



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



*The Global Resource
for Nutrition Practice*

A Quick Review of Study Designs

Main types of studies

Study Design – The architecture of a study

Porta M – Dictionary of Epidemiology, 2008

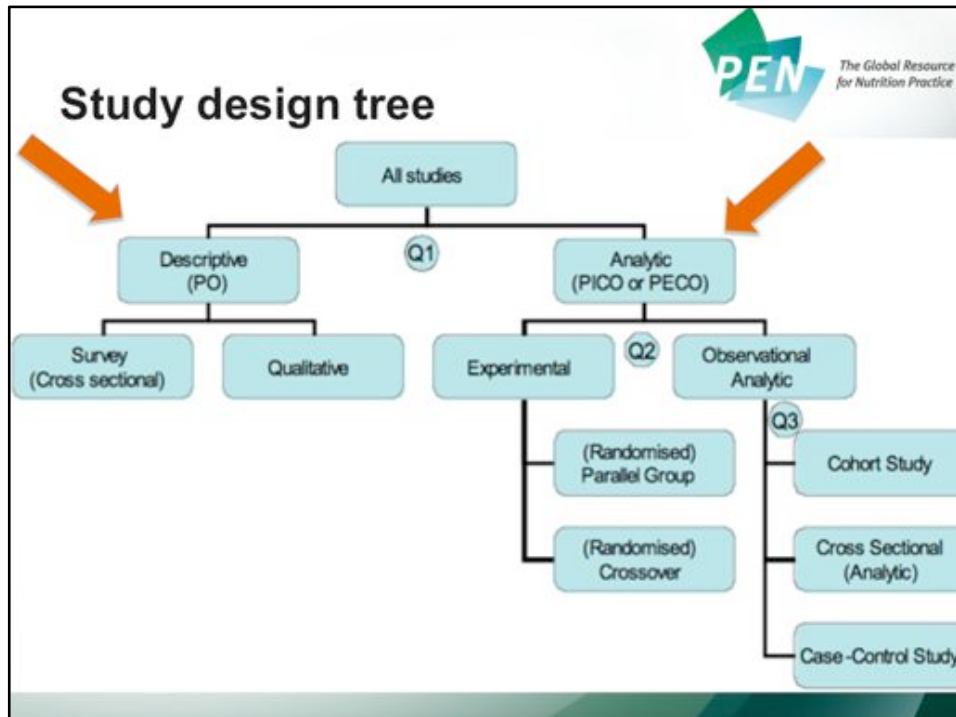
Two main types of studies:

- ◆ To simply describe a situation:
Qualitative research, surveys

- ◆ To analyze a relationship:
Observational/interventions

Read slide.

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.

Qualitative Research



Research that derives data from observation, interviews, or verbal interactions and focuses on the meanings and interpretations of the participants*

E.g. What is the experience of having diabetes?
..... of breastfeeding? ...of receiving care for cancer?

*Holloway I, Wheeler S. Ethical issues in qualitative nursing research. Nurs Ethics; 1995Sep;2(3):223-32.

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>

Main types of analytic studies

Two main types of analytic studies:

- ◆ To simply observe a relationship →

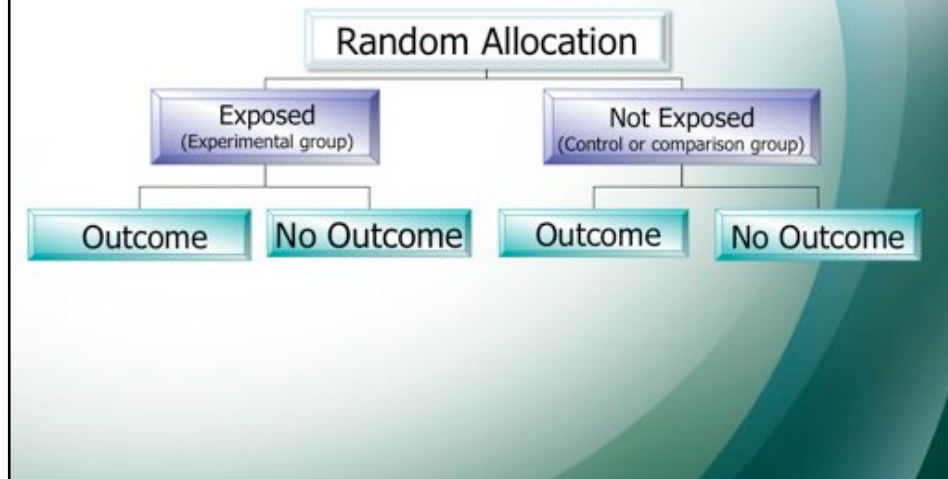
Observational studies

- ◆ To determine whether the relationship is cause and effect →

Trials, perhaps randomized

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 Trial



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.

