Practice-based Evidence in Nutrition (PEN®, www.pennutrition.com) is the global resource for nutrition practice.


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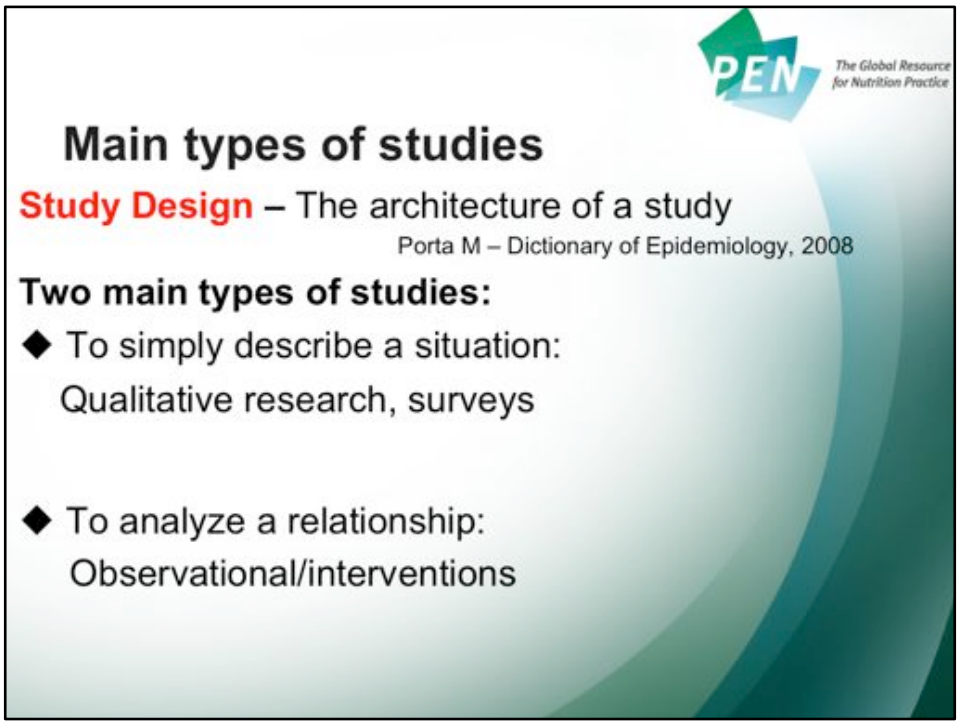
A Quick Review of Study
Designs



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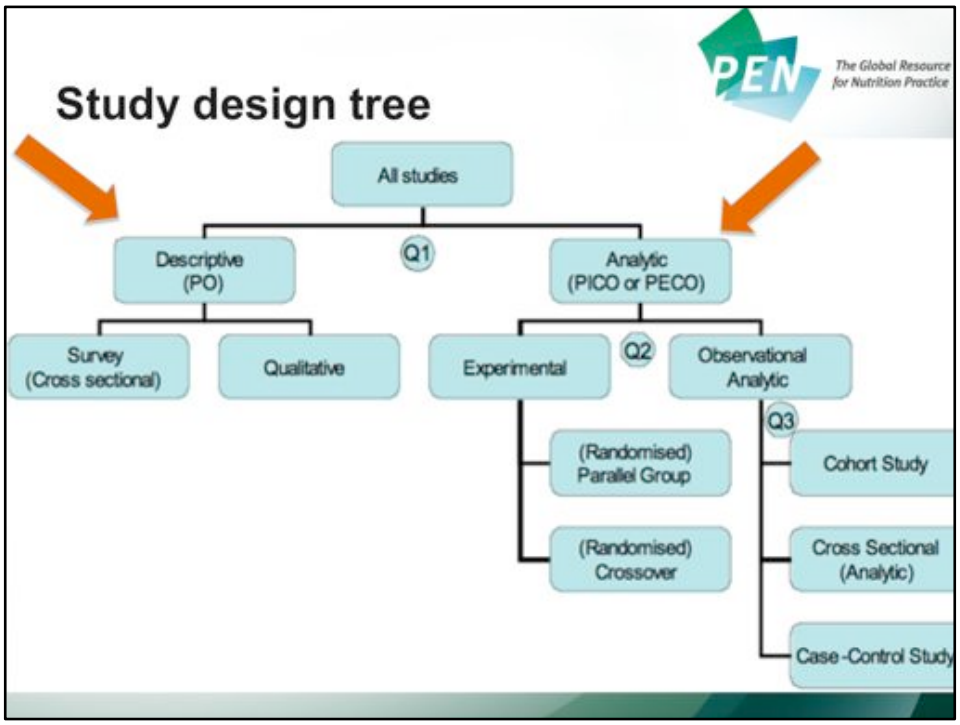
The reference for this is: Porta M, editor. Dictionary of Epidemiology. 5th ed. Oxford University Press: International Epidemiology Association; 2008.

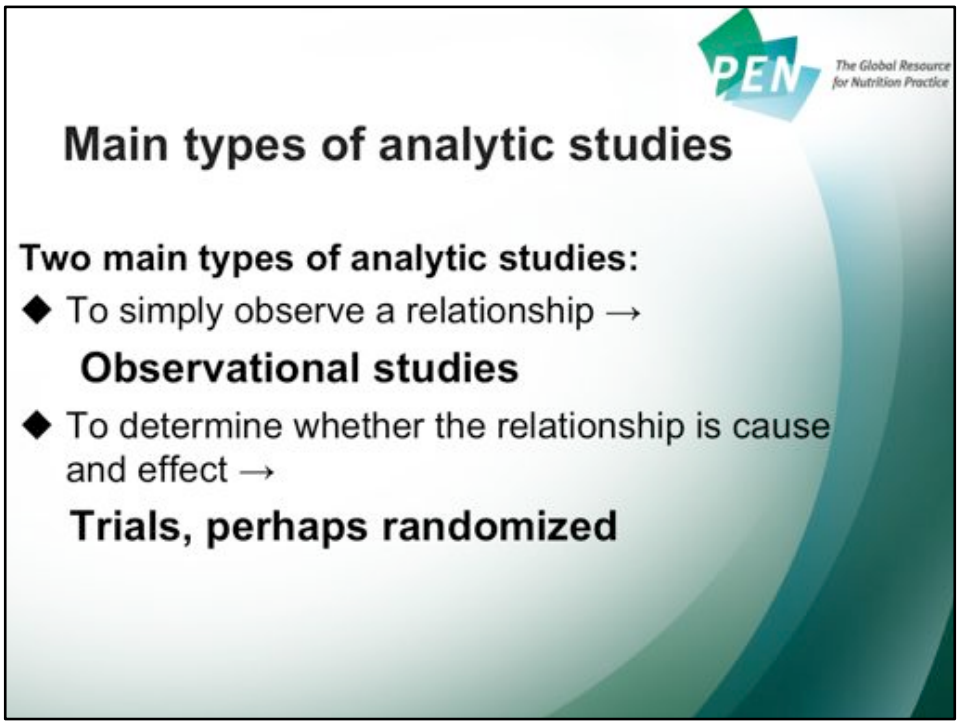


Q1. What was the aim of the study?
To simply describe a population: descriptive
To quantify the relationship between factors: analytic.
Case studies and case series are descriptive studies

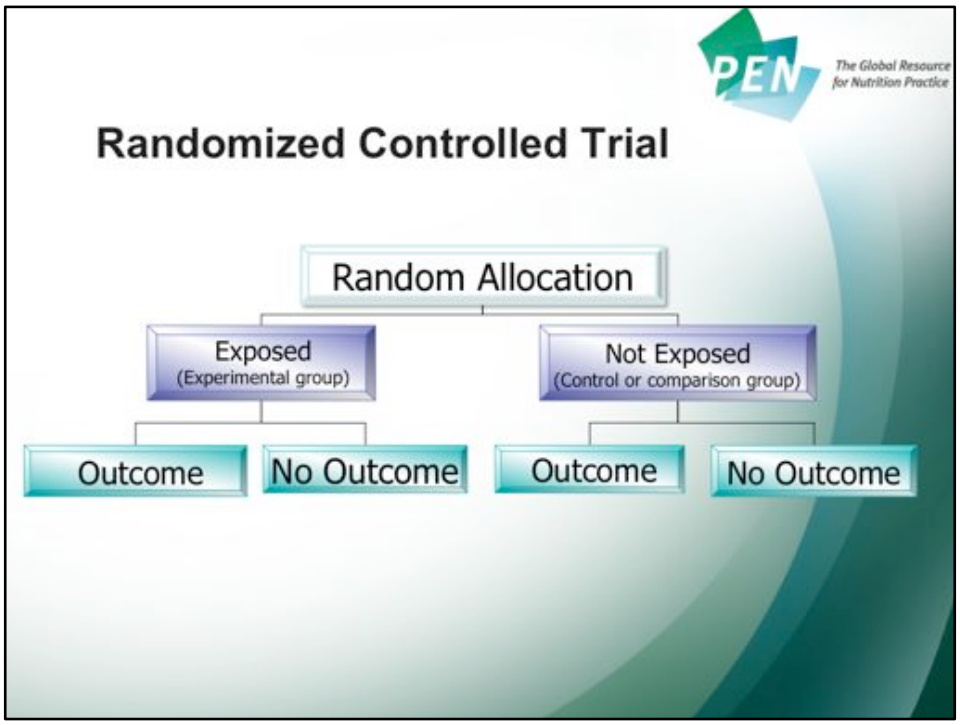
Q2. If analytic, was the intervention randomly allocated?
Yes? RCT
No? Observational Analytic study

For observational studies, the main types will then depend on the timing of the measurement of outcome, which we will get to later in this module.

The reference used here is: Holloway I, Wheeler S. Ethical issues in qualitative nursing research. Nurs Ethics. 1995 Sep [cited 2013 Nov 5];2(3):223-32. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7583428

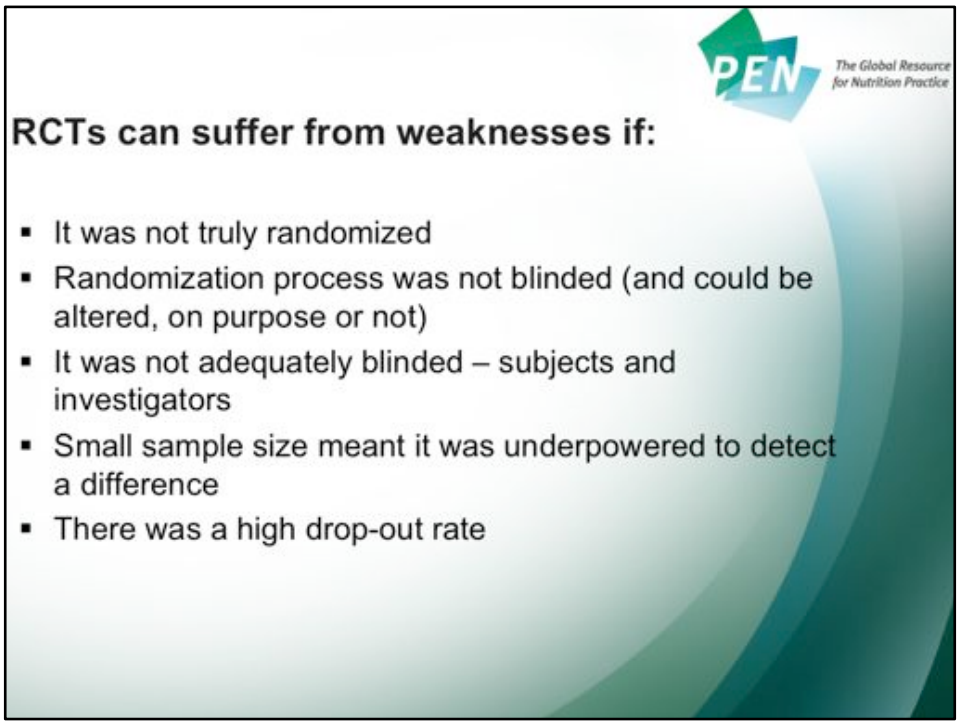


The focus of this module is on analytic studies, as these are the studies of most interest, as they describe relationships, such as between a nutrient and a disease



Randomized controlled trials (RCTs) are used to study the effectiveness of a treatment or therapy and can be used to determine causation.
RCTs are considered the strongest quantitative research design. They compare two or more groups where the participants are assigned to these groups through random allocation. This means that all of the participants have an equal chance of being in the experimental or comparison/control group.
For any outcome, there are known and unknown factors that affect the outcome. Random allocation allows these factors to be evenly represented among the experimental and comparison/control groups. If random allocation works then both the experimental and control groups will be similar on all known and unknown factors, and thus any difference observed between the groups on the outcomes of interest, can be attributed to the intervention.

