How sure?
Basic research designs
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*How sure?**
Basic Research Designs

1. Experimental vs. Observational Studies
2. Randomized trials - true experiments
   - review a classic randomized trial
   - introduce and apply worksheet
3. Observational studies
   - review a classic observational study
   - introduce basic worksheet
   - describe confounding
   - apply complete worksheet
4. Suggested approach for evaluating research

*some examples adapted from Gil Welch

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Ask someone for their opinion

My crazy uncle said, "Miracle-Gro is a miracle"

He also works for Miracle-Gro.

Opinion
Least compelling evidence

Let's look for more evidence

2

How can we do better?

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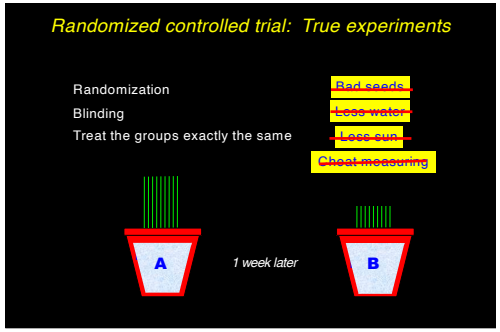

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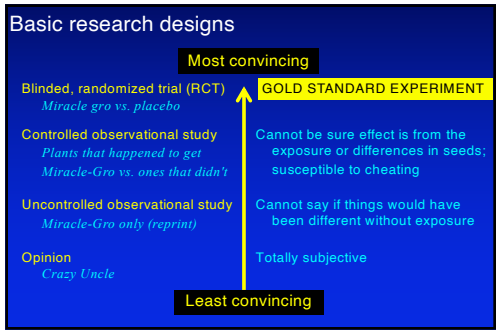

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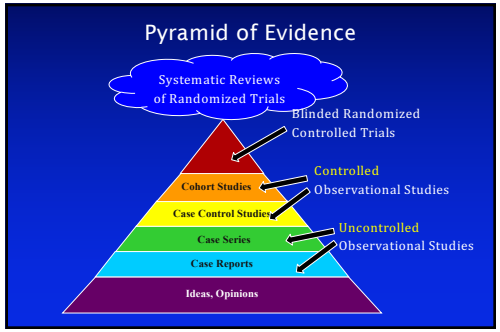

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How would you determine whether there was a relationship between exposure and outcome?

Does treating high blood pressure reduce cardiovascular events (strokes, heart attacks)?

Does smoking increase deaths due to lung cancer?

One can be studied in a true experiment, the other cannot.

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Randomized trials - true experiments

Definition - a study in which participants are assigned by chance to one of two (or more) treatment strategies.

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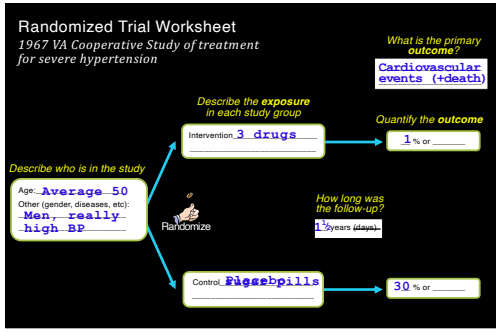

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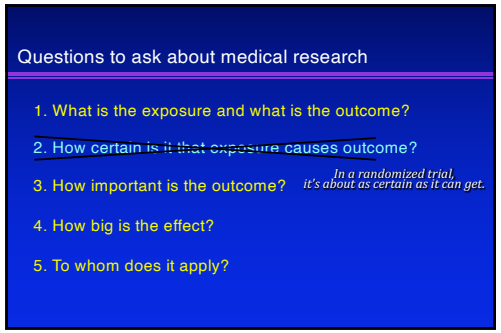

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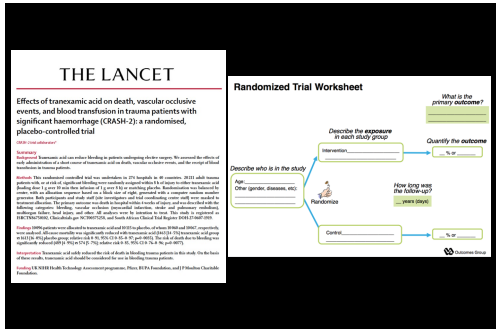

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Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial

Background Tranexamic acid can reduce bleeding in patients undergoing elective surgery. We assessed the effects of early administration of a short course of tranexamic acid on death, vascular occlusive events, and the receipt of blood transfusion in trauma patients.