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

Explanatory versus Pragmatic Trials



Explanatory trial

A trial that aims to test a **treatment** policy in an ideal situation where patients receive the full course of therapy as prescribed, and use of other treatments may be controlled or restricted. It is trying to determine whether a therapy has the ability to make a difference at all (i.e. testing its **efficacy**)

Pragmatic trial

A trial that aims to test a **treatment** policy in a 'real life' situation, when many people may not receive all of the treatment, and may use other treatments as well.

Cochrane Glossary. Available from:
<http://www.cochrane.org/glossary>

Not all trials are created equal!

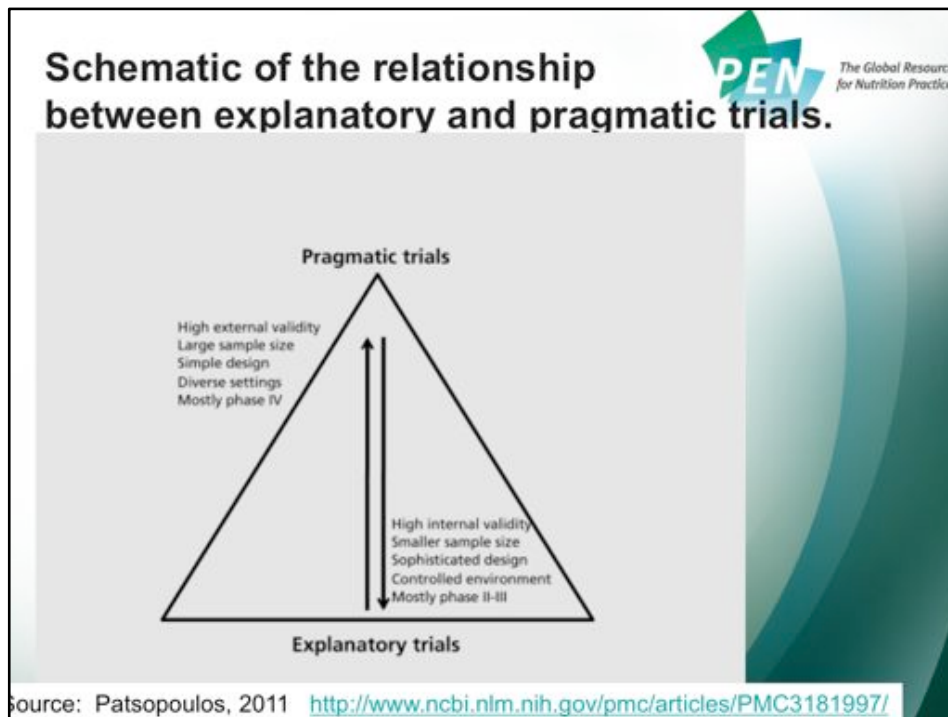
Clinical trials can fall into two broad categories: explanatory and pragmatic. The choice of study design depends on the research question.

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>

RCTs despite their strength, may not always be the best choice



- ❖ In some circumstances RCTs may not be ***ethical***
E.g. Randomly assigning to breast feeding or formula feeding, or to nutrient deficient group, or...

- ❖ In some circumstances RCTs may not be ***feasible***
E.g. Cancer or heart disease can take years to develop making RCT design prohibitively expensive or simply not practical

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

Bottom line on RCTs



- Gold standard for assessing causation
- If RCTs are well designed, and consistent results are seen in several RCTs, then, for the same PICO conditions, one could assume causation.

Read slide.

PICO stands for Population, Intervention, Comparison and Outcome



Some trial studies are not randomized

And if they are not randomized they are:

- Quasi-experimental studies
 - E.g. Before/after studies
 - Natural experiments – some people exposed
- Clinical trials (without randomization)
 - Sometimes trials you might expect to be an RCT

These should be considered **Observational**

The Global Resource
for Nutrition Practice

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

Observational studies



- Do not involve any intervention or experiment
- Nature is allowed to take its course, with changes in one characteristic being studied in relation to changes in other characteristics

Last et al., A Dictionary of Epidemiology, 4th Ed 2001

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

Observational studies



- Subjects are not randomly allocated to their exposures, as they usually chose their lifestyles
- Aspects of peoples lifestyles are related to each other in complex ways
- And different variables in their life could have contributed to the outcome/effect

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.

Observational studies



The lack of random allocation to exposure limits one's ability to tease apart the possible variables, which is called confounding

Let's look at some examples of confounding...

