

*How sure?*  
Basic research designs  
Steven Woloshin & Lisa Schwartz

*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

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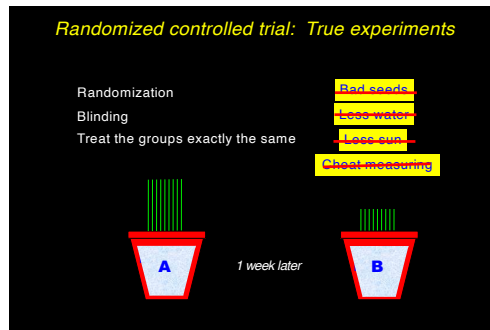
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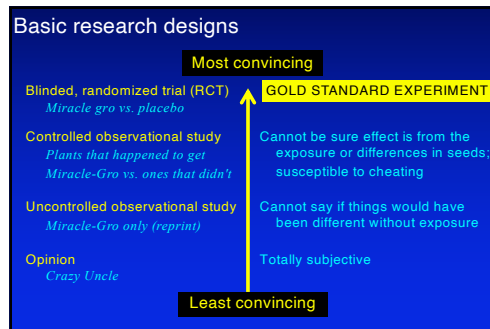
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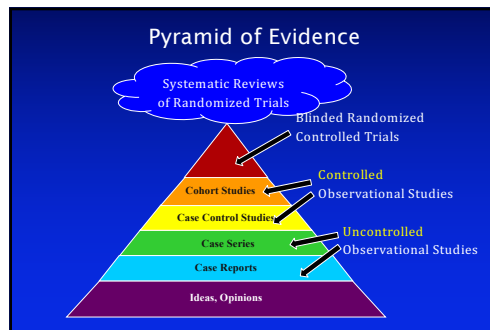
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How would you determine whether there was a relationship between exposure and outcome?

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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

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

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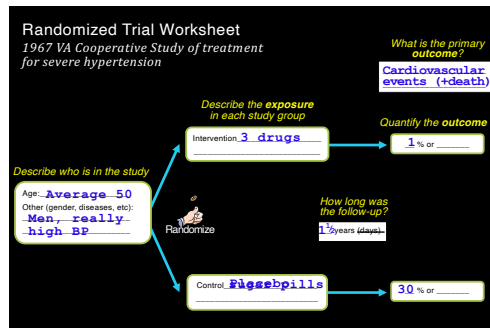
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# How sure?

## Basic research designs

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### Questions to ask about medical research

1. What is the exposure and what is the outcome?
2. How certain is it that exposure causes outcome?
3. How important is the outcome? *In a randomized trial, it's about as certain as it can get.*
4. How big is the effect?
5. To whom does it apply?

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**THE LANCET**

**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**

*Summary*  
Background: Randomised trials on other bleeding agents supporting their use. We assessed the effect of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage.

*Methods*  
This randomised controlled trial was conducted in 25 hospitals in 20 countries. 8191 adult trauma patients who were at least 16 years of age and had significant haemorrhage were randomised to receive either tranexamic acid or placebo. The primary outcome was death due to bleeding. Secondary outcomes were death due to any cause, need for blood transfusion, and need for surgery. The trial was funded by the UK Medical Research Council, the UK Department of Health, and the UK Ministry of Defence.

*Results*  
8191 patients were randomised to receive either tranexamic acid or placebo. At 28 days, 1488 patients had died. Death due to bleeding was significantly reduced in the tranexamic acid group compared with the placebo group (10.5% vs 12.1%, p < 0.001). There was no significant difference in death due to any cause (28.1% vs 28.5%, p = 0.70) or in the need for blood transfusion (50.0% vs 49.8%, p = 0.92). There was no significant difference in the need for surgery (10.0% vs 10.1%, p = 0.92).

*Conclusions*  
Tranexamic acid significantly reduced death due to bleeding in trauma patients with significant haemorrhage. There was no significant difference in death due to any cause or in the need for blood transfusion or surgery.

*Interpretation*  
Tranexamic acid significantly reduced death due to bleeding in trauma patients with significant haemorrhage. There was no significant difference in death due to any cause or in the need for blood transfusion or surgery.

*Registration*  
This study is registered with ClinicalTrials.gov, NCT00222566.

**Randomized Trial Worksheet**

**Describe who is in the study**  
Age: \_\_\_\_\_  
Other (gender, disease, etc): \_\_\_\_\_

**Randomize**

**Describe the exposure in each study group**  
Intervention: Tranexamic acid  
Control: Placebo

**Quantify the outcome**  
What is the primary outcome? Death due to bleeding  
Intervention: 10.5 % of \_\_\_\_\_  
Control: 12.1 % of \_\_\_\_\_

**How long was the follow-up?**  
28 days

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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 (1483 [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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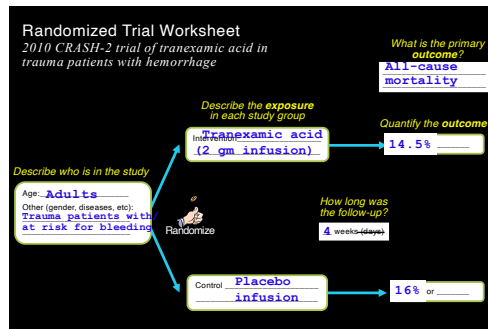
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**How sure?**  
**Basic Research Designs**

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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*




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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.