Put another way:
RCTs reduce bias by providing equivalent groups for the study of the intervention. The control might be usual treatment or you might involve a placebo…which is better depends on what is the best comparison in the situation.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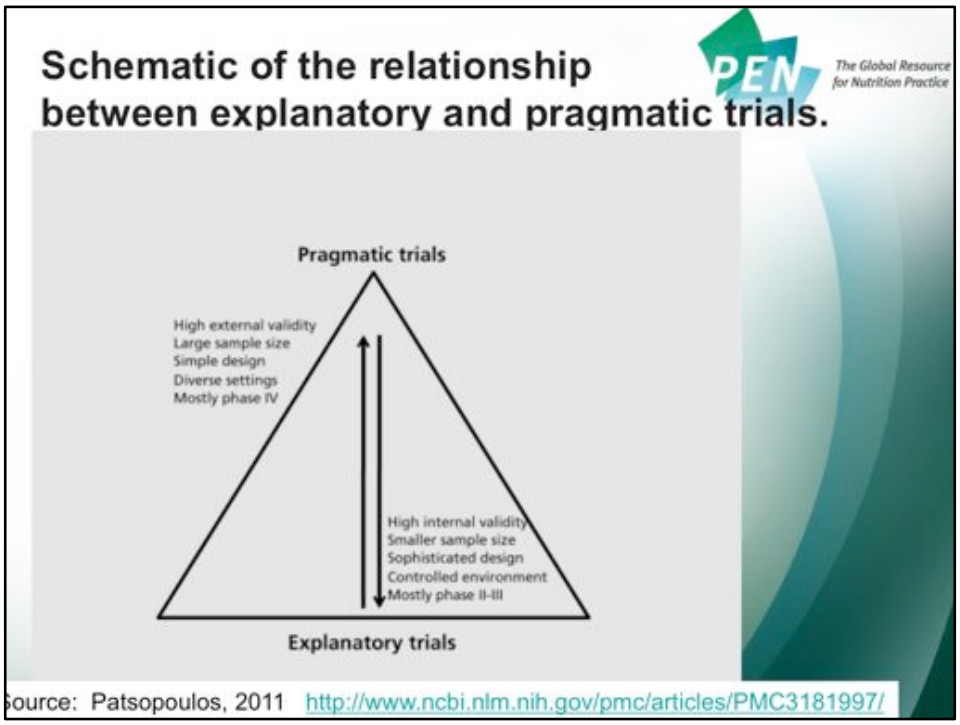
RCTs can suffer from weaknesses if:
It was not truly randomized
Randomization process was not blinded (and could be altered, on purpose or not)
It was not adequately blinded – subjects and investigators
Small sample size meant it was underpowered to detect a difference
There was a high drop-out rate

Read slide

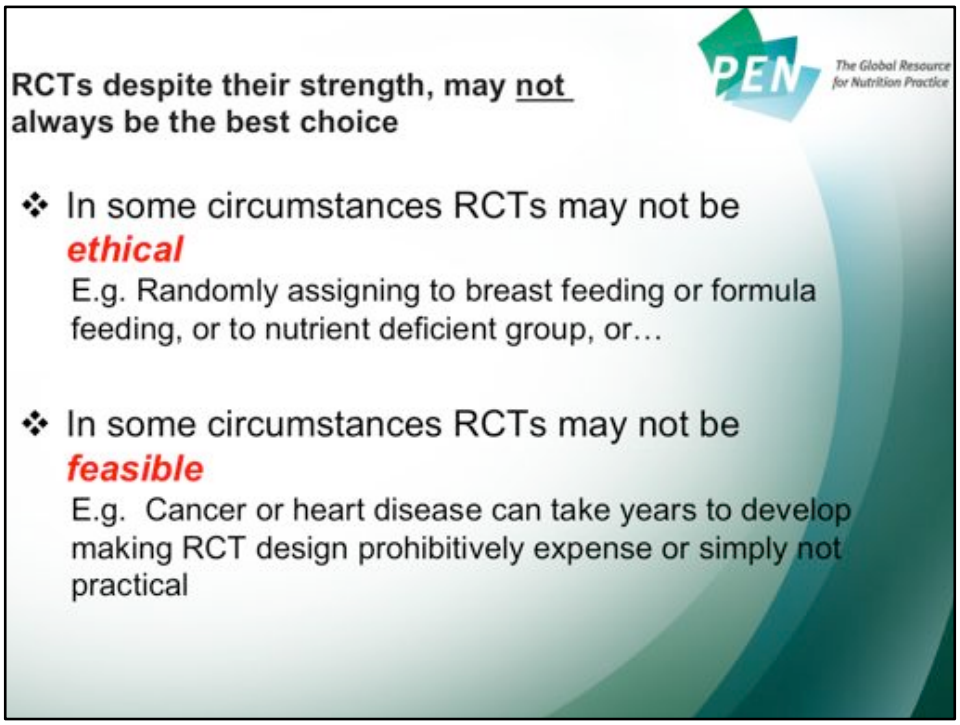
Not all trials are created equal!
Clinical trials can fall into two broad categories: explanatory and pragmatic. The choice of study design depends on the research question.
Explanatory trials test *if and how an intervention works*, whereas pragmatic trials examine *whether an intervention actually works in real life*.
Explanatory trials often evaluate clinical or biological markers, whereas pragmatic trials measure patient-centred outcomes.
Although the current literature includes more explanatory trials, because they may be less generalizable, the "pragmatic design" is gaining popularity.

This definition comes from: Cochrane Glossary available from: http://www.cochrane.org/glossary

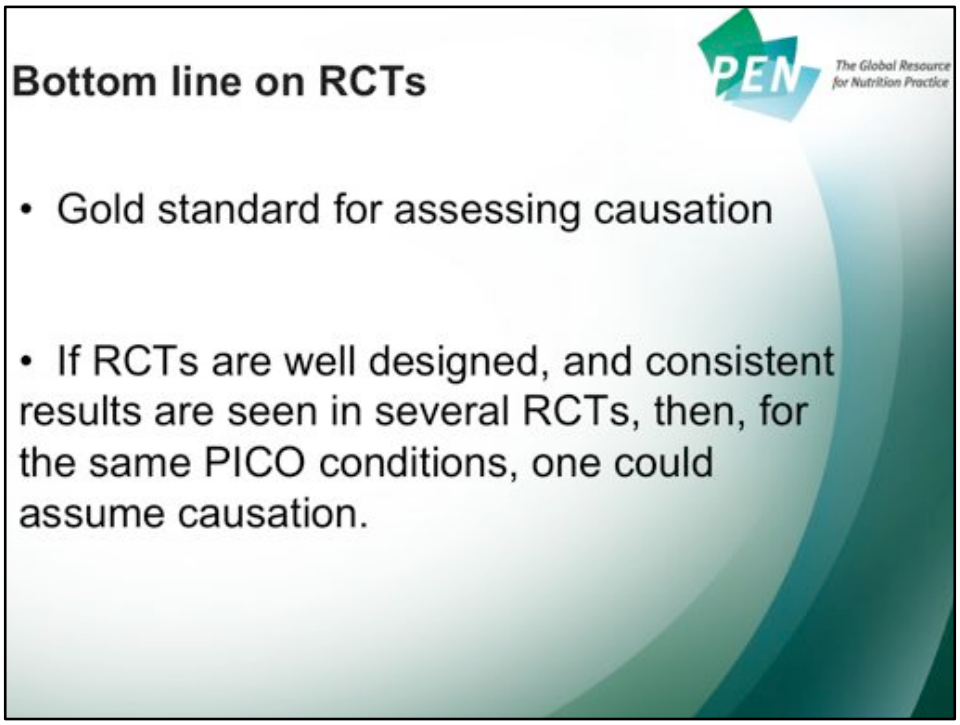


This figure illustrates some main differences between pragmatic and explanatory trials, but many trials have both explanatory and pragmatic aspects, and there are exceptions to this categorization.
When reviewing studies that use a pragmatic design, there may be more sources of bias than explanatory studies, but results may be generalizable and more applicable to a practice setting.

For additional information, this paper (free access) provides a good overview of pragmatic trials: Patsopoulos NA. A pragmatic view on pragmatic trials. Dialogues Clin Neurosci. 2011 June; [cited 2013 Oct 8]13(2): 217–224. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC31819979

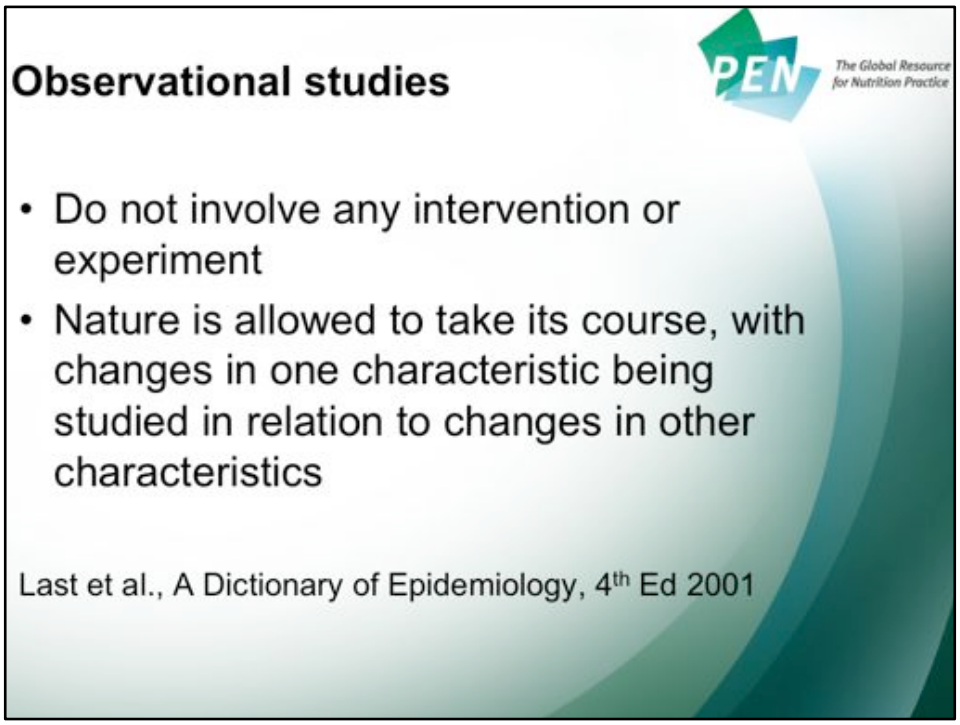


So sometimes the most rigorous design of the RCT is not feasible to do given the research question.

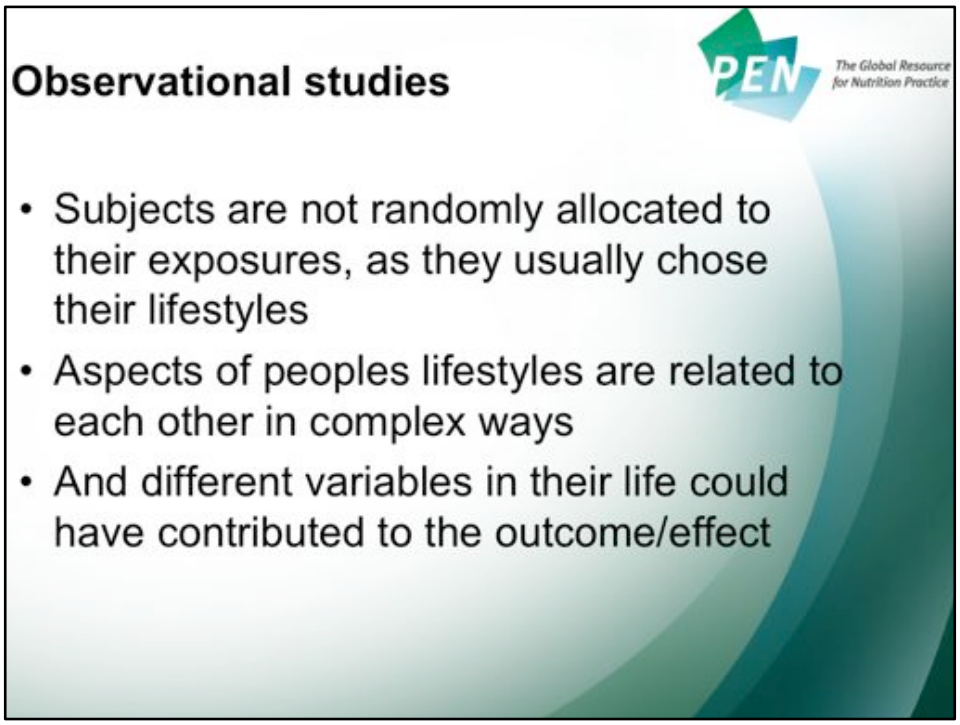


Read slide.
PICO stands for Population, Intervention, Comparison and Outcome

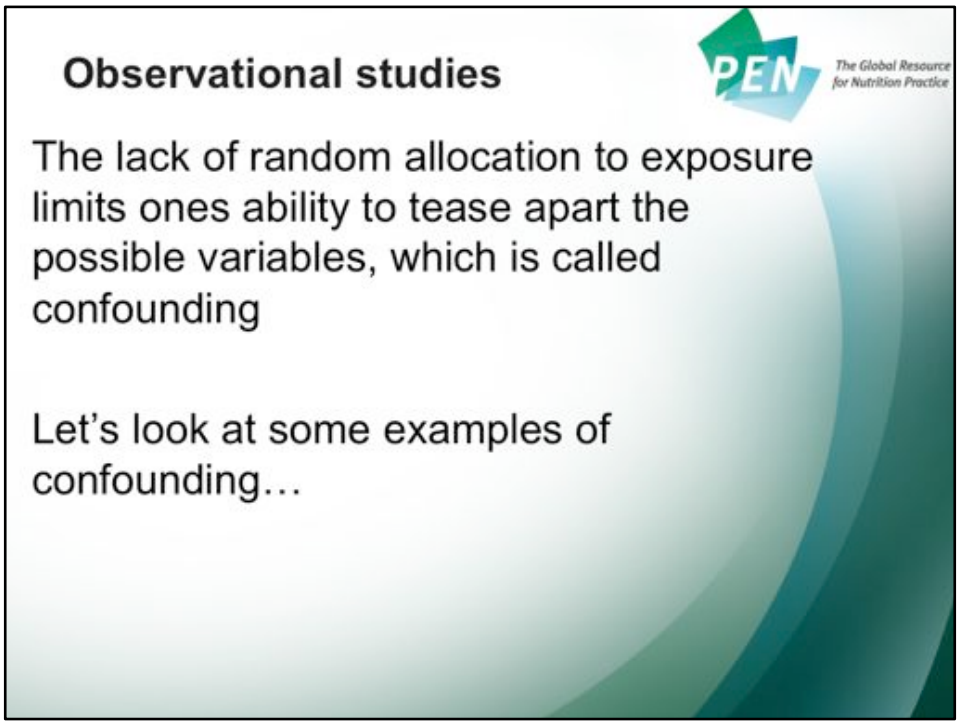
If a clinical trial is not randomized, it should be considered an observational study.



