researchers nor the participants in the study know who is receiving the vitamin supplement and who is receiving the placebo, so expectations of benefit will not influence the health outcome.

The differences between the findings from observational studies versus clinical trials are probably due, at least in part, to the effects of confounding factors in observational studies, as discussed in the Student Handout. There may be other reasons for differences between the findings of the observational studies and clinical trials. For example, the differences in findings may be due in part to differences in the health outcome measured; the observational studies assessed coronary heart disease, whereas many of the clinical trials investigated effects on broader measures of cardiovascular disease or on total mortality (*Amer J Therapeutics*, 2010, 17:e56-e65). (An additional point of interest is that a fourth observational study did not find an association between taking vitamin E supplements and lower risk of death from coronary heart disease (*Med Clin North Am* 2000, 84:239-49).)

The variable results shown in the figure on page 3 of the Student Handout illustrate how risky it is to extrapolate from the results of a single study (particularly a small study). In this figure, the difference in mortality (all-cause mortality risk) on the Y axis was measured in deaths per 10,000 persons. The solid line indicates the overall trend of the results by vitamin E dose, with evidence for harmful effects at higher doses. This finding is not discussed in the Student Handout because more recent meta-analyses of clinical trials have confirmed that participants receiving vitamin E supplements have slightly higher mortality, but have not confirmed the trend to more harmful effects for higher dose vitamin E supplements (see, e.g., the meta-analysis available at <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD007176.pub2/abstract;jsessionid=913A2D9B2047C523D765ACB539F2FC66.d03t04>; this is the meta-analysis summarized on page 4 of the Student Handout).

The contrast between the findings of the clinical trials in China[[3]](#footnote-3) versus the clinical trials in the US and Europe are suggestive of a general phenomenon, namely that for each nutrient there is an optimum level of intake which maximizes the benefit to health, so supplements may be beneficial for people whose diet is deficient in a nutrient, but harmful for people who are already consuming the optimum level. The optimum level of intake typically varies depending on factors such as age and physiological status (e.g. whether a woman is pregnant or lactating). This illustrates the general point that researchers, journalists and the general public need to be very cautious about extrapolating results from one population or set of conditions to other populations or conditions.

Meta-analyses are very useful for synthesizing the available evidence to determine the best overall estimate of an effect. However, the results of meta-analyses may be influenced by methodological problems. For example, many of the clinical trials included in the meta-analysis summarized in the Student Handout used one of the synthetic versions of vitamin E, and some researchers believe that natural versions of vitamin E would have more beneficial health effects.

Laboratory experiments have typically shown that a vitamin or other nutrient has multiple, complex effects on the molecules and cells of the body. Therefore, it is impossible to extrapolate from any single molecular, cellular or physiological effect to whether the overall effect on human health is beneficial or harmful. For the purposes of this activity, it is not necessary to understand the detailed biology of the effects observed in laboratory experiments, but if you would like an introduction to antioxidant effects see "Vitamin E" (available at <http://ods.od.nih.gov/factsheets/VitaminE-HealthProfessional/>). Blood clots can block blood flow in the arteries in the heart or brain, thus causing tissue damage which results in heart disease or stroke, respectively. On the other hand, failure of the blood to clot can contribute to the type of stroke caused by bleeding in the brain where the increased pressure inside the skull can damage brain tissue.

The quotations in the box on page 1 of the Student Handout illustrate how selective citation of a subset of the findings from a large, complex and contradictory body of research evidence can support opposite recommendations. As has been observed for a number of other nutrients, promising results from observational studies and laboratory experiments (mentioned by the first website) have not been confirmed by clinical trials of vitamin E (mentioned by the second website).[[4]](#footnote-4) As discussed above and summarized below, each type of study is subject to methodological problems that contribute to divergent results in different types of studies.

The research on the health effects of vitamin E illustrates how challenging it is to definitively establish the health effects of specific dietary components. Nutritional research has repeatedly produced inconclusive results and persistent controversies due to multiple problems, including the following:

* Researchers have repeatedly found that, even though intake of a vitamin or other nutrient is correlated with better health in observational studies, no benefit is observed in clinical trials. The most likely explanation is that the association in the observational studies was due to confounding factors that the researchers were unable to control for (e.g. because they did not have adequate measures of these confounding factors).
* Clinical trials also have limitations, including variability in results; this variability may be due to multiple factors such as differences in the nutritional status of the population in the clinical trial, differences in the dose, chemical form or duration of the vitamin or other nutritional treatment, and substantial random variation in smaller clinical trials.
* Laboratory experiments typically show multiple effects of a given vitamin or other nutrient, including some beneficial effects and some harmful effects. Therefore, it is generally not possible to use the results of laboratory studies to predict the net effect of a vitamin supplement or other nutrient on human health.