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>)

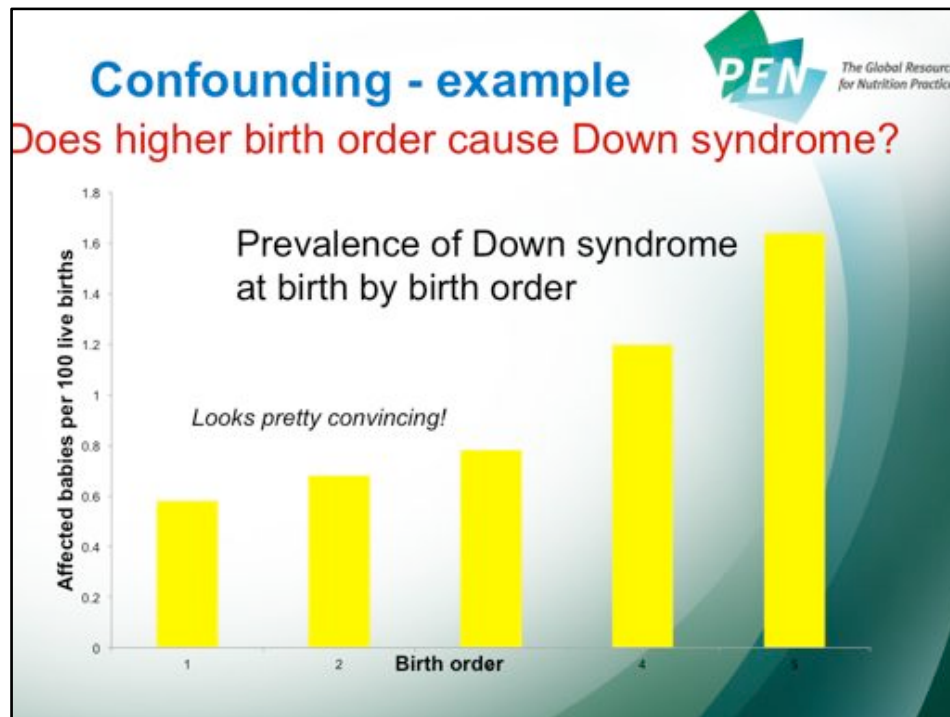
Confounding – why we cannot determine causality

Does higher birth order cause Down syndrome?



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

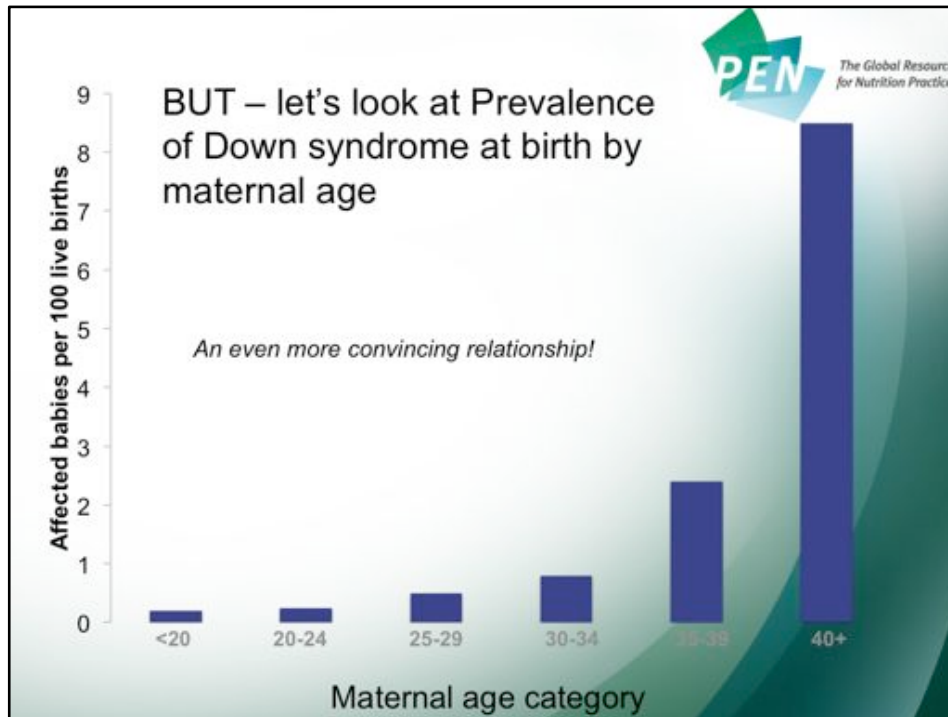
Example from: Rothman – Epidemiology An Introduction, 2002. The study reference, published in 1966 is: Stark CR, Mantel N. Effects of maternal age and birth order on the risk of mongolism and leukemia. J Natl Cancer Inst. 1966 Nov [cited 2013 Nov 11]; 37(5):687-98. Abstract available from: <http://www.ncbi.nlm.nih.gov/pubmed/4224604>