This information comes from: Last JM, Spasoff RA, Harris SS (eds). A Dictionary of Epidemiology, 4th Ed., 2001



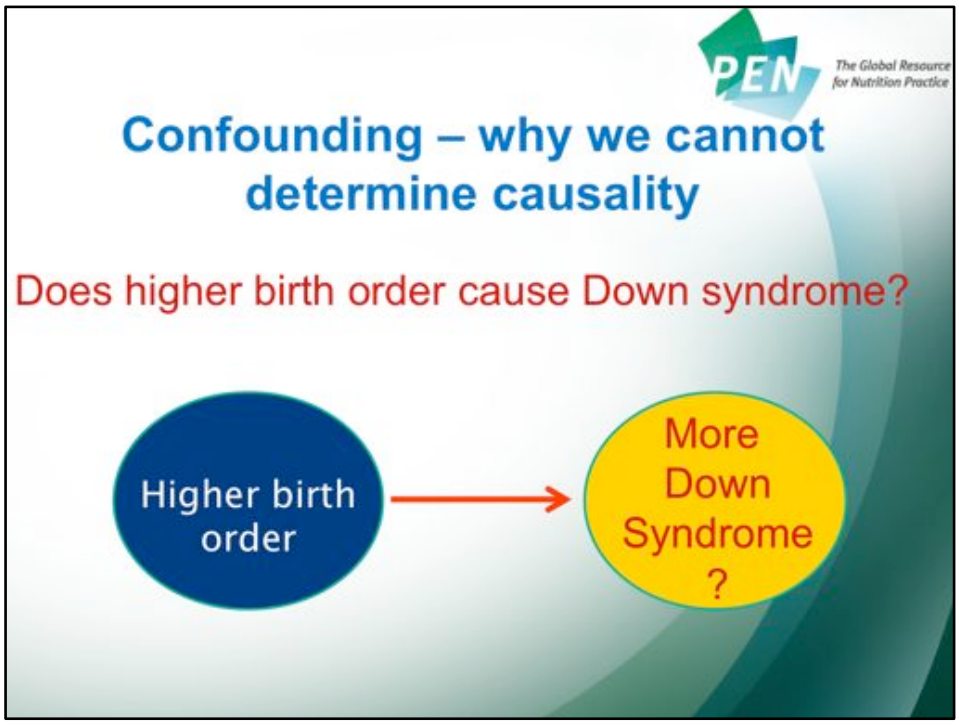
Lifestyles often have characteristics that are related to each other:
- those who smoke cigarettes may eat fewer vegetables and may drink more alcohol
- those who exercise regularly may be less likely to smoke, may eat more fruit and vegetables, have a better job, more social support, drink only moderately, etc.



The Grades of Recommendation, Assessment, Development and Evaluation (GRADE) Working Group (http://www.gradeworkinggroup.org/) comments on confounding:

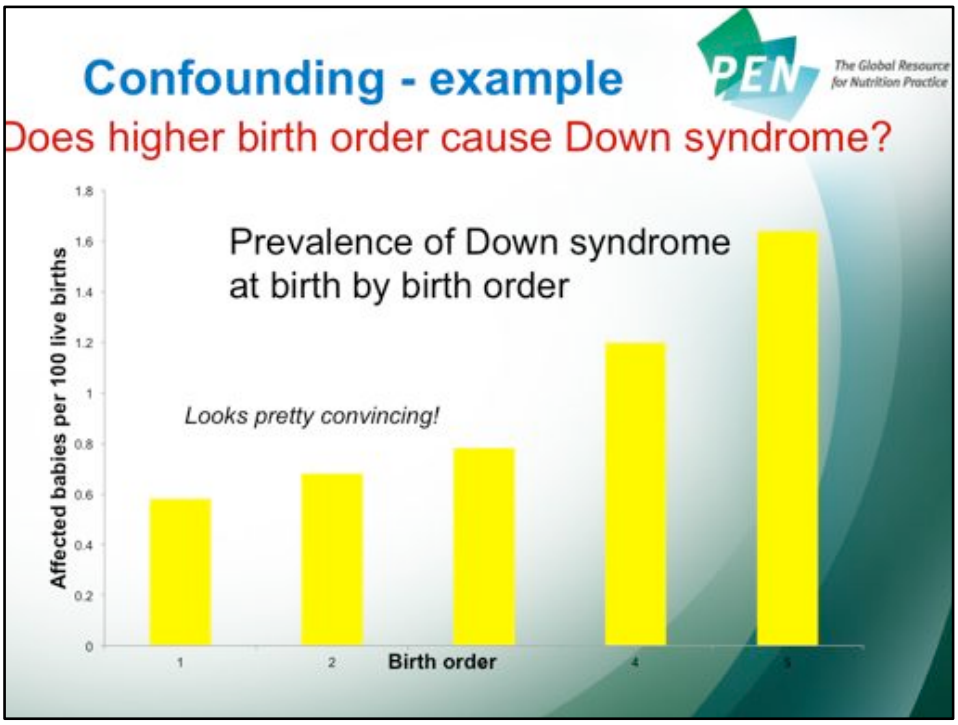
A major limitation in observational studies is a "Failure to adequately control confounding" (Guyatt GH, et al. GRADE guidelines: 4. Rating the quality of evidence--study limitations (risk of bias). J Clin Epidemiol. 2011 Apr;64(4):407-15. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21247734)

"The reason in most instances we consider observational studies as providing only low-quality evidence is that unmeasured or unknown determinants of outcome unaccounted for in the adjusted analysis are likely to be distributed unequally between intervention and control groups. The technical language of observational epidemiology characterizes this phenomenon as ''residual confounding'' or ''residual biases.''" (Guyatt GH, et al. J Clin Epidemiol. 2011;64:1311-16. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21802902)



This slide summarizes the association noted between higher birth order (referred to as parity) with Down syndrome

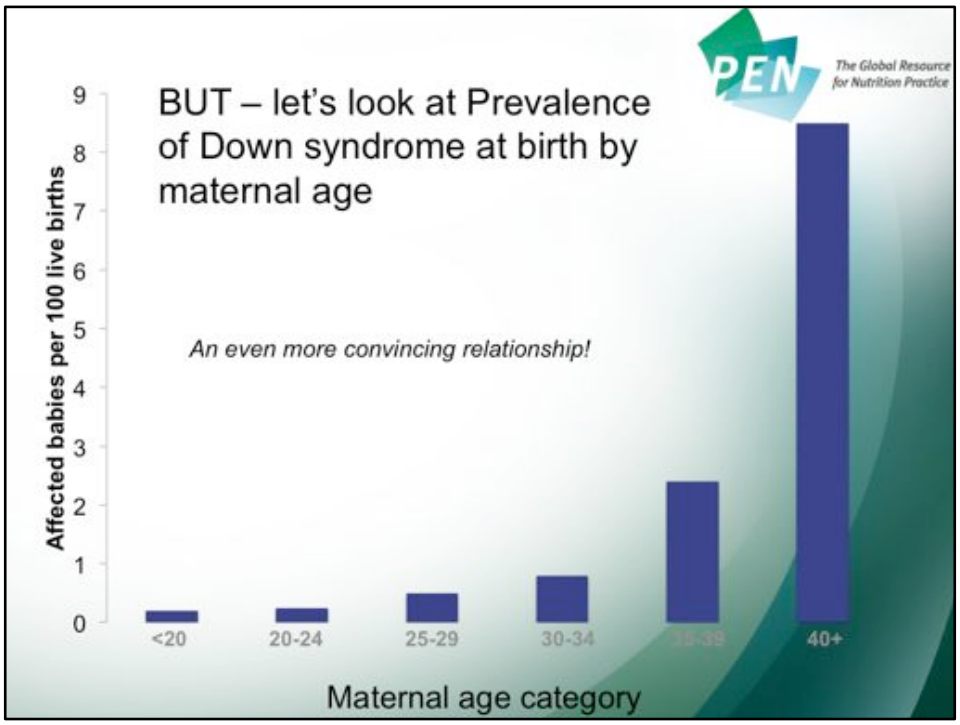
Example from: Rothman – Epidemiology An Introduction, 2002. The study reference, published in 1966 is: Stark CR, Mantel N. Effects of maternal age and birth order on the risk of mongolism and leukemia. J Natl Cancer Inst. 1966 Nov [cited 2013 Nov 11]; 37(5):687-98. Abstract available from: http://www.ncbi.nlm.nih.gov/pubmed/4224604



An example of confounding:

Here is the graph of the association noted between birth order with Down syndrome. Note the higher rates of Down with higher birth number, especially for 5th babies, and you can see a dose-response effect, with increases across the range of parity. This looks important.

Example from: Rothman – Epidemiology An Introduction, 2002. The study reference, published in 1966 is: Stark CR, Mantel N. Effects of maternal age and birth order on the risk of mongolism and leukemia. J Natl Cancer Inst. 1966 Nov [cited 2013 Nov 11]; 37(5):687-98. Abstract available from: http://www.ncbi.nlm.nih.gov/pubmed/4224604

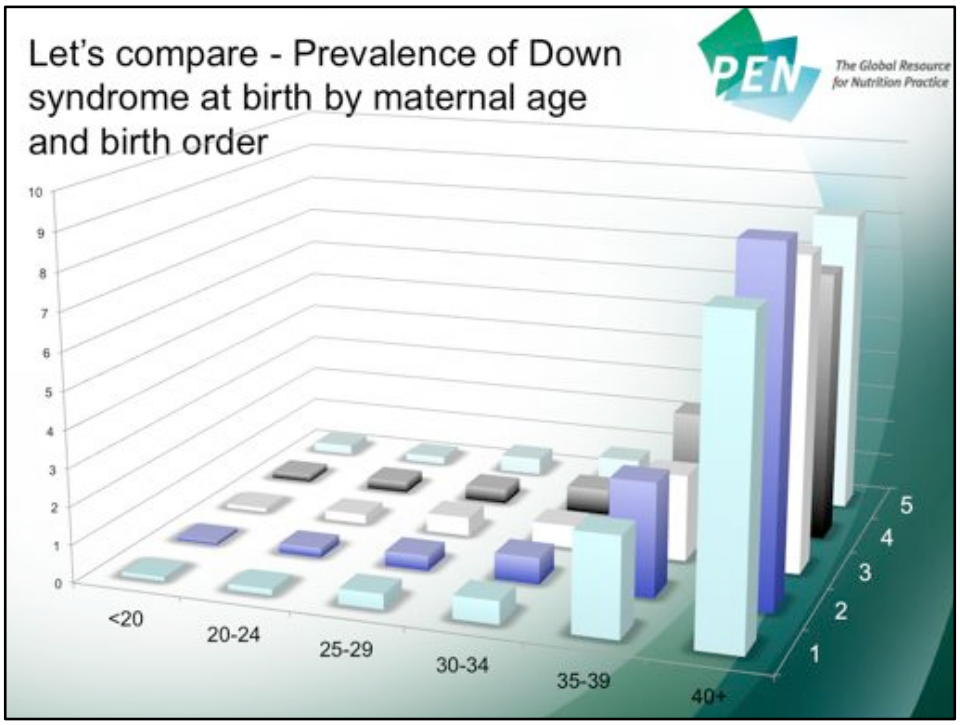


This slide shows the relationship between the occurrence of Down and maternal age – it indicates an even stronger relationship than did birth order. Again we see a dose response relationship. The prevalence changed from 0.2 per 1000 births for the youngest age to 8.5 per 1000 for the oldest age group – a 40 times difference. This is a remarkably strong effect.

Birth order and age are co-related, as mothers who are having their fifth baby are more likely to be older as a group than mothers having their first babies. Therefore when we examine birth order we are also examining age-effects as a related variable. The variables are mixed together.