These methodological problems contribute to the problem of inconsistent dietary advice, depending on both the bias of the expert who is giving the advice and on the accumulation of new evidence so that the best advice in one year may require revision in a later year. One typical sequence is that advice to take a vitamin that was based on laboratory experiments and observational studies is withdrawn based on the results of clinical trials. Fortunately, many aspects of nutritional advice are based on enough evidence (including clinical trials) that we have reasonable confidence in this advice (including, for example, fortification or supplements with folic acid before and during pregnancy to prevent neural tube defects in the baby; replacing saturated fatty acids with unsaturated fatty acids to reduce the risk of heart disease; correcting vitamin and mineral deficiencies, which are especially common in children in poor countries).

The methodological problems discussed in this activity have caused similar difficulties for research about other factors that may affect human health, including:

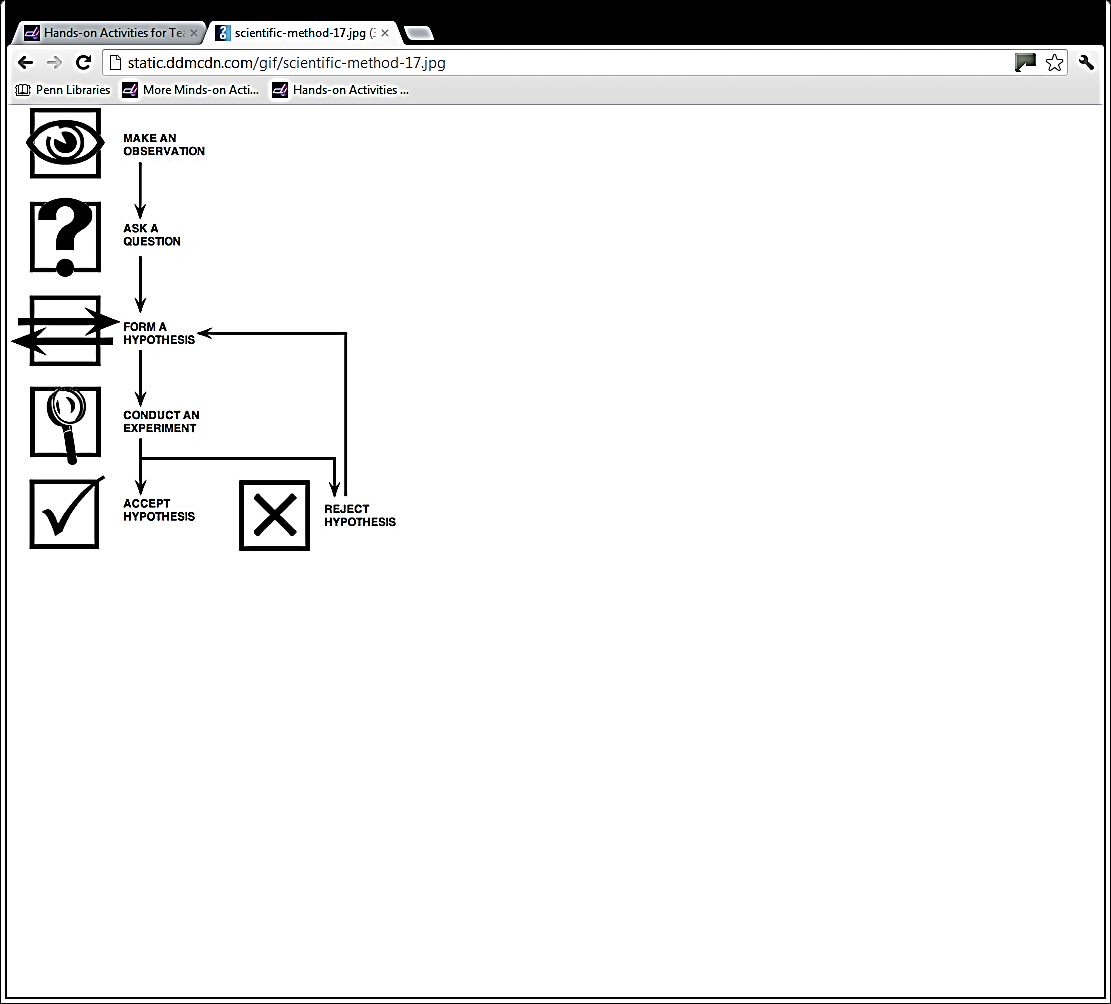
* medical treatments (e.g. hormone replacement therapy for postmenopausal women; see "Do we really know what makes us healthy?"*,* available at <http://www.nytimes.com/2007/09/16/magazine/16epidemiology-t.html?ex=1347768000&en=ce4415cbf0042a76&ei=5124&partner=permalink&exprod=permalink>),
* the benefits of dieting to reduce obesity (see "Weight Science: Evaluating the Evidence for a Paradigm Shift", available at <http://www.nutritionj.com/content/10/1/9>), and
* the effects of environmental exposures (e.g. pollution or population density).