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


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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*

Exposed **Smokers** → 4 years → Quantify the outcome: \_\_\_\_\_ % or 2.94/1000

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

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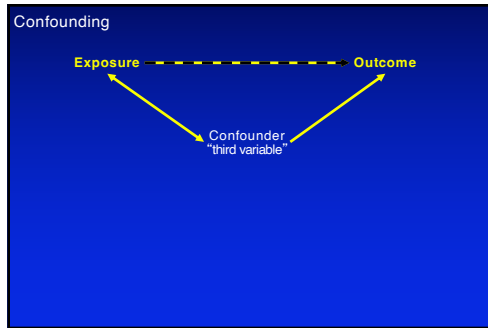
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Confounding is not a concern in randomized trial.

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: for Health: 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**

Control: **Non-smokers** → 4 years → **\_\_\_ % or 0.17/1000**

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?**

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**JAMA**  
**Belt-Positioning Booster Seats and Reduction in Risk of Injury Among Children in Vehicle Crashes**

**Objective:** To quantify the association of belt-positioning booster seats with compared with high-back child safety seats in motor vehicles.

**Design, Setting, and Population:** Case-control study of children aged 4 to 7 years in motor vehicles in 19 states, with data collected from 1997 to 2002. Parents and guardians were interviewed about their child's use of child safety seats and whether they used a booster seat.

**Main Outcome Measure:** Parent report of clinically significant injuries.

**Results:** Parents reported clinically significant injuries to 14% of their 4- to 7-year-old children. Children in belt-positioning booster seats had a 51% lower risk of injury compared with children in high-back child safety seats. Children in belt-positioning booster seats had a 30% lower risk of injury compared with children in high-back child safety seats.

**Conclusion:** Belt-positioning booster seats were associated with a 51% lower risk of injury compared with high-back child safety seats. Children in belt-positioning booster seats had a 30% lower risk of injury compared with children in high-back child safety seats.

**Observational Study Worksheet**

**Describe who is in the study**  
Age: \_\_\_\_\_  
Other (gender, diseases, etc): \_\_\_\_\_

**What is the primary outcome?**  
\_\_\_\_\_

**Describe the exposure in each study group**  
Exposed: \_\_\_\_\_ → \_\_\_\_\_ years → \_\_\_\_\_ % or \_\_\_\_\_/1000

Control: \_\_\_\_\_ → \_\_\_\_\_ years → \_\_\_\_\_ % or \_\_\_\_\_/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: \_\_\_\_\_

Differences you can imagine (perhaps related to someone's choice): \_\_\_\_\_

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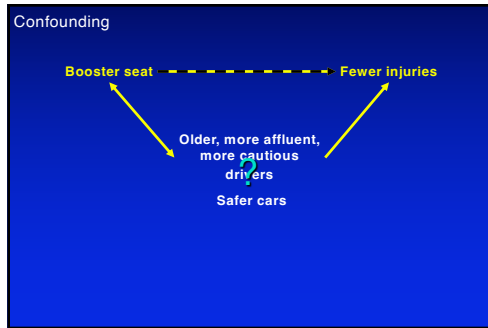
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Describe who is in the study

Age: 4-7 years  
 Other (gender, diseases, etc): in car crashes in 15 states

Describe the exposure in each study group

Exposed: Booster seat + seat belt

Control: Seat belt only

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

What is the primary outcome?  
Significant injury\* Note: if there is more than one choice the one you think is most important.

Quantify the outcome

Exposed: 0.77% or \_\_\_\_\_

Control: 1.95% or \_\_\_\_\_

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

Reported differences:  
Seat belt group more likely to have younger drivers, child in front seat

Differences you can imagine: (perhaps related to someone's choice)  
Safer cars, more cautious drivers?

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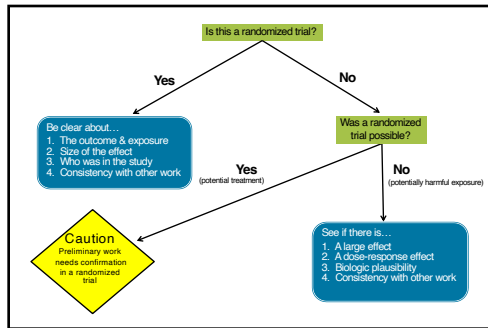
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