Basic Epidemiology

Prevalence

- All cases, new and old, alive at a given time or during a given period in a specific population
- Prevalence =

$$\frac{\text{Number of existing cases}}{\text{Number of people in the population}}$$

- Answers: What proportion of a group of people have a condition?

Prevalence of cardiovascular risk factors in patients with psoriasis

J AM ACAD DERMATOL NOVEMBER 2006

- Results: We identified 127,706 patients with mild psoriasis and 3854 with severe psoriasis
- prevalence rates of risk factors in those with severe psoriasis, mild psoriasis, and in controls
- diabetes (7.1%, 4.4%, 3.3%)
- hypertension (20%, 14.7%, 11.9%)
- hyperlipidemia (6%, 4.7%, 3.3%)
- obesity (20.7%, 15.8%, 13.2%)
- smoking (30.1%, 28%, 21.3%)

Be careful what you conclude from Prevalence studies

- Conclusion: Multiple cardiovascular risk factors are associated with psoriasis. Cardiovascular risk factors that are key components of the metabolic syndrome are more strongly associated with severe psoriasis than with mild psoriasis
- Limitations: The study was cross-sectional and therefore the directionality of the associations could not be determined

Incidence

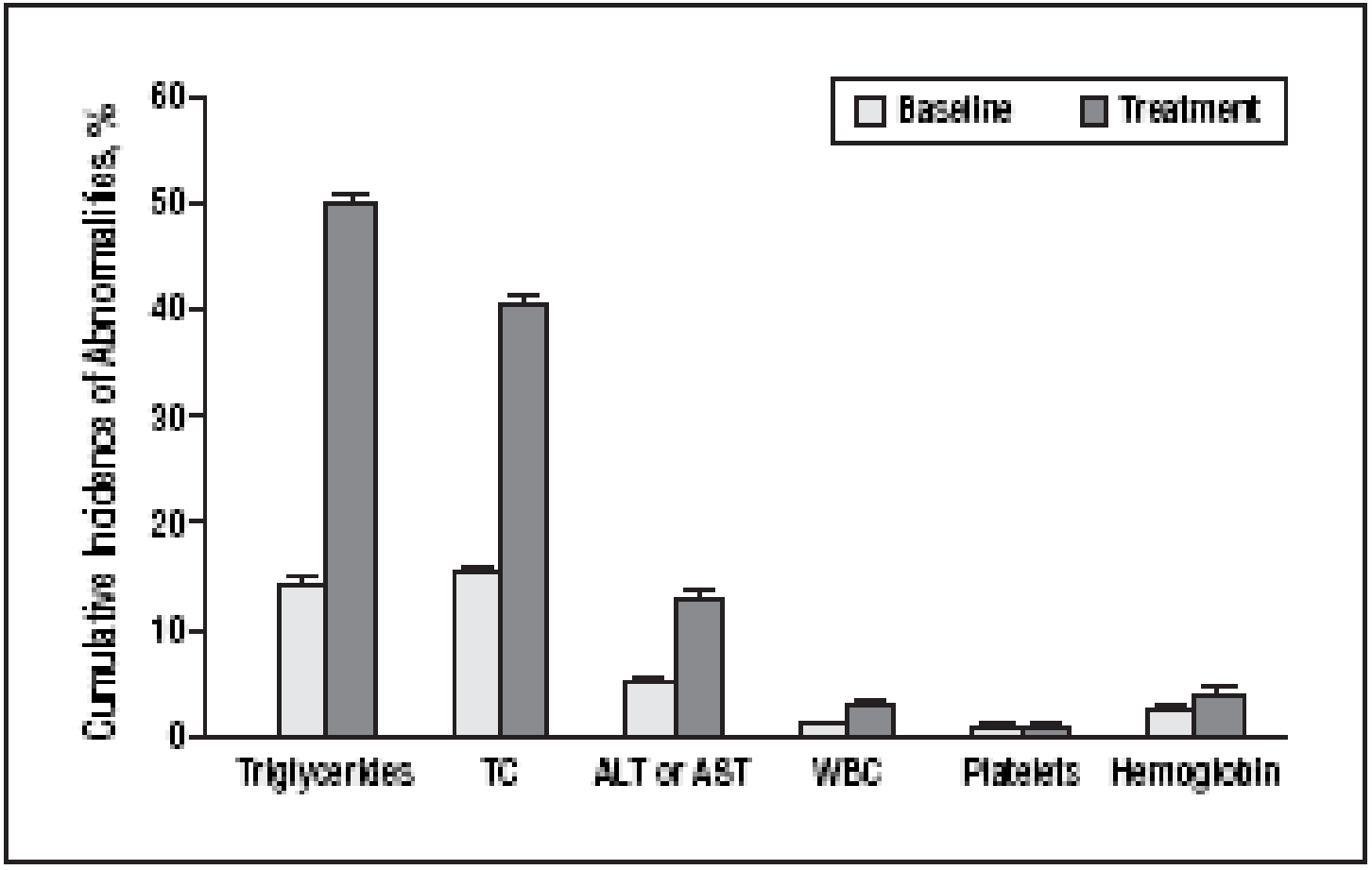
- All new cases occurring within a given time period in a specific population initially free of disease