The effect we saw of birth order being related to Down syndrome is due to the confounding effect of maternal age.

Example from: Rothman – Epidemiology An Introduction, 2002. The study reference, published in 1966 is: Stark CR, Mantel N. Effects of maternal age and birth order on the risk of mongolism and leukemia. J Natl Cancer Inst. 1966 Nov [cited 2013 Nov 11];37(5):687-98. Abstract available from: http://www.ncbi.nlm.nih.gov/pubmed/4224604

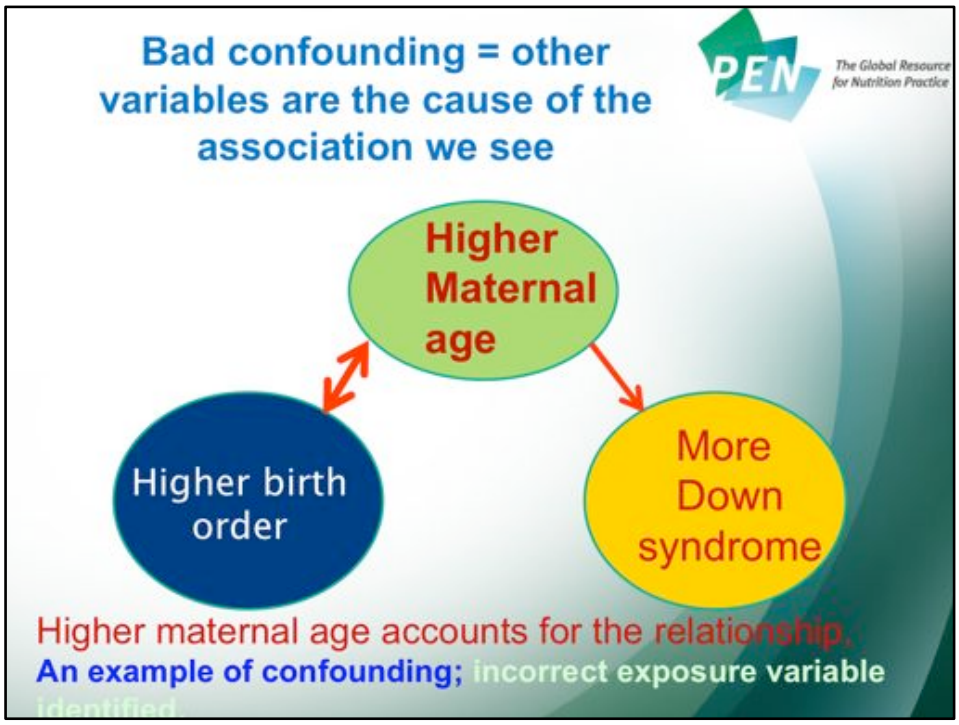


A way to examine which variable is the important one and which is the extraneous one is to examine them together in the same dataset. This figure illustrates the effects of both of the variables together and their association with Down syndrome.

Within each category of birth order, which you can see as you look left to right across each row of this graph, you can see the striking effect of maternal age – even older mothers who are having their first babies are at higher risk for having a baby with Down syndrome. In contrast, looking across the age categories, front to back in each of the age categories, there doesn't seem to be a trend for birth order. Thus the apparent trend by birth order was solely due to the maternal age relationship. Birth order does not have an effect of its own, so it does not confound the relationship between maternal age and Down syndrome.

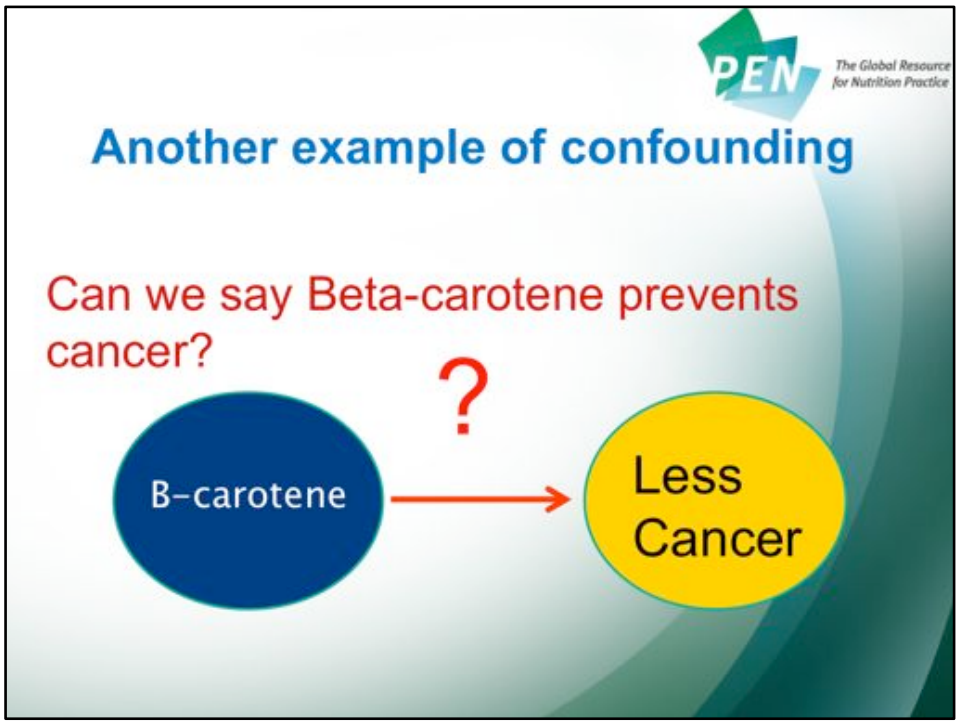
This mixing of effects is called confounding. Making use of information about potential confounders in research is referred to as "adjusting for" or "controlling for" the confounders. It is not possible to completely control for confounding in observational studies since not all confounders are known and not all can be practically measured. Therefore there is always residual confounding remaining in observational studies. The only way to avoid confounding is random allocation to groups, in an RCT.

Example from: Rothman – Epidemiology An Introduction, 2002. The study reference, published in 1966 is: Stark CR, Mantel N. Effects of maternal age and birth order on the risk of mongolism and leukemia. J Natl Cancer Inst.. 1966 Nov [cited 2013 Nov 11];37(5):687-98. Abstract available from: http://www.ncbi.nlm.nih.gov/pubmed/4224604

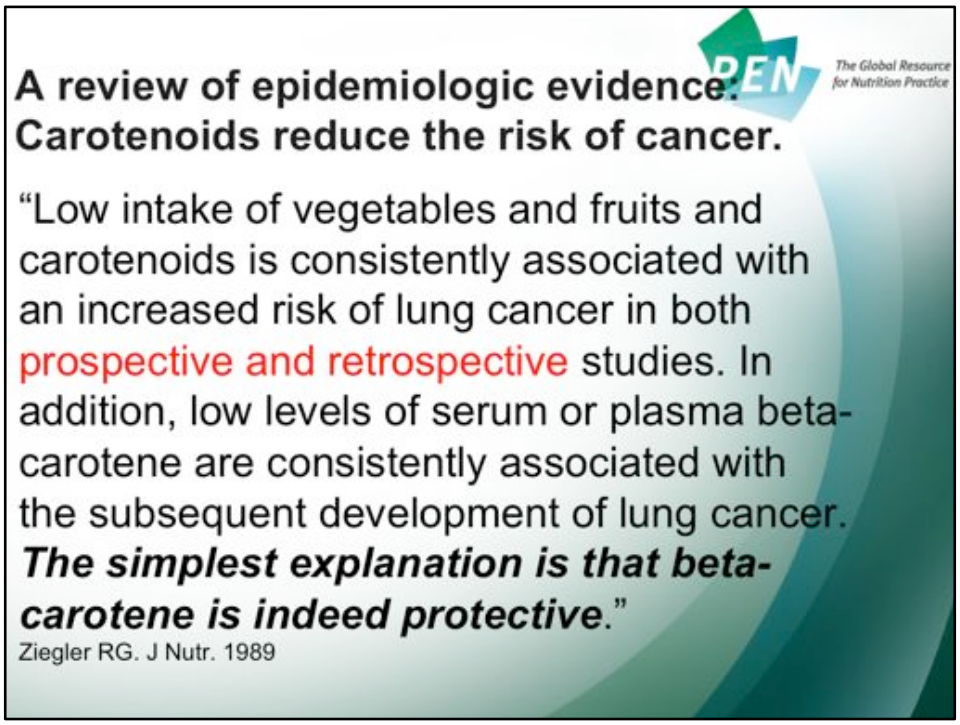


However, this association noted between birth order and Down syndrome was found to actually be due to the close association between birth order and another variable, that is with maternal age.

Example from: Rothman – Epidemiology An Introduction, 2002. The study reference, published in 1966 is: Stark CR, Mantel N. Effects of maternal age and birth order on the risk of mongolism and leukemia. J Natl Cancer Inst. 1966 Nov [cited 2013 Nov 11]; 37(5):687-98. Abstract available from: http://www.ncbi.nlm.nih.gov/pubmed/4224604



Let's take a look at this relationship – numerous observational studies consistently reported lower cancer rates among people who consumed more beta-carotene

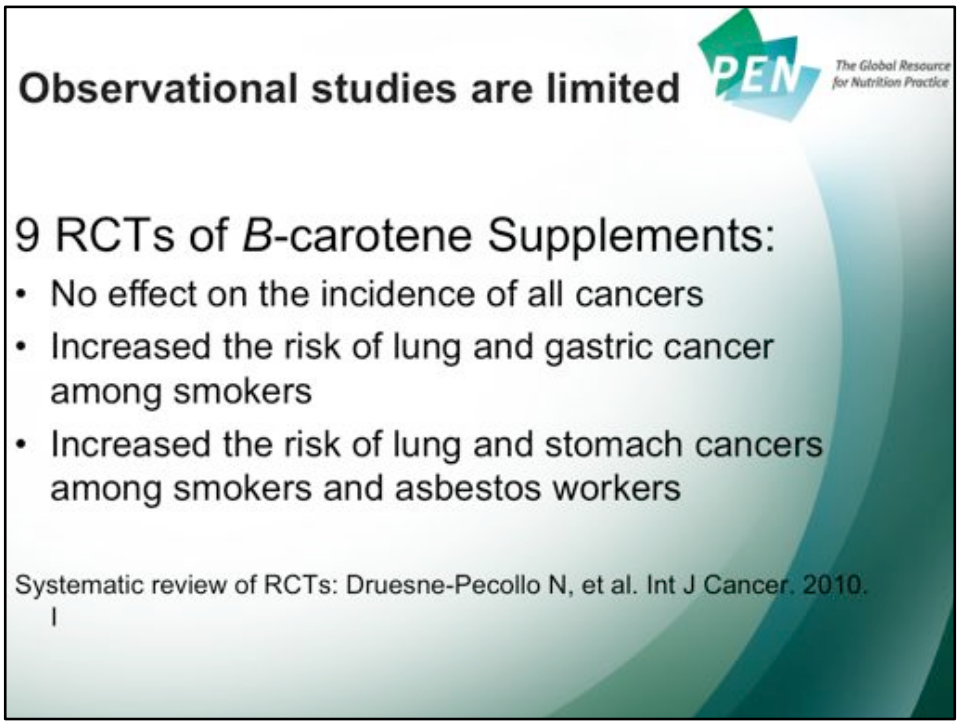


A 1989 review paper summarized the observational evidence regarding beta-carotene and cancer and concluded that "The simplest explanation is that beta-carotene is indeed protective" in terms of cancer (reference below)

"Prospective and retrospective studies" were observational studies since they were not RCTs. It was confirming that not only measures of carotenoid intakes were associated with lower prevalence of cancer, but also serum levels were also associated with better cancer rates.

Luckily for us, beta-carotene is easy to supplement, and several large RCTs evaluated this association further.

