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Clinical Trials vs. Potential Outcomes

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Slides at www.StatLit.org/pdf/2012Schield-ASA6up.pdf

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Main Claim

Big claim in the intro statistics course (Stat 101):

Association is not causation

What are some other explanations for associations?

1. Confounding. Schield (2006).
2. Coincidence. Schield (2012) eCOTS webinar.
3. Potential Outcomes (This talk)

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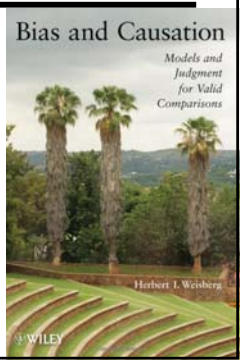
Causal Effects

In some cases, "the population parameter remains relevant to any member of the population."

In other cases, there may be subgroups "for which the overall parameter value is misleading." Weisberg (2011)



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Weed-Killer Treatment

Response	Treatment	Control	%
1. Doomed	**Die**	**Die**	P1
2. **Intended Result**	**Die**	Live	P2
3. **Opposite Result**	Live	**Die**	P3
4. Immune	Live	Live	P4

P1+P2+P3+P4 = 100%

Observables. Treatment: Die (P1+P2) or Live (P3+P4)
Control: Die (P1+P3) or Live (P2+P4)

Four observables (equations) and four unknowns.
But not independent. Thus, **potential outcomes**.

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Potential Outcomes: Causal Heterogeneity

Response	Treatment	Control	%
1. Doomed	**Die**	**Die**	P1
2. **Intended Result**	**Die**	Live	P2
3. **Opposite Result**	Live	**Die**	P3
4. Immune	Live	Live	P4

P1+P2+P3+P4 = 100%

The proportions in the control group are determined by the nature of (proportions in) the treatment group.

Random assignment controls for confounders – but not for causally-related heterogeneity within the subjects.

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Potential Outcomes: Treatment vs. Control

Response	Treatment	Control	%
1. Doomed	**Die**	**Die**	P1
2. **Intended Result**	**Die**	Live	P2
3. **Opposite Result**	Live	**Die**	P3
4. Immune	Live	Live	P4

Association: Relative Risk of death
Relative Risk = RR = (P1+P2) / (P1+P3)

Simplest case: No adverse effects so P3 = 0.
Relative Risk: RR = (P1+P2)/P1.

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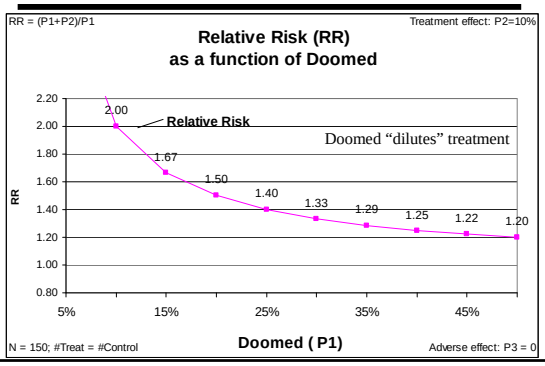
As "Doomed" Increases, Relative Risk Decreases



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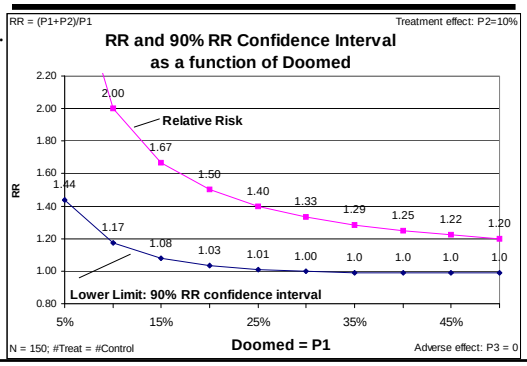
"Doomed" Influences Confidence Interval



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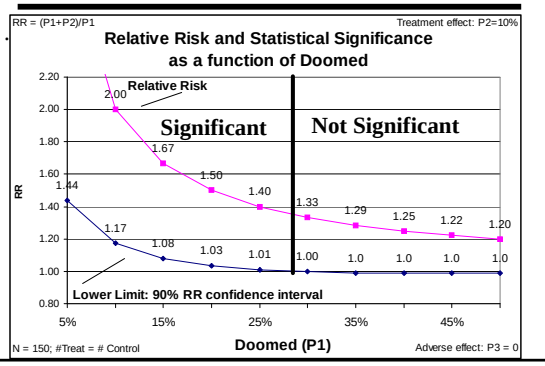
"Doomed" Changes Statistical Significance



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Results are Not Statistically Significant

Two kinds of explanations in a clinical trial:

1) No real difference in the averages for the two groups

2) Difference is real but is not visible because it is:

- confused with (masked by) chance in a small sample
- offset by confounders introduced after randomization
- diluted/masked by *causal heterogeneity*

How important is this causal heterogeneity?

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Causal Heterogeneity is a Big Deal

Drug companies spend billions per year on clinical trials.

Many – if not most – give results that are not statistically-significant, or they are rejected because of adverse effects.

What if many of these rejected treatments
* *were extremely effective for a population subgroup?*
* *had minimal adverse effects for a subgroup?*

Could it be that our model of statistical significance and the design of clinical trials is largely responsible for the high cost of new drugs in the US?

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Conclusion

Complex subjects involve four potential outcomes relative to a given treatment. For death: Doomed, Immune, Killed by Treatment, and Saved by Treatment.

People are complex subjects. Social statistics are radically different from mathematical and non-social statistics.

In clinical trials with *complex subjects*, statistical significance is determined by sample size and *potential outcomes*.

Statistical education should
* study all sources of influence on a statistic
* show how *potential outcomes* affect statistical-significance
* show importance of *potential outcomes* in clinical trials

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References

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Schield, M. (2012) e-COTS: Big Data Generates Beguiling Coincidences. See www.causeweb.org/ecots/posters/19/

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Weisberg, Herbert I. (2011). Statistics and Clinical Trials: Past, Present and Future. ASA Proceedings of the Section on Statistical Education. [CD-ROM], 1547 – 1561. www.StatLit.org/pdf/2011Weisberg-JSM.pdf.

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Statistical Significance for Relative Risks

	GOOD OUTCOME		
TREATED	YES	No	ALL
YES	A	B	A+B
NO	C	D	C+D
ALL	A+C	B+D	N

PTreat = A/(A+B).
PControl = C/(C+D)
RR = PTreat/PControl
LnRR = Log_e(RR)
Var[Ln(RR)] = [(B/A)/(A+B)] + [(D/C)/(C+D)]
Std. Error = Sqrt{Var[Ln(RR)]}. (A+B) = (C+D) = N/2
Confidence Level = 90% to get two 5% tails.
Zcutoff = NORMINV(0.95, 0, 1) = 1.64
90% Margin of Error = Zcutoff * Std. Error
Limits 90% LnRR CI: LnRR ± 90%_Margin_of_Error
Limits 90% RR CI: [Exp (LnRRLow), Exp(LnRRHigh)]

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Weisberg's Conclusion

"Rather than narrowly focusing on whether or not the treatment "works" in general, we should ask a better question.

For whom (if anyone) is the treatment beneficial and *for whom* is it harmful?

What individual and circumstantial characteristics are conducive to a positive (or negative) response?

To answer such questions will require a more flexible approach to design and analysis of RCTs."

Weisberg (2011)