- Incidence = $$\frac{\text{Number of new cases}}{\text{Number of susceptible patients}}$$

- Answers: At what rate do new cases arise in a group of people as time passes?

# of Laboratory Abnormalities During Isotretinoin Therapy for Acne Vulgaris

Arch Dermatol. 2006;142:1016-1022



Measures of Effect

Results of a cohort study

	Disease	No Disease
Exposure	a	b
No exposure	c	d

Risk of disease with exposure = $a / (a + b)$

Risk of disease with no exposure = $c / (c + d)$

Relative risk

- How many times more likely are exposed persons to become diseased, relative to nonexposed persons?
- Risk ratio
- RR =
- $RR = I_E / I_E$

$$\frac{\text{Incidence in Exposed persons}}{\text{Incidence in Nonexposed persons}}$$

Isotretinoin Use and Risk of Depression, Psychotic Symptoms, Suicide, and Attempted Suicide

Table 3. Independent Relative Risk Estimates for Suicide or Attempted Suicide in Isotretinoin Users and in Patients With Acne Treated With Antibiotics by Exposure Status, Sex, and History of Depression or Psychosis (Saskatchewan Health Data)*

	All Subjects		Subjects With No Psychiatric History	
Variable	No. of Cases/ Person-years	Adjusted Relative Risk Estimate (95% Confidence Interval)	No. of Cases/ Person-years	Adjusted Relative Risk Estimate (95% Confidence Interval)
Exposure status				
Nonexposed†	17/13 894	1.0	8/12 136	1.0
Current isotretinoin use	4/4003	0.9 (0.3-2.4)	4/3553	1.3 (0.3-4.6)
Current acne with antibiotic use	11/11 051	0.8 (0.4-1.7)	3/9617	0.5 (0.1-1.6)
Recent isotretinoin use	2/1678	1.1 (0.2-3.7)	1/1499	1.0 (0.1-5.7)
Recent acne with antibiotic use	3/5133		2/4433	0.7 (0.1-2.7)
Sex				
Male†	14/16 510	1.0	8/15 101	1.0
Female	24/19 247	1.2 (0.6-2.5)	10/16 136	1.4 (0.5-3.8)
Previous depression or psychosis				
No†	18/31 237	1.0	. . .	. . .
Yes	20/4520	8.0 (4.1-15.5)	. . .	. . .

Arch Dermatol. 2000;136:1231-1236

Variable	All Subjects	
	No. of Cases/ Person-years	Adjusted Relative Risk Estimate (95% Confidence Interval)
Exposure status		
Nonexposed†	17/13 894	1.0
Current isotretinoin use	4/4003	0.9 (0.3-2.4)
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Recent isotretinoin use	2/1678	1.1 (0.2-3.7)
Recent acne with antibiotic use	3/5133	0.5 (0.1-1.4)
Sex		
Male†	14/16 510	1.0
Female	24/19 247	1.2 (0.6-2.5)
Previous depression or psychosis		
No†	18/31 237	1.0
Yes	20/4520	8.0 (4.1-15.5)

Absolute risk reduction

- How much does the treatment reduce the incidence of disease?
- Risk difference
- ARR = Incidence in Control group - Incidence in Experimental (treatment) group

Tacrolimus ointment for the treatment of atopic dermatitis in adult patients:

- J Am Acad Dermatol 2001;44:S28-38
- A 90% or greater improvement from baseline
- 6.6% of patients on the vehicle
- 36.8% of patients on 0.1% tacrolimus ointment
- ARR = 36.8% - 6.6%
- "Therapy with topical tacrolimus will result in 30% more patients achieving a 90% or greater improvement from baseline when compared to the base vehicle."