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>

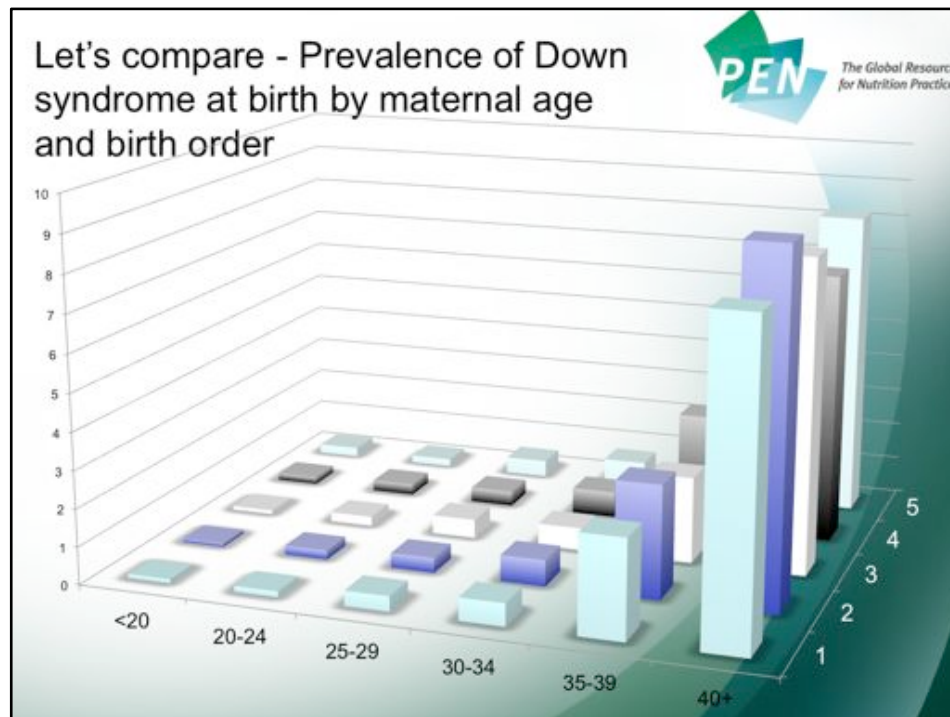


This slide shows the relationship between the occurrence of Down and maternal age – it indicates an even stronger relationship than did birth order. Again we see a dose response relationship. The prevalence changed from 0.2 per 1000 births for the youngest age to 8.5 per 1000 for the oldest age group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

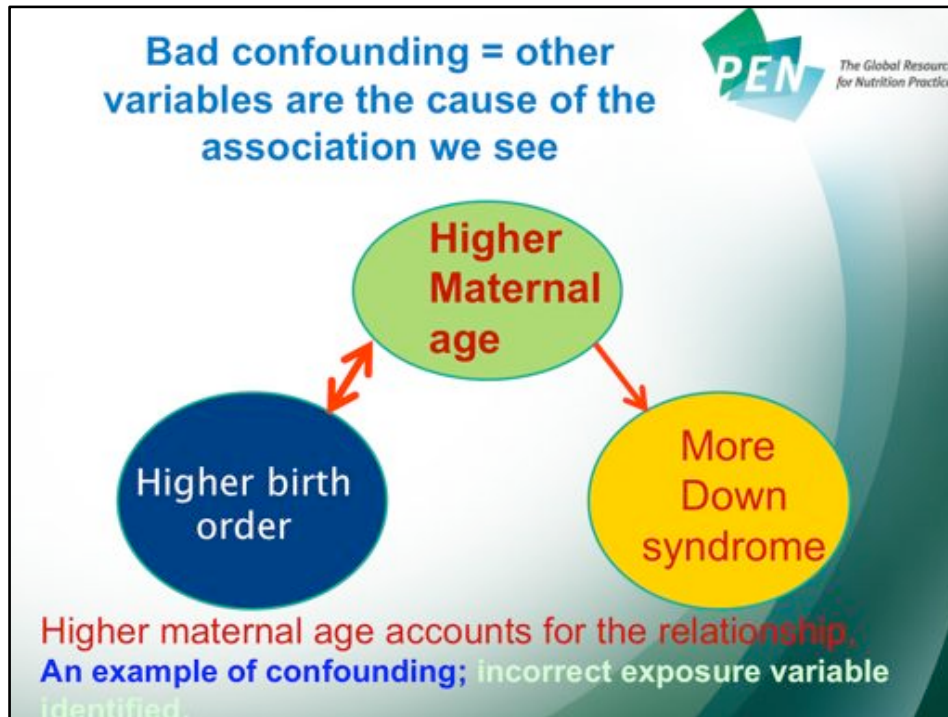


A way to examine which variable is the important one and which is the extraneous one is to examine them together in the same dataset. This figure illustrates the effects of both of the variables together and their association with Down syndrome.

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>

Another example of confounding

Can we say Beta-carotene prevents cancer?