Methods This randomised controlled trial was undertaken in 274 hospitals in 40 countries. 20,211 adult trauma patients with, or at risk of, significant bleeding were randomly assigned within 8 h of injury to either tranexamic acid (loading dose 1 g over 10 min then infusion of 1 g over 8 h) or matching placebo. Randomisation was balanced by centre, with an allocation sequence based on a block size of eight, generated with a computer random number generator. Both participants and study staff (site investigators and trial coordinating centre staff) were masked to treatment allocation. The primary outcome was death in hospital within 4 weeks of injury, and was described with the following categories: bleeding, vascular occlusion (myocardial infarction, stroke and pulmonary embolism), multiorgan failure, head injury, and other. All analyses were by intention to treat.

Findings 10,096 patients were allocated to tranexamic acid and 10 115 to placebo, of whom 10,060 and 10,067, respectively were analysed. All-cause mortality was significantly reduced with tranexamic acid (1463 [14·5%] tranexamic acid group vs 1613 [16·0%] placebo group; relative risk 0·91, 95% CI 0·85–0·97; p=0·0035). The risk of death due to bleeding was significantly reduced (489 [4·9%] vs 574 [5·7%]; relative risk 0·85, 95% CI 0·76–0·96; p=0·0077).

Interpretation Tranexamic acid safely reduced the risk of death in bleeding trauma patients in this study. On the basis of these results, tranexamic acid should be considered for use in bleeding trauma patients.

Describe who is in the study

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Randomized Trial Worksheet

2010 CRASH-2 trial of tranexamic acid in trauma patients with hemorrhage

*What is the primary **outcome**?*
All-cause mortality

*Describe the **exposure** in each study group*

*Quantify the **outcome***

Describe who is in the study

Intervention: Tranexamic acid (2 gm infusion) → 14.5%

Age: Adults

Other (gender, diseases, etc): Trauma patients with at risk for bleeding

Randomize

How long was the follow-up?
4 weeks ~~(days)~~

Control: Placebo infusion → 16% or ____

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   introduce basic worksheet

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Observational studies - not true experiments

Definition - a study in which one group of people is compared to another. Although the people differ in their exposure, because they were not assigned to the exposure by chance, they may differ in other ways as well.

Two basic "controlled" designs
- Cohort studies
- Case-control studies

Note: If uncontrolled – no comparison group

Stop

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Classic Observational Study

1957 Doll & Hill study of smoking and lung cancer

	Lung cancer deaths	Number of doctors	Risk (per 1000)
Ever smoked	83	28226	2.94
Never smoked	1	5774	0.17

Meaning smokers were 17 times more likely than non-smokers to die from lung cancer in this study.

Relative Risk (smokers vs. non-smokers) $= \frac{2.94}{0.17} = 17$

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Observational Study Worksheet

Describe who is in the study

Age:_____
Other (gender, diseases, etc): Male doctors in Britain

*What is the primary **outcome**?*

Lung cancer death

Note: if there is more than one choose the one you think is most important.

*Describe the **exposure** in each study group*

*Quantify the **outcome***

Exposed Smokers → *4 years* → __% or 2.94/1000

Control Never smokers → *4 years* → __% or 0.17/1000

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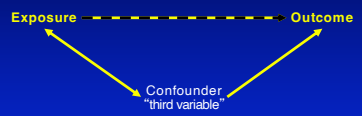
Confounding



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Confounding is not a concern in randomized trial.

Confounding is a concern in any observational study.

Confounding is more likely when someone's choice (patient, doctor, etc.) determined who was in the exposed and control group.