Risk of DVT from BCPs

- Incidence among those not on BCP
  - 0.8 per 10,000 women per year
- Incidence among those on BCP
  - 3.0 per 10,000 women per year
- RR = 3.7 (3.0 / 0.8)
  - "You are four times as likely to develop a blood clot in your legs while taking birth control pills."
- ARI = 2.2 per 10,000 per year
  - "There will be an additional two women who develop a blood clot for every 10,000 women that take birth control pills for a year."

Summarizing Treatment Effects

- Relative Risk (RR)
  - Proportion of original risk still present when pts receive the experimental treatment
- Relative Risk Reduction (RRR)
  - (1 – Relative Risk)
- Absolute Risk Reduction (ARR)
  - What proportion of pts avoid the adverse outcome if they receive the experimental rather than control tx ?
- Number needed to treat (NNT)
  - The number of pts one would need to treat to prevent one adverse outcome

Example of ARR and NNT

- Absolute risk reduction:

  Control event rate - Treated event rate

  ARR = 20% - 15% = 5%

  "For every 100 people treated, 5 deaths would be prevented"

- Number needed to treat:

  1 / ARR = 100/5 = 20

  "Twenty people need to be treated to prevent one death."

From the Tacrolimus example

- 6.6% of patients on the vehicle
- 36.8% of patients on 0.1% tacrolimus ointment
- ARR = 36.8% - 6.6% = 30.2%
- NNT = 100 / 30.2 = 3
- "Three pts with atopic dermatitis would need to be treated with topical tacrolimus for 12 weeks for one pt to have a 90% or greater improvement."

TABLE 2B2-6

Relationship Between the Baseline Risk, the Relative Risk Reduction, and the Number Needed to Treat*

Control Event Rate	Intervention Event Rate	Relative Risk	Relative Risk Reduction	Risk Difference	NNT
0.02	0.01	50%	50%	0.01	100
0.4	0.2	50%	50%	0.2	5
0.04	0.02	50%	50%	0.02	50
0.04	0.03	75%	25%	0.01	100
0.4	0.3	75%	25%	0.1	10
0.01	0.005	50%	50%	0.005	200

* Relative risk is equal to the intervention event rate/control event rate; the relative risk reduction is equal to 1– relative risk; the risk difference is equal to control event rate – intervention event rate; the NNT is equal to 1 / risk difference.

Hypothesis Testing and the Role of Chance in Study Results

O.J. Simpson trial: jury decisions

- In **criminal trial**: The evidence does not warrant rejecting the assumption of innocence. Behave as if O.J. is innocent.
- In **civil trial**: The evidence warrants rejecting the assumption of innocence. Behave as if O.J. is guilty.
- ***Was an error made in either trial?***

Errors in Trials

	Truth	
Jury Decision	**Innocent**	**Guilty**
Innocent	OK	ERROR
Guilty	ERROR	OK

If O.J. is innocent, then an error was made in the civil trial.

If O.J. is guilty, then an error was made in the criminal trial.

Errors in Hypothesis testing

True Difference

Conclusion Of Statistical Test

	Present	Absent
Significant	Correct	Type I Error (α)
Not Significant	Type II Error (β)	Correct

Definitions

- Null hypothesis H_0
  - No true difference in outcome between two treatment groups
- Alternative hypotheses H_1 and H_2
  - A true difference in outcomes exists
  - The new treatment may be better, or may be worse

Definitions: Types of Errors

- Type I error: The null hypothesis is rejected when it is true

  The study found a difference, when in reality there isn't one

- Type II error: The null hypothesis is not rejected when it is false

  The study found no difference, when in reality there is one

Errors in Hypothesis testing

True Difference

Conclusion Of Statistical Test

	Present	Absent
Significant	Correct	**Type I Error (α)**
Not Significant	**Type II Error (β)**	Correct

How do we know that a treatment works?

- Compare treatment group to control group
- Determine effect of treatment (difference)
- Statistical test to estimate probability of chance occurrence
- Probability < prestated value (α) then result considered "significant"
- "difference this large is unlikely to have occurred by chance alone"
- α is commonly 0.05

How do we know that a treatment doesn't work?