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



**A review of epidemiologic evidence.
Carotenoids reduce the risk of cancer.**

“Low intake of vegetables and fruits and carotenoids is consistently associated with an increased risk of lung cancer in both **prospective and retrospective** studies. In addition, low levels of serum or plasma beta-carotene are consistently associated with the subsequent development of lung cancer.
The simplest explanation is that beta-carotene is indeed protective.”

Ziegler RG. J Nutr. 1989

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>

Observational studies are limited



9 RCTs of *B*-carotene Supplements:

- No effect on the incidence of all cancers
- Increased the risk of lung and gastric cancer among smokers
- Increased the risk of lung and stomach cancers among smokers and asbestos workers

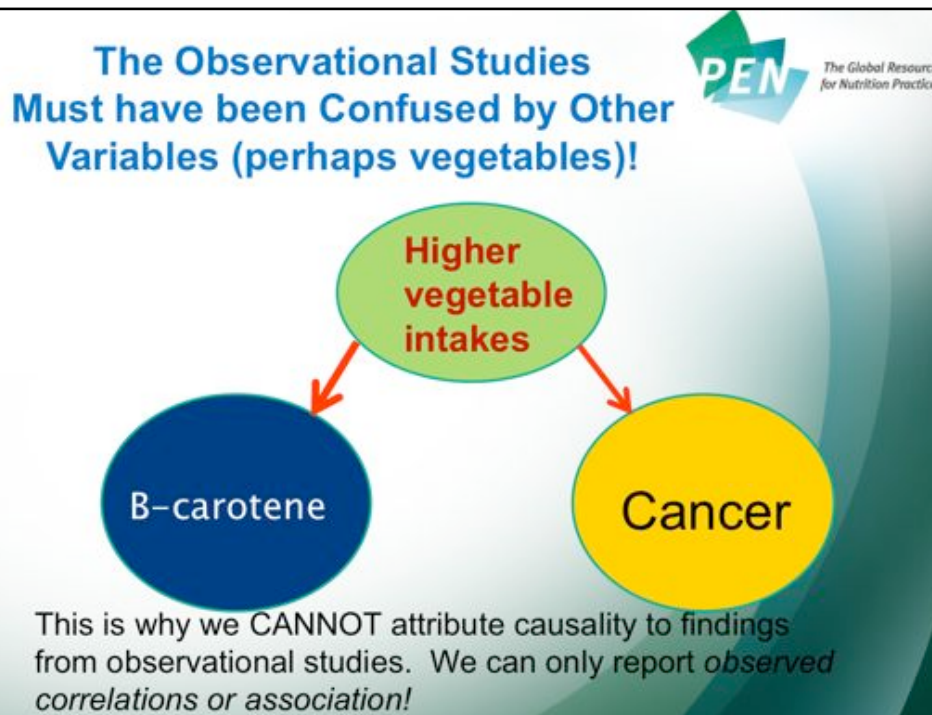
Systematic review of RCTs: Druesne-Pecollo N, et al. Int J Cancer. 2010.

1

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!

Causation vs. Correlation in Observational Studies

Often misinterpreted by journalists
and reported in sensational-sounding
headlines!

Read slide



Causation vs Correlation

Headline:

Breastfeeding improves IQ

When later controlling for some variables...

“...after adjusting for mother’s cognitive competence and other socio-environmental measures in a large cohort of 5475 children from the national longitudinal survey of youth... the study **identifies maternal IQ as the main variable** that accounts for the association between breast feeding and childhood IQ.”

Jacobson SW. BMJ. 2006

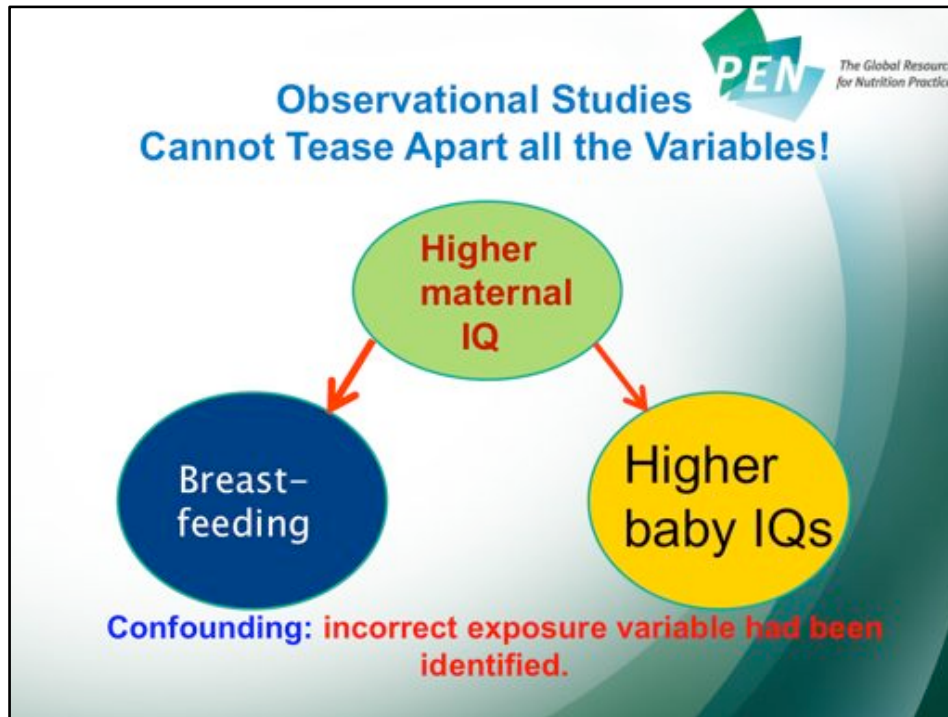
A headline read:

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.

Many Claims from Observational Studies Don't Hold Up in RCTs



Study	Neg.	Treatment(s)	References
1	+	Vitamin E, beta-carotene	NEJM 1994; 330: 1029-1035
2	+	Hormone Replacement Ther.	JAMA 2003; 289: 2651-2662, 2663-2672, 2673-2684
3	+	Vitamin E, beta-carotene	JNCI 2005; 97: 481-488
4	0	Vitamin E	JAMA 2005; 293: 1338-1347
5	0	Low Fat	JAMA 2006; 295: 655-666
6	0	Vitamin D, Calcium	NEJM 2006; 354: 669-683
7	0	Folic acid, Vitamins B6, B12	NEJM 2006; 354: 1567-1577
8	0	Folic acid, Vitamins B6, B12	NEJM 2006; 354: 2764-2772
9	0	Low Fat	JAMA 2007; 298: 289-298
10	0	Vitamins C, E + beta-carotene	Arch Intern Med 2007; 167: 1610-1618
11	0	Vitamin C, Vitamin E	JAMA 2008; 300: 2123-2133
12	0	Vitamin E, Selenium	JAMA 2009; 301: 39-51

Adapted from Young and Karr: Significance 2011;116-120 by Dr. Dennis Bier, ASPEN Conf 2013

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>)

Another example: Observational studies are limited



B vitamins, homocysteine, and risk of CVD

→ Based on observational studies: “Highly significant results, strong evidence that the association between homocysteine and cardiovascular disease is causal.”

“On this basis, lowering homocysteine concentrations ... achievable by increasing folic acid intake, would reduce the risk of ischaemic heart disease by 16% and stroke by 24%”

Wald DS et al. BMJ. 2002

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>

Observational studies are limited



- Systematic review: 8 large, randomized, placebo-controlled trials of 37,485 individuals at increased risk of CVD
- Folic acid allocation → 25% reduction in homocysteine levels
- BUT → no significant effects on vascular outcomes, for major vascular events, major coronary events, and for stroke. Or overall vascular mortality.

Clarke R et al. Arch Intern Med. 2010

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>

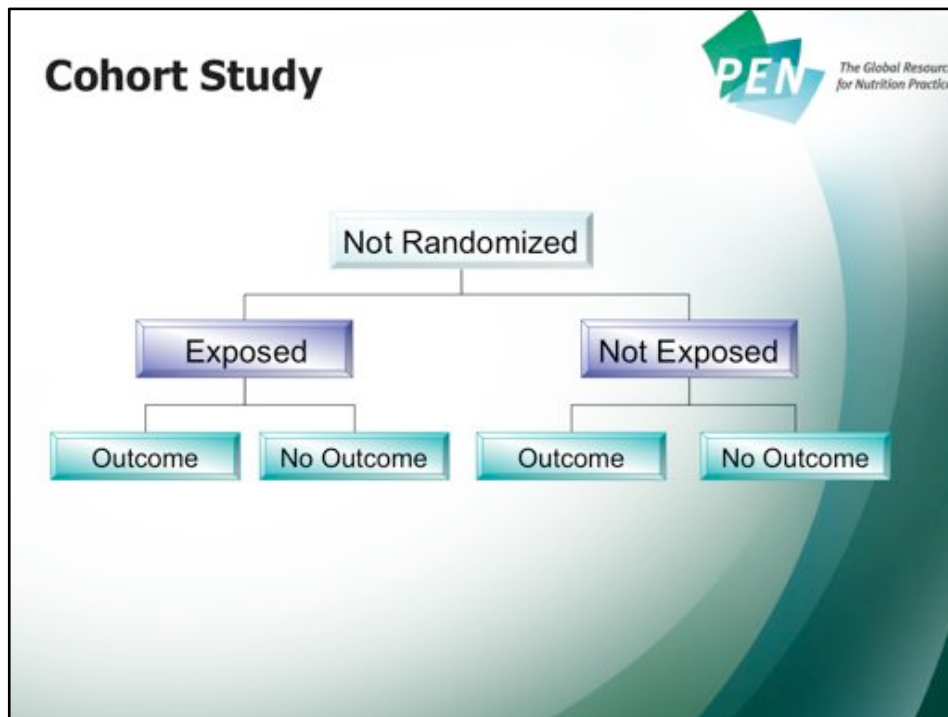
3 Types of Observational studies



If observational, when were the outcomes determined?