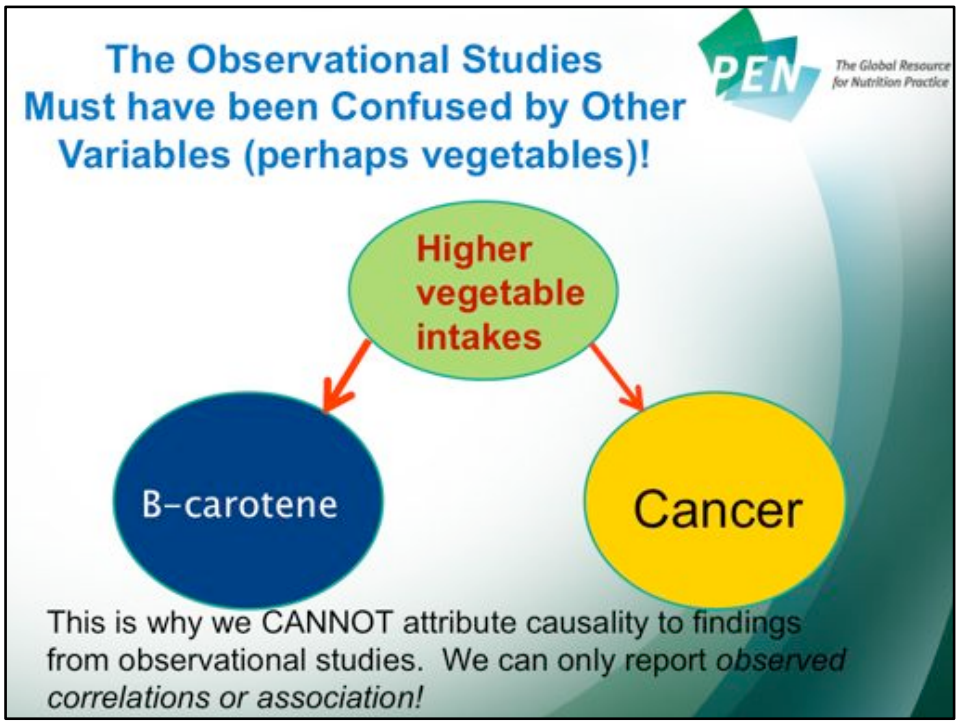
The reference for this quote comes from: Ziegler RG. A review of epidemiologic evidence that carotenoids reduce the risk of cancer. J Nutr. 1989 Jan [cited 2013 Nov. 8];119:116-22. Abstract available from: http://www.ncbi.nlm.nih.gov/pubmed/2643694



Large RCTS were conducted on this topic: "A total of 182,323 participants from 9 trials were randomly assigned to intervention or control groups. The number of participants in each trial ranged from 1,621 to 39,876." (The reference for the systematic review is: Druesne-Pecello N. et al. Beta-carotene supplementation and cancer risk: a systematic review and metaanalysis of randomized controlled trials. Int. J Cancer. 2010 Jul 1 [cited 2013 Nov 8];127(1):172-84. Abstract available from: http://www.ncbi.nlm.nih.gov/pubmed/19876916)

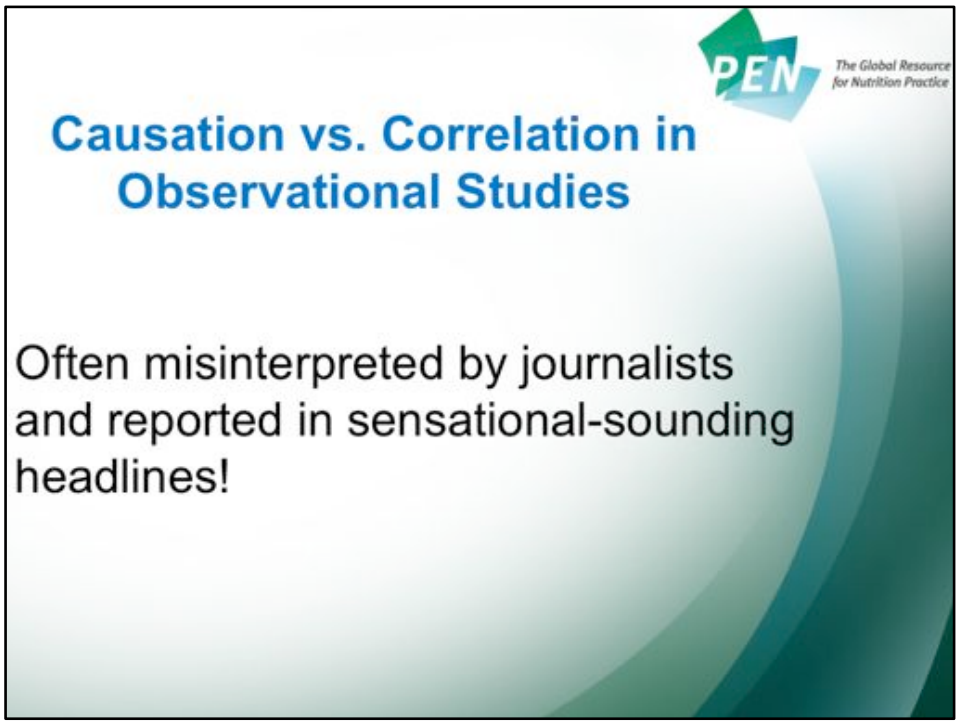
Conversely, beta-carotene increased not only lung cancer but also gastric cancer at doses of 20–30 mg/day, in smokers and asbestos workers.

How could this be – how could the RCTs give the opposite finding to observational studies??



In this case it may be higher vegetable intakes that are confounding the relationship. This apparent relationship could be due to people in the observational studies who ate more fruit and vegetables, and thus reported higher vegetable intakes and had higher serum levels of beta-carotene, had a protective effect from the vegetables, that was not due directly to the beta-carotene. By identifying beta-carotene as the important exposure, the observational study researchers were wrong in identifying the important factor.

We just don't know exactly.
However, this highlights how important RCTs are in testing the hypotheses put forth by observational studies, since they allow us to control for variables and can help us determine causality!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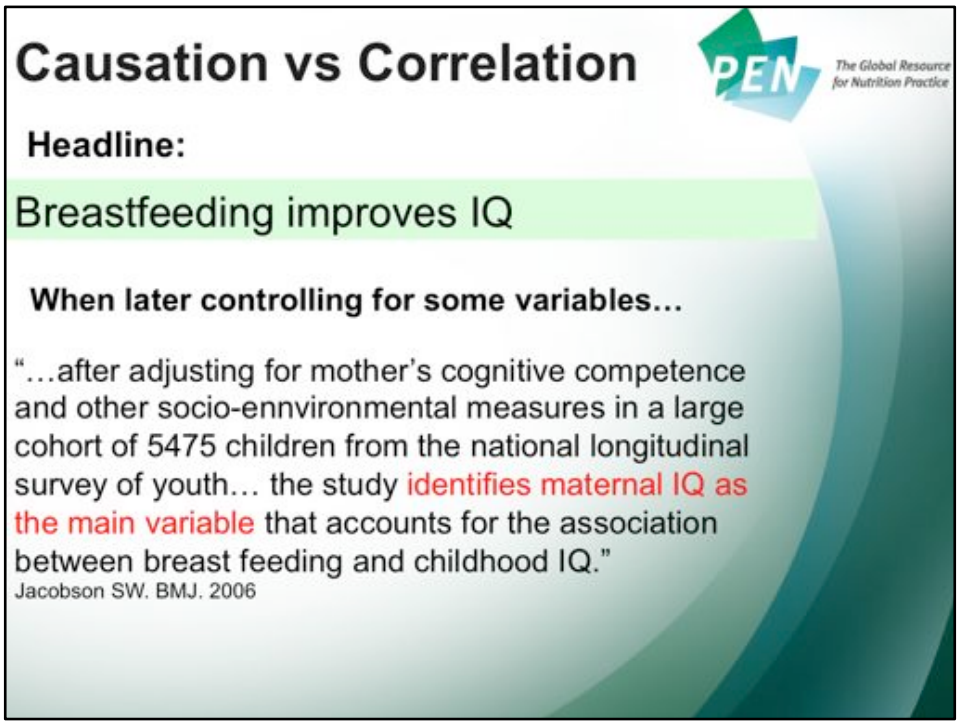
Causation vs. Correlation in Observational Studies
Often misinterpreted by journalists and reported in sensational-sounding headlines!

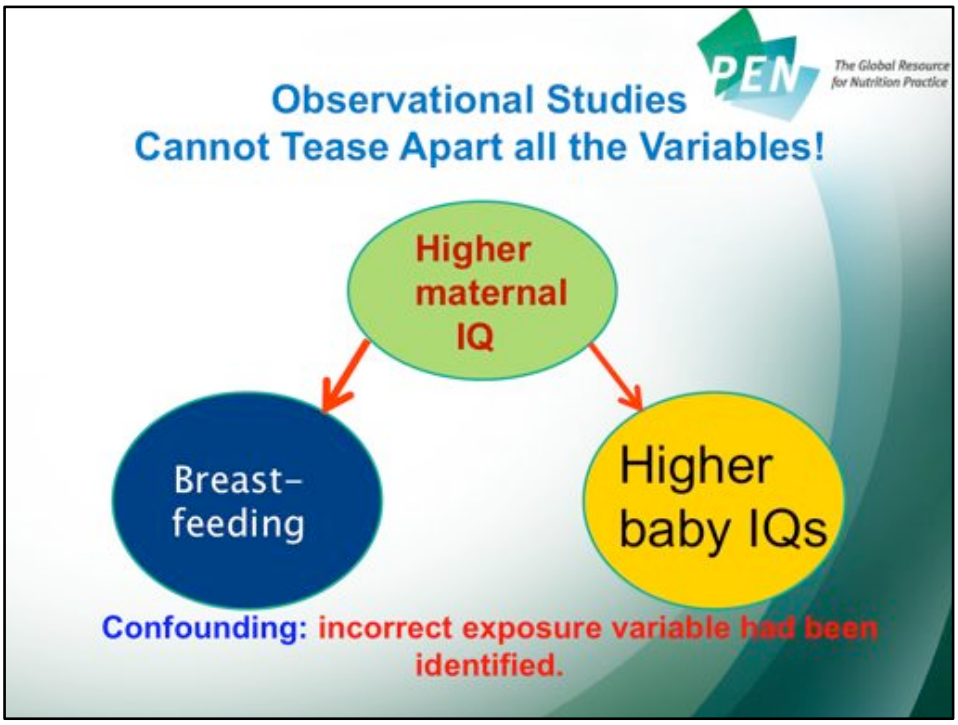
Read slide



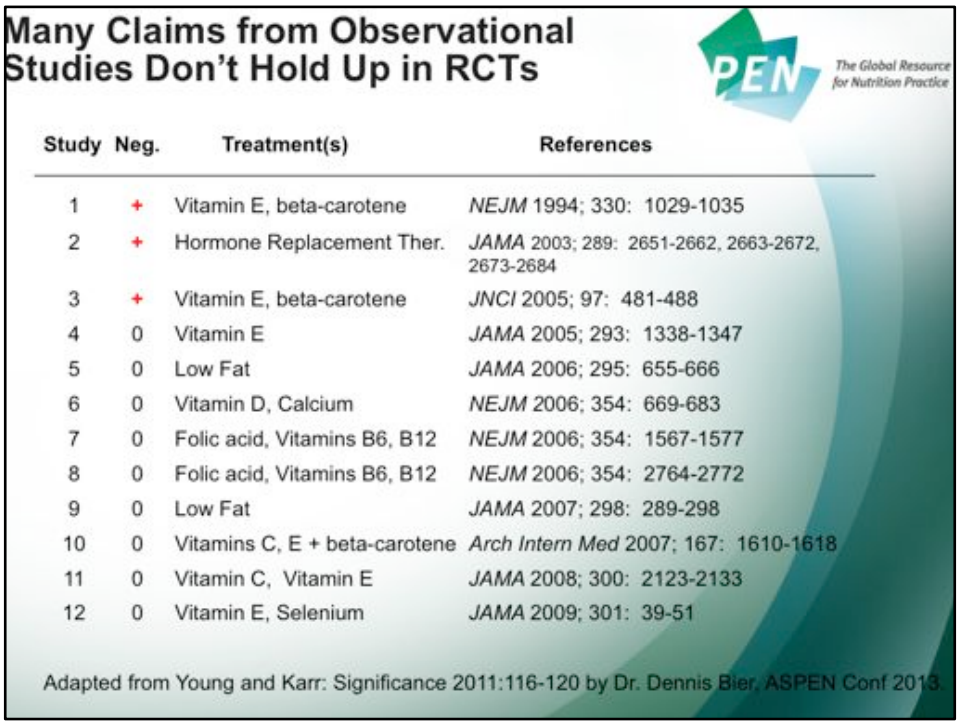
A headline read:
Breast feeding improves IQ…. And they go one to cite a meta analysis published in 1999 which reports IQ s measured in breast fed infants and compares them to IQs measured in formula fed infants. From the described relationship between IQ and mode of feeding, they draw the conclusion that breast feeding improves IQ.

Now a newer study (dated 2006) controlled for maternal IQ in the analysis, and found that maternal IQ explained the relationship between IQ and breastfeeding. More women with higher IQ choose to breast feed and this explains higher IQ of infants who are breast fed.
The reference for this quote comes from: Jacobson SW. Breast feeding and intelligence in children: Mediated by mother's intelligence rather than better nutrition. BMJ 2006 Nov. 4 [cited 2013 Nov 11];333(7575): 929-30. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1633786/

Another point that this example demonstrates is how we tend to ignore data that does agree with our values or firmly held beliefs.