With respect to question 8, my own interpretation is summarized in option “b”, primarily because I give special weight to the findings from the meta-analyses of clinical trials. The most interesting points for discussing this question will probably be the students' arguments in support of their interpretations.

Question 9 provides the opportunity to discuss the problem that media coverage of science tends to focus on single studies, often based on a press release from the university or other research organization which is eager to emphasize the importance of the research carried out at their institution. As illustrated in this activity, the results of a single study can be misleading for a number of reasons, including a study design that does not support causal conclusions about the overall effects on health and the variability of findings from individual studies of the same design. Thus, the most useful news reports either provide an overview of the research results related to the question of interest or summarize the results of a meta-analysis of multiple studies of good design. In discussing this question, you will probably want to mention that the popular press often uses wording that implies causal effects (e.g. "Vitamin D Improves Health") to describe findings from observational studies that can only show associations, not causation.

**Possible Additional Question**

Based on this overview of research on vitamin E, revise the following diagram of the scientific method to make it more accurate, complete and realistic.



(Figure from <http://static.ddmcdn.com/gif/scientific-method-17.jpg>)

**Additional Useful Sources on Methodological Issues**

* The Toolkit, available at <http://www.healthnewsreview.org/toolkit/> (including e.g. "Surrogate Markers May Not Tell the Whole Story" and "Does the Language Fit the Evidence? – Association Versus Causation")
* "Battling Bad Science" is an entertaining and informative talk about the errors and deceptions behind misleading nutritional or medical advice, available at

<http://www.ted.com/talks/ben_goldacre_battling_bad_science.html> (the first 7.5 minutes are the most relevant).

* Additional resources for helping students learn about and understand the scientific process are provided in the Teacher Notes for **"Carbohydrate Consumption, Athletic Performance and Health – Using Science Process Skills to Understand the Evidence" (available at http://serendipstudio.org/exchange/bioactivities/sciproc).**

**Additional Useful Sources on Nutrition**

* "Dietary Supplement Fact Sheets", including "Vitamin E", a comprehensive and readable overview, available at <http://ods.od.nih.gov/factsheets/VitaminE-HealthProfessional/>
* "Vitamin E" (another comprehensive and readable overview) and overviews of other dietary components, available at <http://www.mayoclinic.com/health/drug-information/DrugHerbIndex>
* USDA Food and Nutrition Information Center (<http://fnic.nal.usda.gov/nal_display/index.php?info_center=4&tax_level=1> ) provides nutrition information, some educational resources and recipes

1. By Dr. Ingrid Waldron, Department of Biology, University of Pennsylvania, copyright 2012. These Teacher Notes, the Student Handout and additional activities are available at <http://serendipstudio.org/exchange/bioactivities/vitamins> . [↑](#footnote-ref-1)
2. Reverse causation can also contribute to correlations in some types of observational study (although not in any of the studies discussed in this activity). For example, if a study finds that cancer patients have different diets than healthy people, these dietary differences may be the result of effects of cancer on appetite rather than the cause of cancer risk. [↑](#footnote-ref-2)
3. You should be aware of two caveats relevant for the interpretation of the results from the large clinical trial in Linxian, China. The supplement in this clinical trial contained β-carotene and selenium, as well as vitamin E, so it is unclear whether vitamin E per se had a benefit. (Inclusion of more than one supplement is a problem in roughly half of the clinical trials of vitamin E supplements.) In addition, this large Linxian clinical trial was carried out in 1986-1991, and it seems likely that nutrition for this population has improved since then, so it is unknown whether a contemporary clinical trial would find the same results. [↑](#footnote-ref-3)
4. For the purposes of the Student Handout, I have selectively quoted from the second website. This website provides a more balanced account, including mention of some results that suggest a possible benefit of vitamin E. This website concludes that the harmful results observed in many clinical trials are more persuasive than the evidence suggesting benefit (similar to the conclusion of this activity). [↑](#footnote-ref-4)