- ◆ Some time **after** the exposure or intervention - **cohort** study ("prospective study")
- ◆ At the **same time** as the exposure or intervention - **cross sectional** study or survey
- ◆ **Before** the exposure was determined - **case-control** study ("retrospective study" based on **recall** of the exposure)

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



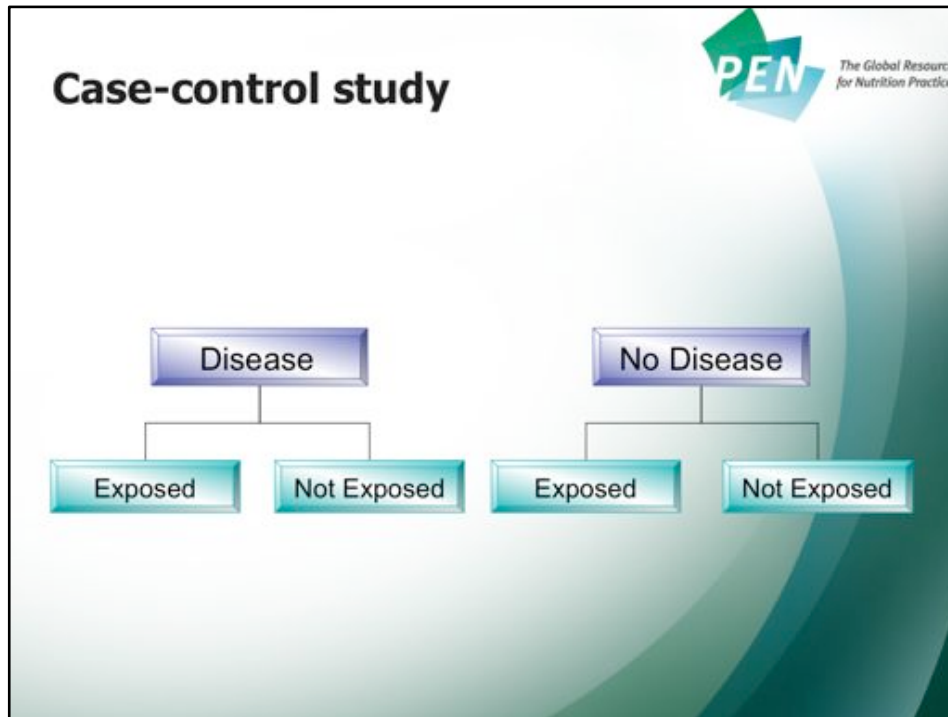
After RCTs, Cohort studies are the next most rigorous to measure a relationship. The strength of a cohort study is that we know that the outcome happened after the exposure.

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).

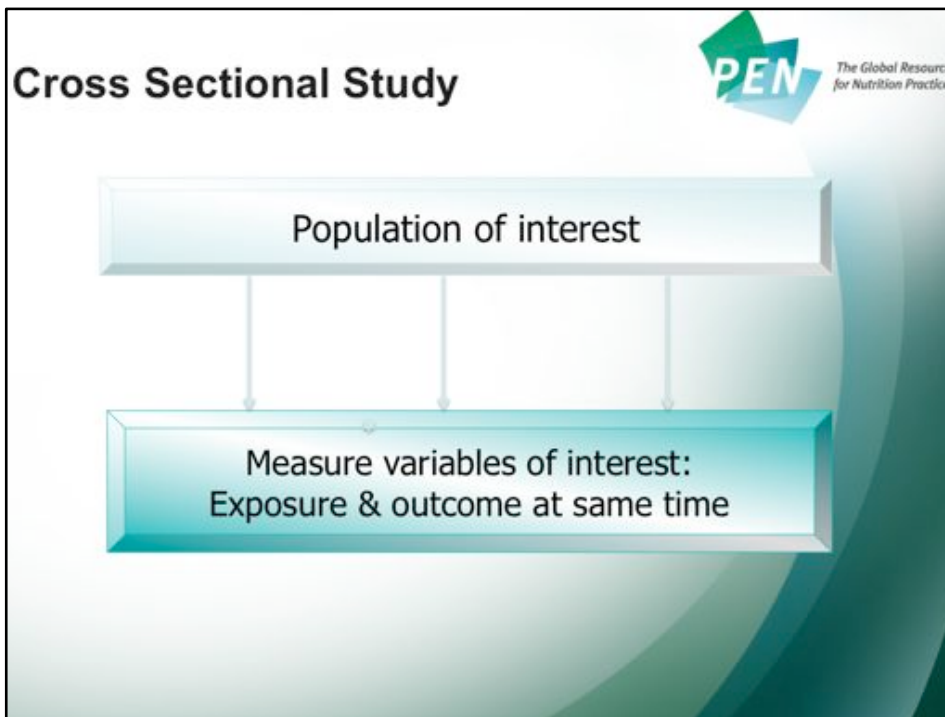
When an outcome is rare or takes years to occur, it may only be feasible to examine it