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Dose - response

Average Daily Consumption	Lung Cancer Deaths	Number of doctors	Risk (per 1000)	Relative Risk (vs. never smoked)
25 or more	34	5994	5.67	32.8
15 to 24	27	10539	2.56	14.8
1 to 14	22	11693	1.88	10.9
Never smoked	1	5774	0.17	1.0 (ref)

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What makes confounding less likely?

Findings that make it more likely that the exposure causes outcome.

1. **The relationship exposure & outcome makes biologic sense.**
(so-called "biologic plausibility")

2. **The relationship between exposure and outcome is strong.**
(those who are exposed are much more likely to get the outcome)

3. **The more exposure, the more outcome.**
(so-called "dose-response" relationship)

4. **Other studies have observed the same relationship.**
(studies by different investigators, in different places, times, and circumstances)

5. **Interventions changing the exposure , change the outcome.**
(reducing the dust level reduces the amount of lung disease, stopping smoking lowers the risk of lung cancer, increased fluoride reduces tooth decay)

(adapted from Sir Austin Bradford Hill)

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Observational Study Worksheet

Describe who is in the study

Age:_____
Other (gender, diseases, etc):
Male doctors in Britain

*What is the primary **outcome**?*
Lung cancer death
Note: if there is more than one choose the one you think is most important.

*Describe the **exposure** in each study group*

Exposed Smokers

4 years

__ % or 2.94/1000

Did someone's **choice** (patient, doctor, etc) determine who was in which group?
☒ yes ☐ no ☐ maybe

Beside the exposure, are there other differences between the study groups that might explain the difference in outcome?

Reported differences:
None

Differences you can imagine:
(perhaps related to someone's **choice**)
Alcohol, coffee, urban living, chest x-rays?

Control Non-smokers

4 years

__ % or 0.17/1000

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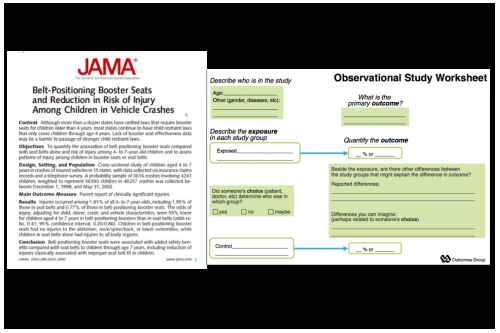

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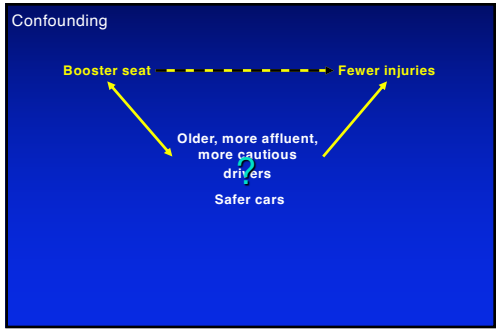

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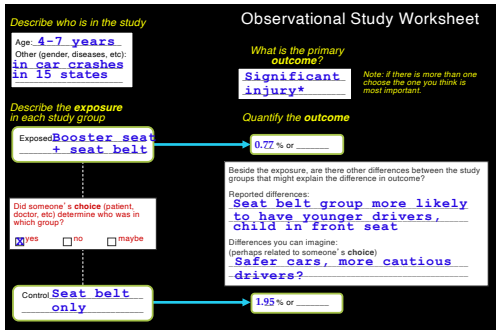

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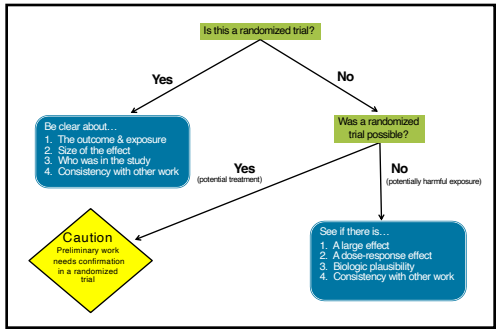

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