- If a trial concludes that one treatment is not different from another, how do we know that is the truth?

- Could there be a true effect and, by chance alone, we did not detect it in this study?
- (a false negative study, a type II error)

What's a p value?

- α error (aka type I error): For any given result, α error is the probability that the result shown occurred by random chance
- a p value is a measure of the alpha error
- Ex: $p = 0.02$
  - Interpretation: the probability is 0.02 (2 % chance) that the result in question happened because of random chance
  - Alternate interpretation: the probability is 0.98 that you would see the same result if you repeated the study

Statistical Significance

- In the medical literature, a 'statistically significant' result requires that $p < 0.05$
  - less than 1 in 20 chance that the result is due to random chance
  - you would see the same result 95 out of 100 times if you repeated the experiment
- $p < 0.05$ is an arbitrary convention: other fields of study may have different cutoffs

What can affect p?

- sample size
- effect size
- effect consistency

What do p values tell us?

674 patients w/ moderate to severe CHF (EF < 40%) randomized to amiodarone or placebo, median f/u = 4 y

outcome	amiodarone	placebo	p
Δ EF	+8.8%	+1.9%	< 0.001
hospitalizations	11.1%	13.6%	0.18
hosp. and cardiac death	RR = 0.82	ref	0.08

Massie BM, Fisher SG, Deedwania PC, et.al. Effect of amiodarone on clinical status and left ventricular function in patients with congestive heart failure. *Circulation* 1996; 93: 2128-34.

Highly Significant p values

Δ EF +8.8% +1.9% $p < 0.001$

- Results like this tell us:
  - If n small, the effect was large, or the effect was consistent, or both
  - If n large, the effect size might not be that big—a large sample will drive the p value down even for effect sizes that are clearly not clin sig

Topical Metronidazole in Seborrheic Dermatitis - A Double-Blind Study

- *Dermatology* 2001;202:35-37
- metronidazole 1% gel or placebo for 8 weeks
- *Results:* Thirty-eight patients completed the study; 21 patients in the metronidazole group and 17 patients in the placebo group
- At 8 weeks, 14 patients in the metronidazole group showed marked improvement to complete clearance as compared to only 2 patients having moderate improvement in the placebo group ($p < 0.001$)
- ARR = 55%
- NNT = 2

Non-Significant p values

hospitalizations 11.1% 13.6% $p = 0.18$

- Results like this tell us:
  - The sample size was not large enough

    OR
  - If n was large (the study was appropriately powered), there is either no effect or the effect is not consistent

Borderline p values

hosp. and cardiac death RR = 0.82 p = 0.08

- Results like this tell us:
  - The result may become stat sig with a larger n
  - The effect size may be small or the effect may be inconsistent
  - Further study is needed

Stat Sig vs. Clin Sig

- a result must be statistically significant before it can be evaluated for clinical significance
- BUT, stat sig does not imply clin sig
- Ex: weight loss intervention

Outcome	Drug A	Drug B	p
change in LDL	-2 mg/dL	-24 mg/dL	0.23
change in BMI	-2.2 kg/m^2	-2.1 kg/m^2	<0.01

Type II error (β)

- Traditionally

  β is usually 0.20 or less
- Power is the probability that a trial will find a statistically significant difference when a difference really exists
- Power = 1 – β
- Power should be > 0.80

Factors which influence power

- Sample size
- Treatment effect size
- Variation among patients
- Number of patients with the outcome of interest