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

Different observational study designs

- Confounding occurs in all types of observational studies, and some observational designs have additional limitations.
- Cross-sectional – Exposure and outcome measured at same time, so direction not clear – which came first?
- Case-control – since exposure is not measured, but remembered, prone to recall bias

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.

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

Review:

Observational studies & bias



- ◆ Observational studies are particularly susceptible to bias
- ◆ There is no allocation of exposure made by the researchers, rather, subjects chose their lifestyles
- ◆ **AND:** those who chose healthy eating also are more likely to exercise regularly, not smoke, drink moderately, drive carefully... & thus live longer and healthier
- ◆ Any of these lifestyle factors could be the important cause of a better outcome (so we can't say it was a specific nutrient or food)

Bias is defined as a systematic error or deviation in results. There are many kinds of bias...

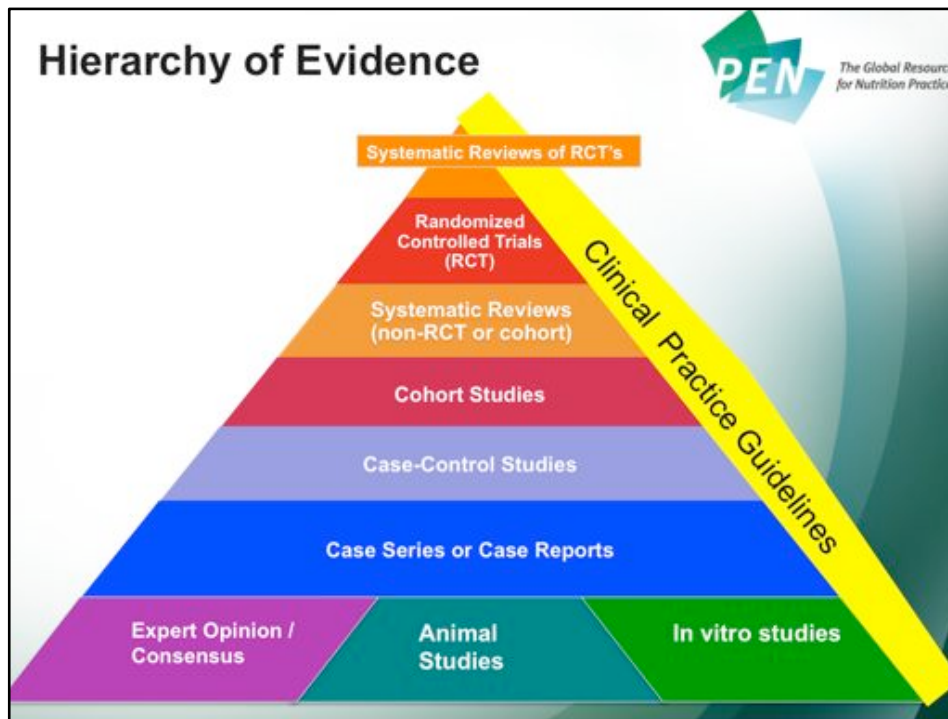
The main types of bias arise from systematic differences in the groups that are compared (selection bias), the care that is provided, exposure to other factors apart from the intervention of interest (confounding), withdrawals or exclusions of people entered into a study (attrition bias) or how outcomes are assessed (detection bias).

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.

How do you identify the study design?

THREE QUESTIONS:

- ◆ **What was the aim of the study?**
- ◆ **If analytic, was the intervention randomly allocated?**
- ◆ **If observational, when were the outcomes determined?**

In summary.....Read slide

PEN® Training Modules



The following other PEN® Training Modules are available:

- Evidence-based Process
- Asking the Question
- PubMed Module
- Appraising the Literature

The other PEN® Writer training modules can be accessed at: <http://www.pennutrition.com/WriterGuide.aspx>



*The Global Resource
for Nutrition Practice*

**Thank you for your time in
reviewing this module.**

Come be social with PEN



pennutrition



PENNutrition



PEN Nutrition