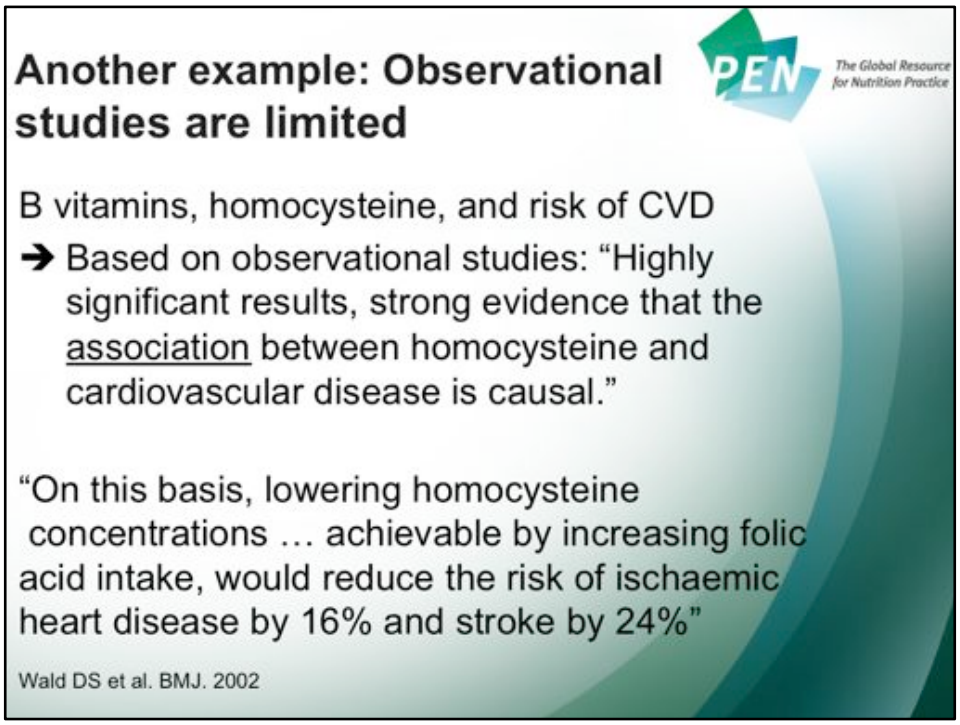


The Jacobson study identified that once you control for maternal IQ, the association between breastfeeding and higher IQs disappears.



Here is a list of associations noted in observational studies that failed to replicate, or be found of importance in randomized trials. The + Negative column means that the results from the RCTs were statistically significant in the opposite direction from the observational evidence. Most of these associations are nutrition related.

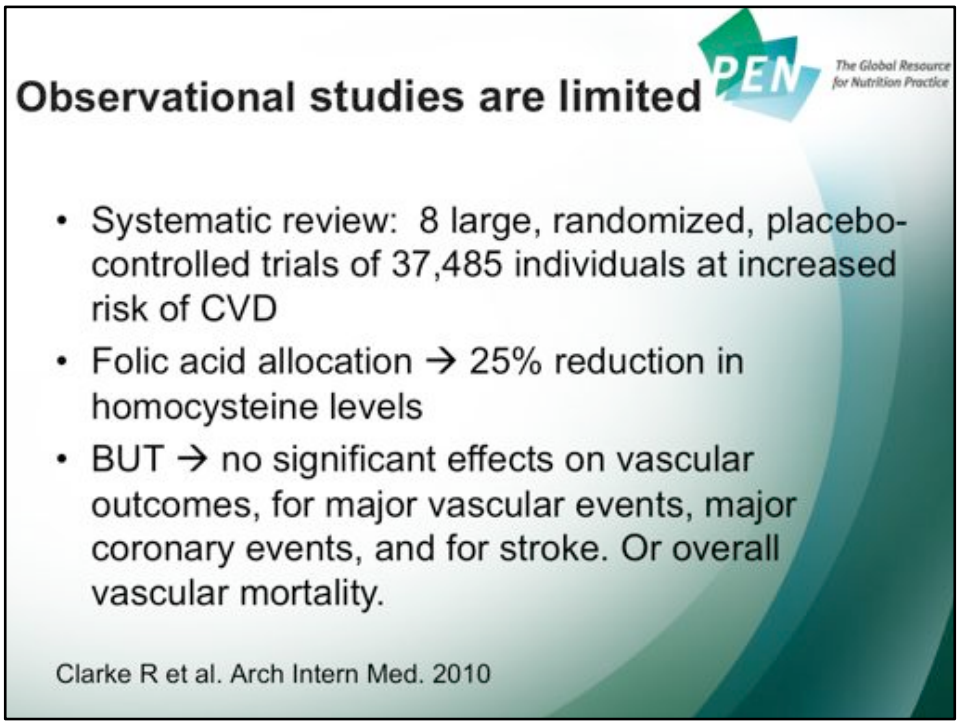
Young & Karr "carried out an informal but comprehensive accounting of 12 randomised clinical trials that tested observational claims" – this slide reports Table 1 in their paper. "The 12 clinical trials tested 52 observational claims. In all of these instances, the RCTs did not confirm the claims in the direction of the observational claims. To put it another way, 100% of the observational claims failed to replicate. In fact, five claims (9.6%) are statistically significant in the clinical trials *in the opposite direction* to the observational claim. To us, a false discovery rate of over 80% is potent evidence that the observational study process is not in control." (This quote comes from: Young SS, Carr A. Deeming, data and observational studies. A process out of control and needing fixing. Significance. September 2011 [cited 2013 Nov 11]; 8(3):116-20. Abstract available from: http://onlinelibrary.wiley.com/doi/10.1111/j.1740-9713.2011.00506.x/abstract)



These quotes from this systematic review of observational studies looks pretty important. We can understand the mechanism: folate lowers homocysteine, homocysteine is a risk factor for CVD. They even estimated a predicted numerical benefit that looks very impressive.

Note the use of the word association.

The reference for these quotes: Wald DS, Law M, Morris JK. Homocysteine and cardiovascular disease: evidence on causality from a meta-analysis. BMJ. 2002 Nov 23 [cited 2013 Nov 11];325(7374):1202. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12446535

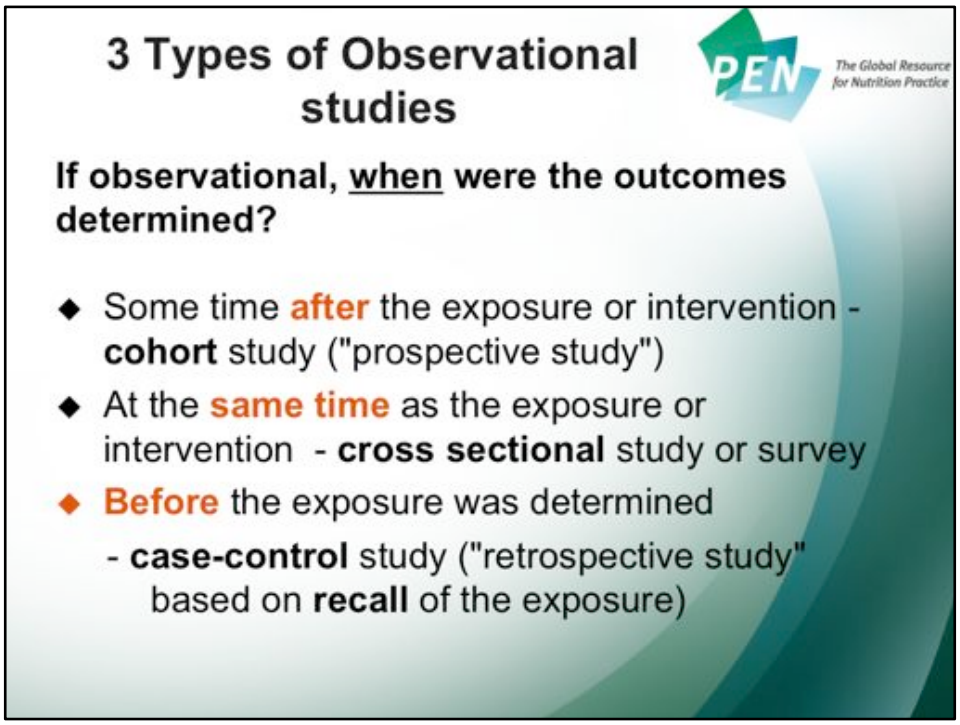


Again, the RCTs give different results than the weaker observational evidence
Elevated plasma homocysteine levels have been associated with higher risks of cardiovascular disease, but the effects on disease rates of supplementation with folic acid to lower plasma homocysteine levels do not substantiate these findings.

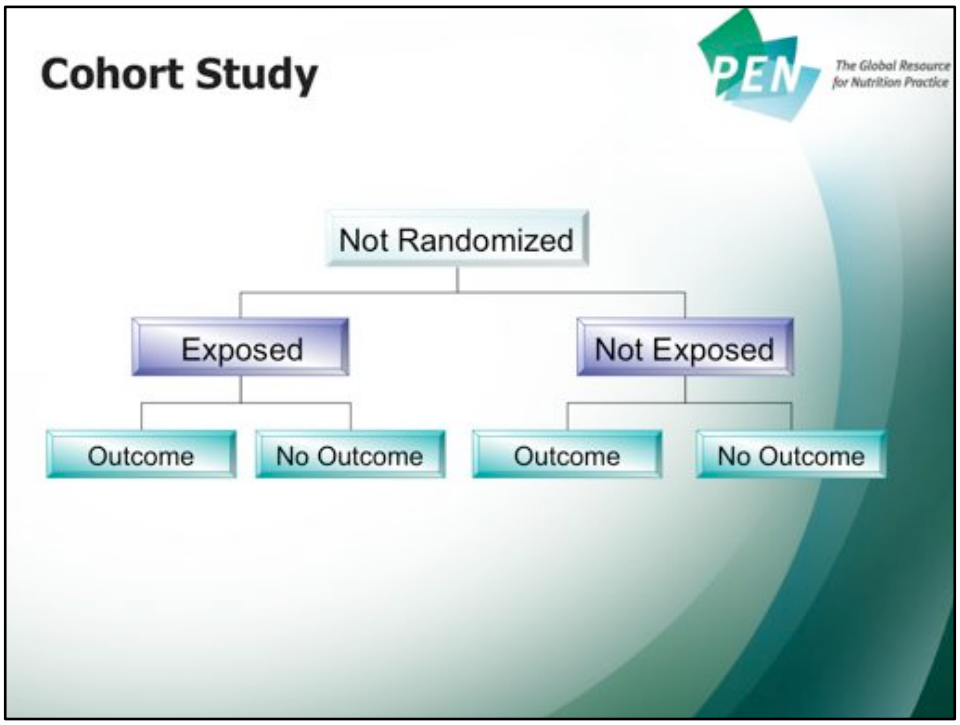
Individual participant data were obtained for a meta-analysis of 8 large, randomized, placebo-controlled trials of folic acid supplementation involving 37 485 individuals at increased risk of cardiovascular disease. There were 9326 major vascular events (3990 major coronary events, 1528 strokes, and 5068 revascularizations), 3010 cancers, and 5125 deaths. Folic acid allocation yielded an average 25% reduction in homocysteine levels. However, dietary supplementation with folic acid to lower homocysteine levels had no significant effects within 5 years on cardiovascular events or on overall cancer or mortality in the populations studied.

Put more simply, the folic acid supplements did lower the elevated homocysteine levels. Contrary to expectations, the participants did not have lower rates of vascular events. Therefore it appears that elevated homocysteine is a marker of CVD, but it does not look like it is on the causal pathway, since lowering it did not improve outcomes.

Meta-analysis reference: Clarke R et al. B-Vitamin Treatment Trialists' Collaboration. Effects of lowering homocysteine levels with B vitamins on cardiovascular disease, cancer, and cause-specific mortality: Meta-analysis of 8 randomized trials involving 37 485 individuals. Arch Intern Med. 2010 Oct 11 [cited 2013 Nov 11];170(18):1622-31. Abstract available from: http://www.ncbi.nlm.nih.gov/pubmed/20937919



As mentioned earlier, observational studies can be divided into three main types, depending on the timing of the measurement of outcome….



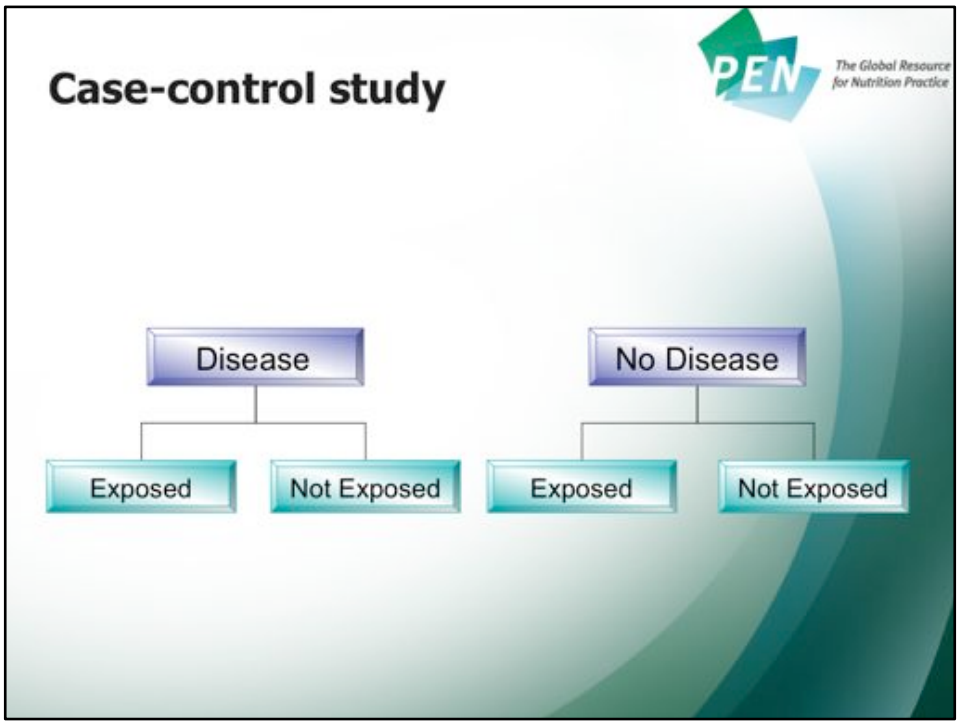
After RCTs, Cohort studies are the next most rigorous to measure a relationship. The strength of a cohort study is that we know that the outcome happened after the exposure.

Cohort studies are observational longitudinal studies with 2 groups of patients (the cohorts). In cohort studies, the diets, body composition or physical activity levels of a large group of people, who are assumed to be healthy, are assessed and the group is followed over a period of time (prospectively) to measure the development of different outcomes. During the follow-up period, some members of the cohort will develop and be diagnosed with a condition or a particular outcome, while others will not and comparisons are made between these 2 groups.

Because measures are made before the outcome, cohort studies are not subject to recall bias. Some cohort studies are very large (tens or hundreds of thousands) of participants, thus making them expensive studies, performed in high-income countries. Because the groups are not randomly formed, they may differ in important ways other than in the variable under study. These possibly important related variables are referred to as confounding factors. For example…the groups may be different in terms of lifestyle risk factors, socioeconomic status, health status and you are never certain if the exposure being studied or one of these other factors or "confounders" accounts for the outcome.

An example of a Cohort study – those with high soy intakes and those with low soy intakes… follow them and monitor for presence of breast cancer (compare rates between groups).

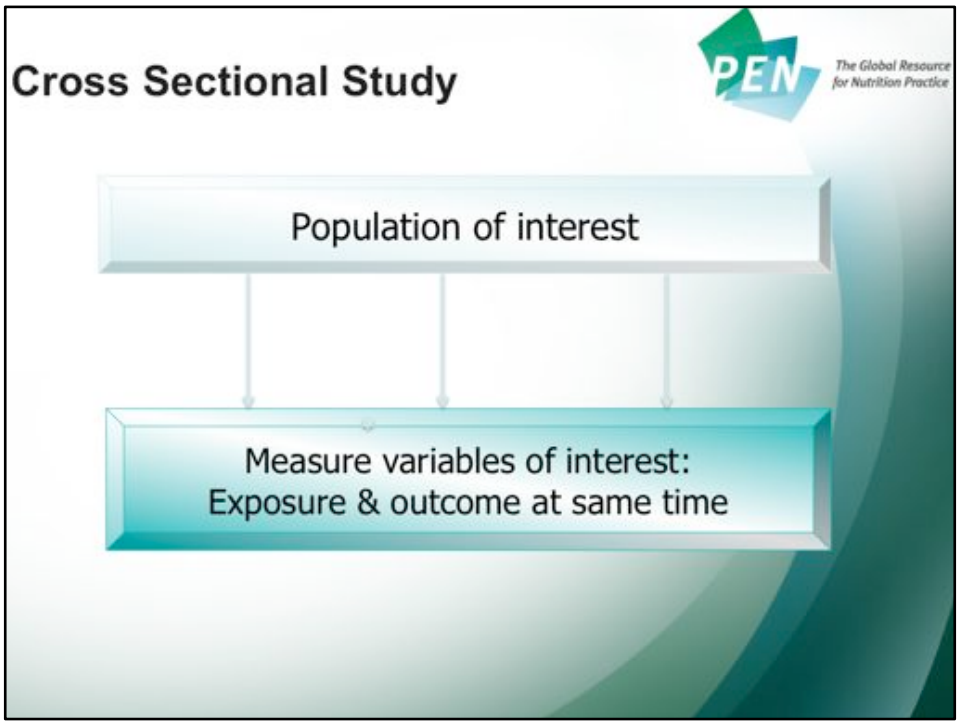
When an outcome is rare or takes years to occur, it may only be feasible to examine it



When an outcome is rare or takes years to occur, a Case control study might be used. Case-control studies are studies in which patients who already have a specific condition are compared with people who do not. Researchers may rely on medical records and/or patient recall for data about their exposures.

These types of studies are less reliable than RCTs because showing a statistical relationship does not mean that one factor necessarily caused the other. The subjects in a case-controls study are at risk of recall bias. Recall bias occurs when participants' reporting of various exposures (e.g. dietary intake, medication, physical activity) is affected by whether they are cases or controls or their memory of events (Recall bias). Because the researchers might not identify the exact cause of the disease, you can't claim cause and effect with a case control study (though the media often does). BUT they are Less expensive and can be completed in shorter periods of time than cohort studies

An example of a Case-control study – to determine the association between metabolic syndrome and the beverages consumed by adults when they were children

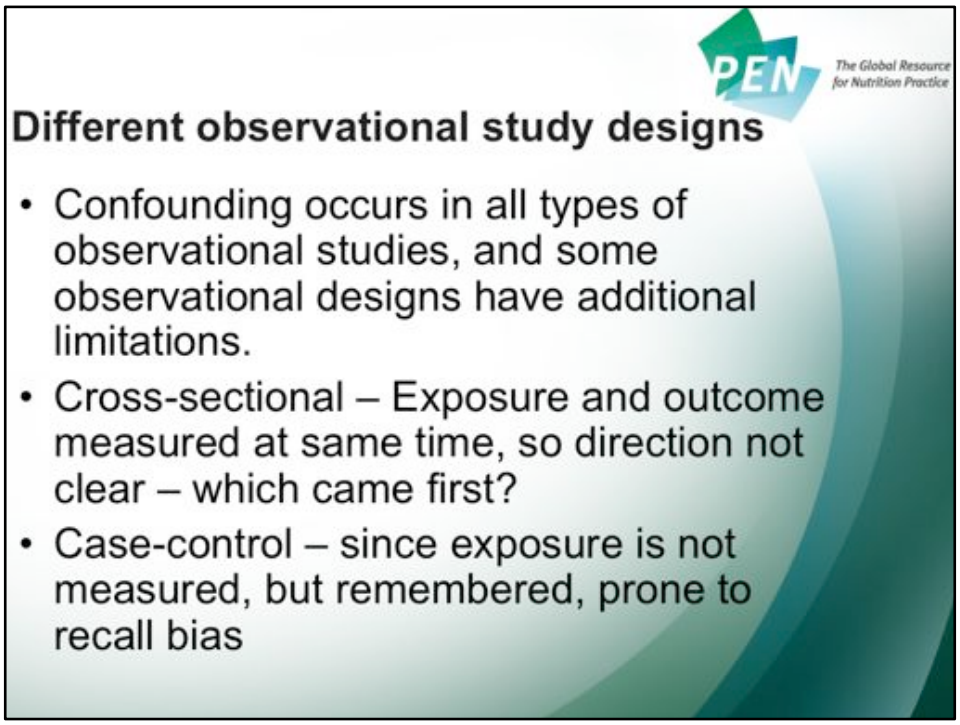


The most frequent observational studies and the easiest to conduct are those in which both the exposure and outcome are measured at the same time. These studies are called cross-sectional studies.

You examine your population of interest at a particular point in time and measure a range of variables – could include current dietary intakes, or perhaps you might measure the prevalence of obesity in children and adolescents living in food insecure households to examine the association between food insecurity and over weight/ obesity.

Cross-sectional studies do not tell us the order of events i.e. did the purported cause precede the effect. For example: in a study of overweight and breast cancer… did the cancer occur before the weight gain or did the weight gain precede the breast cancer?

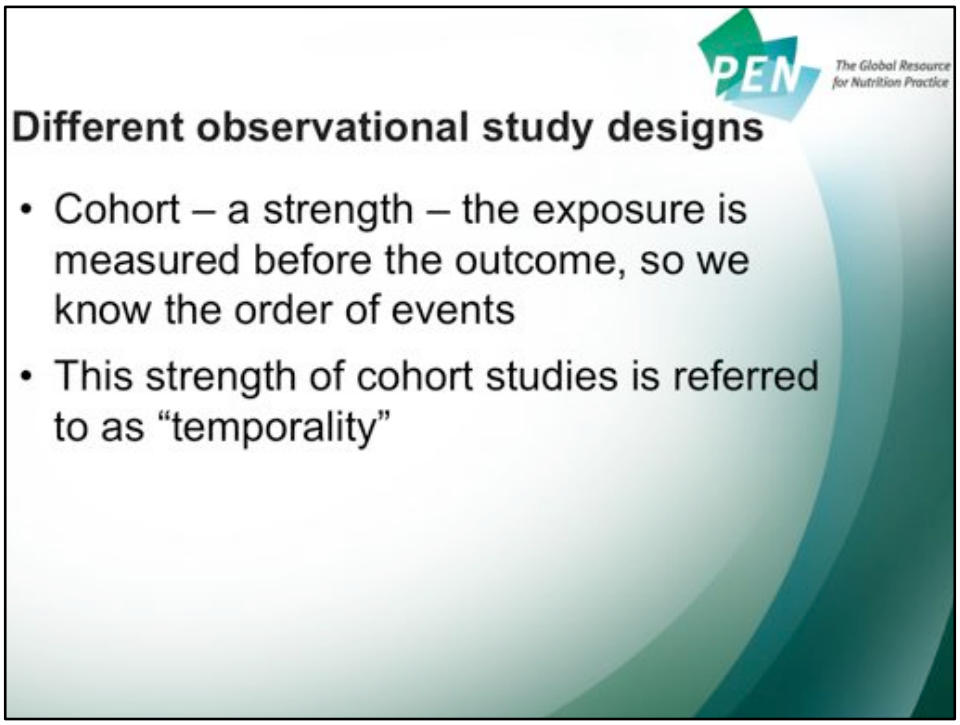
Can also be called a prevalence survey – used to describe the burden of disease in a community and or its distribution
An example of a Cross Sectional study - Measure fruit and vegetable intakes in a group of grade 5 students



Example from PEN: Cohort and case-control studies provide reasonably consistent evidence for a protective effect of fruits against the risk of lung cancer after adjustment for smoking status.

However, if the association were only from case-control studies, then we have a risk of bias since the nutrition exposure information is all recalled.

Recall bias happens when there is a systematic difference since those who have a disease have more specific recall of their exposures, since they may have thought about the potential causes of their disease, and provide different information (difference accuracy or completeness) compared to the controls who do not have the disease. For example – a mother whose child died of cancer may recall more pregnancy exposures compared to those who have healthy children.


PEN
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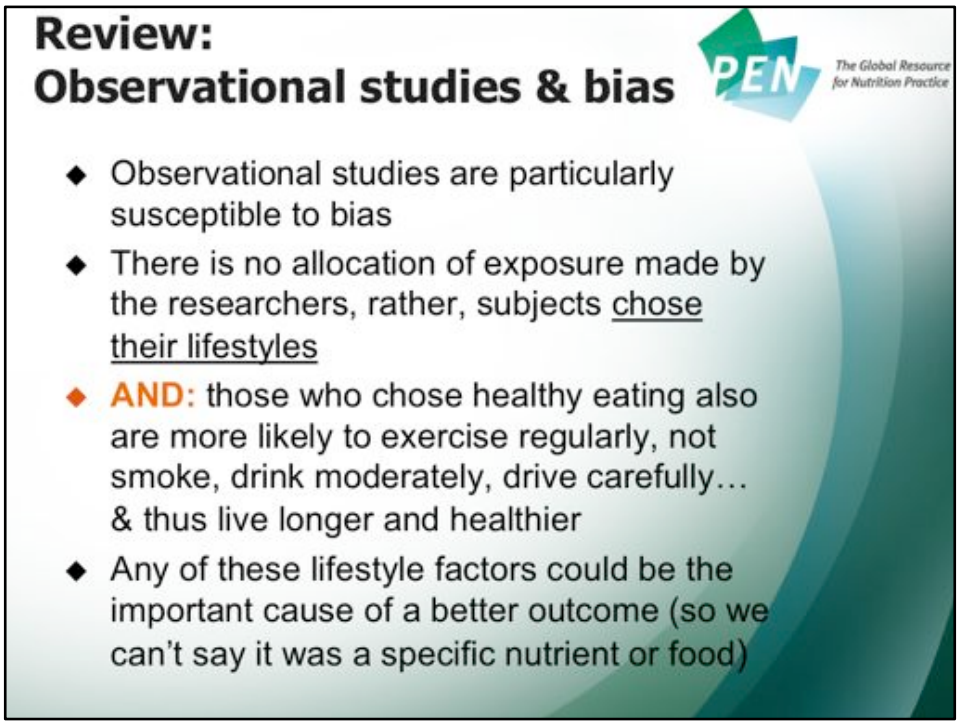
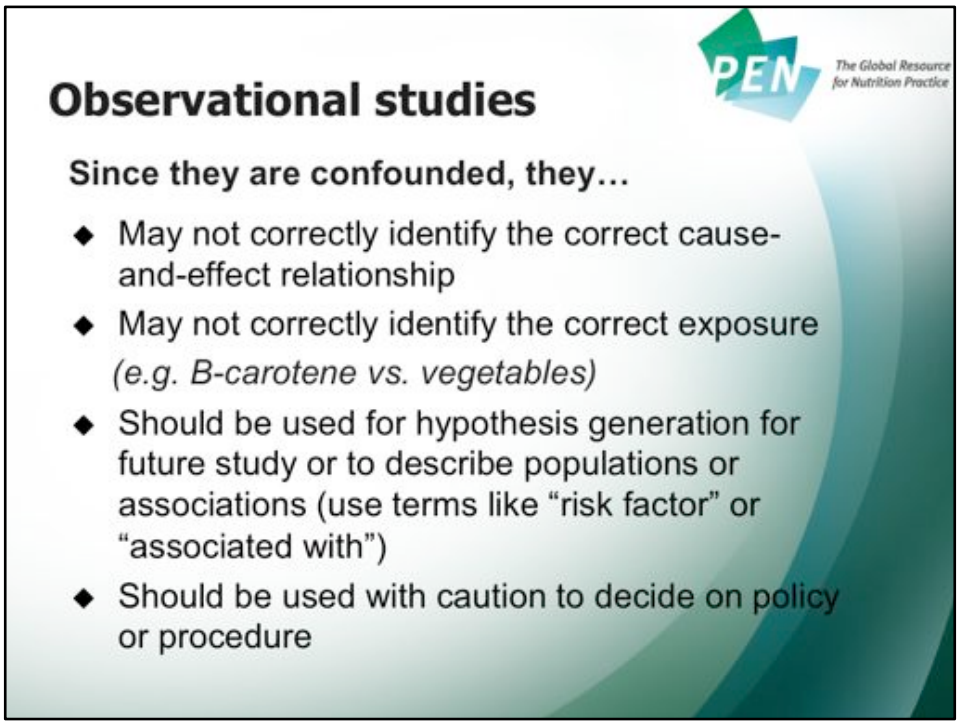
Different observational study designs
• Cohort – a strength – the exposure is measured before the outcome, so we know the order of events
• This strength of cohort studies is referred to as “temporality”

Read slide



Bias is defined as a systematic error or deviation in results. There are many kinds of bias…
The main types of bias arise from systematic differences in the groups that are compared (selection bias), the care that is provided, exposure to other factors apart from the intervention of interest (confounding), withdrawals or exclusions of people entered into a study (attrition bias) or how outcomes are assessed (detection bias).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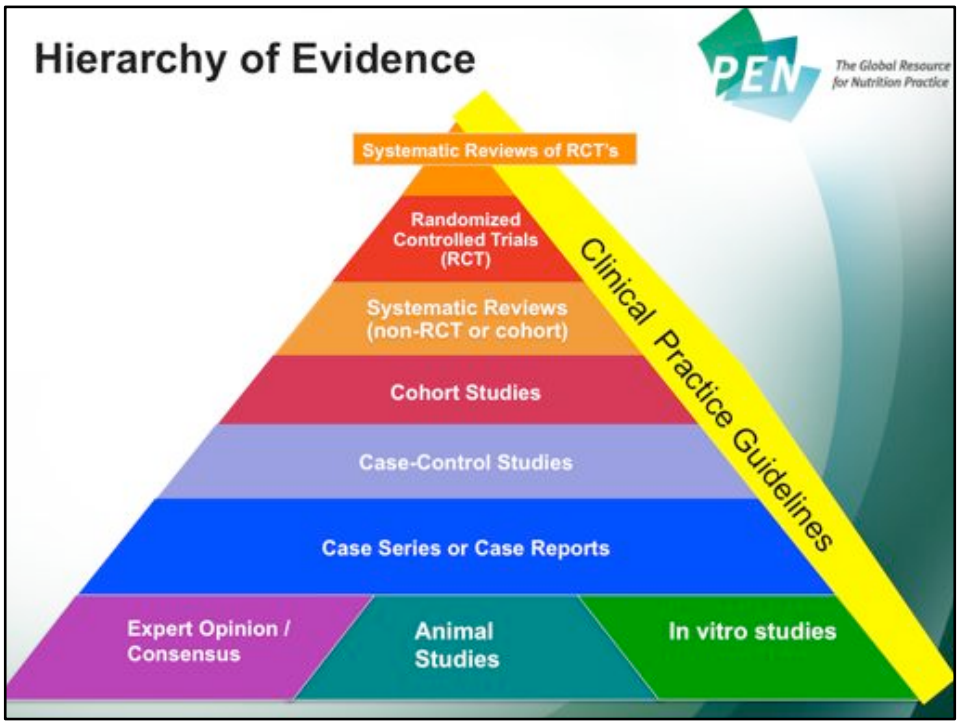
Observational studies
Since they are confounded, they…
May not correctly identify the correct cause-and-effect relationship
May not correctly identify the correct exposure
(e.g. B-carotene vs. vegetables)
Should be used for hypothesis generation for future study or to describe populations or associations (use terms like "risk factor" or "associated with")
Should be used with caution to decide on policy or procedure

Read slide



Hierarchy of Evidence: to help us understand that every study is not created equal and some are better quality evidence than others. Some types of studies are more appropriate depending on the question being asked. In addition to the type or design of the study, the quality of the study (e.g. well designed, size, risk of bias…) is a key component in determining how it contributes to the graded evidence used in PEN®. Review the "Appraising the Literature" training module for more on assessing the quality of the study. It can be accessed from: http://www.pennutrition.com/WriterGuide.aspx

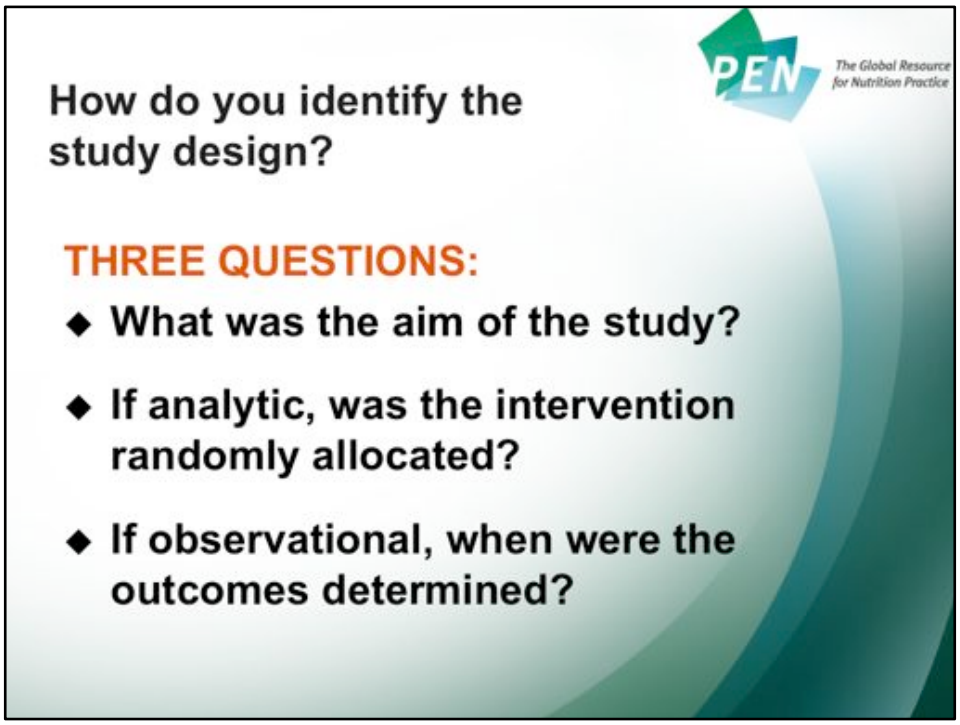
Depending on your quality assessment of the document then generally the higher quality evidence in terms of design is from:

Higher quality:

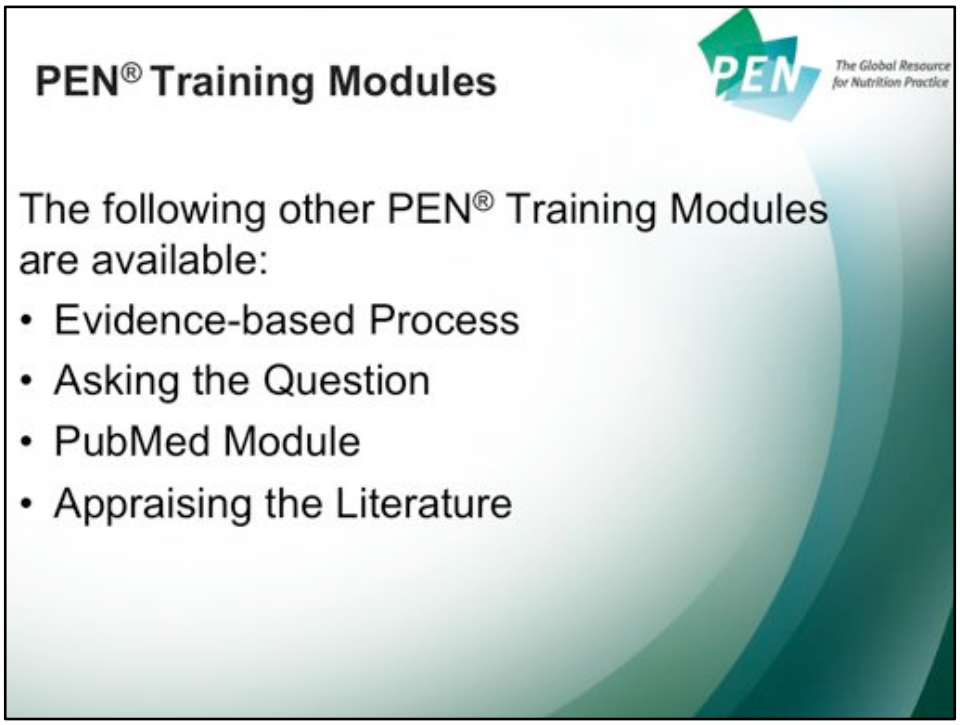
Systematic reviews – to be highest quality must be of RCTs
RCTs
THEN systematic reviews of nonrandomized or cohort studies
Cohort studies
Case-control studies

Lower quality:

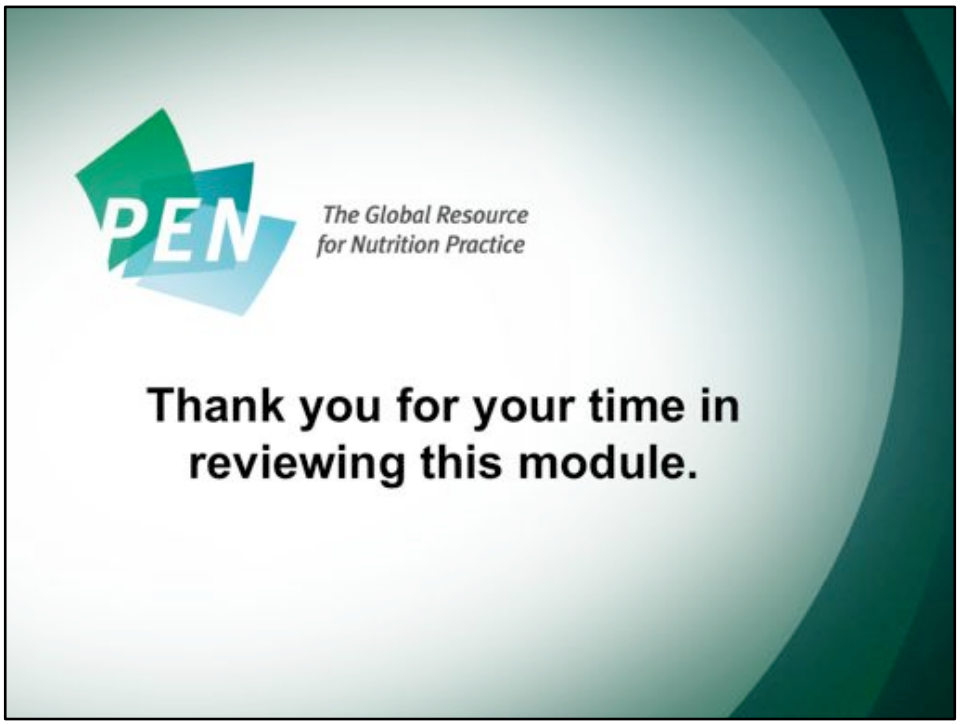
Case series or Case reports – descriptions of a single or a series of cases of some illness or disease
Expert opinion – not actually evidence, but opinion
Animal research – studies conducted on animals cannot be applied directly to humans as the biology may be different
In vitro - a biological process conducted in a laboratory container such as a test tube or petri dish.
It should be noted that there are some issues/questions where animal and in vitro studies are the most appropriate research design but the grade assigned to the resulting KPP would still be graded low.
As noted in PEN's grading checklist; clinical impact, generalizability and applicability also are considered in assigning Grades A, B, C and D.
Note: (October 1, 2013) This is the current hierarchy of evidence but we are aware of continuing discussions taking place within groups such as Cochrane and GRADE on grading hierarchies. The PEN® team continues to monitor these discussions.



In summary…….Read slide



The other PEN® Writer training modules can be accessed at: http://www.pennutrition.com/WriterGuide.aspx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Thank you for your time in
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