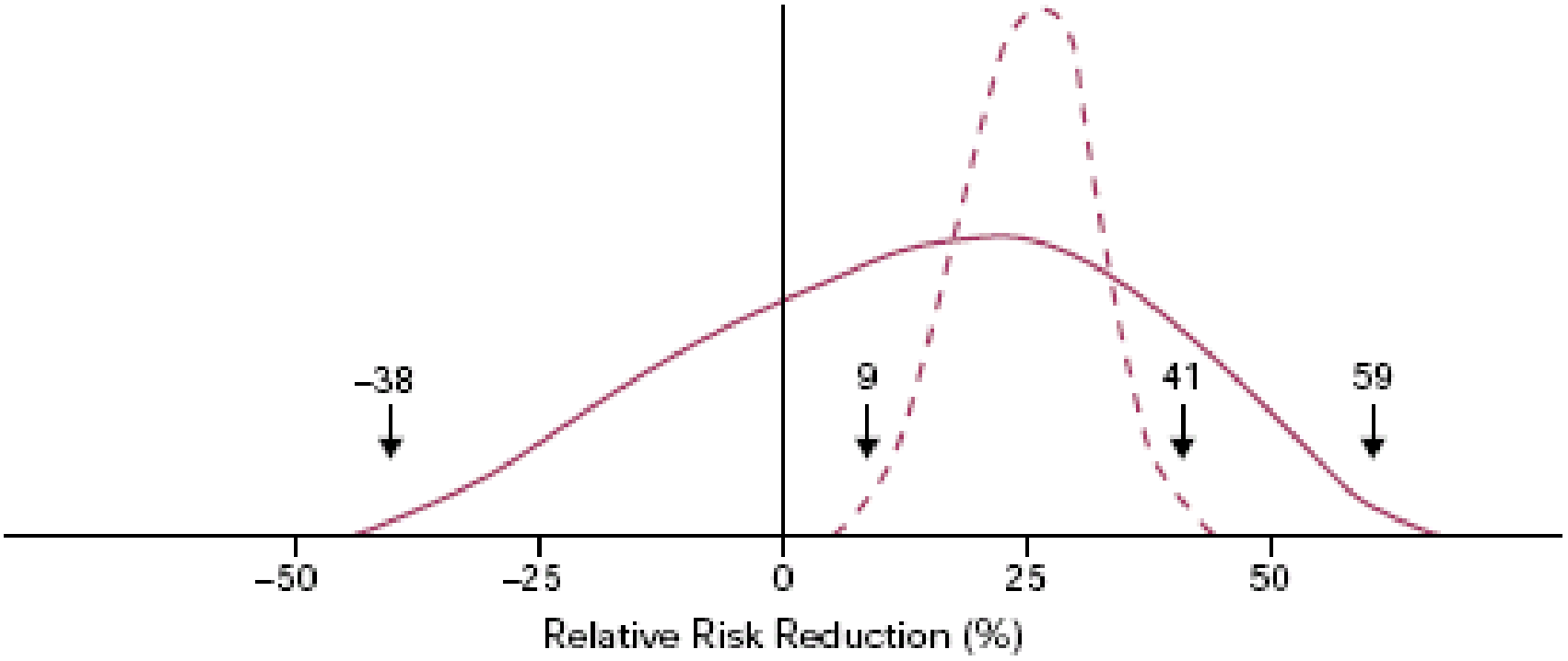
Acceptable Power

- most medical studies should have 90% power
- 80% is sometimes OK but not ideal
- studies examining new topics can generally get away with lower power
- <80% is sometimes seen if there is a good reason (i.e. tx for an extremely rare disease)

Confidence Intervals

- 95% confidence interval
  - If the study is unbiased, there is a 95% chance that the interval includes the true effect size
  - If the study were repeated 100 times, we would expect these results would fall within this range 95% of the time
- The true value is likely to be close to the point estimate, less likely to be near the outer limits

Confidence Intervals Around Relative Risk Reduction



Two studies with the same point estimate, a 25% relative risk reduction, but different sample sizes and correspondingly different confidence intervals. The solid line represents the confidence interval around the first example, in which there were 100 patients per group and the numbers of events in active and control were 15 and 20, respectively. The broken line represents the confidence interval around the first example in which there were 1000 patients per group, and the numbers of events in active and control were 150 and 200, respectively.

Confidence Intervals

- a statistic is an estimate—a CI gives the accuracy of the estimate
- 95% CIs are traditional, but double check
- Convey more information than just a statistic and a p value

Table 5. Independent Relative Risk Estimates for Newly Diagnosed Depression or Psychosis by Exposure Status, Age, and Sex (GPRD Data)*

Variable	No. of Cases/ Person-years	Adjusted Relative Risk Estimate	95% Confidence Interval
Isotretinoin and Antibiotic Users With Acne			
Exposure status			
Nonexposed†	27/1349	1.0	. . .
Current isotretinoin use	3/88	1.8	0.4-5.2
Current acne with antibiotic use	32/1284	1.5	0.9-2.5
Recent isotretinoin use	2/59	1.8	0.3-6.1
Recent acne with antibiotic use	11/347	1.7	0.8-3.4
Age, y			
<20†	17/1176	1.0	. . .
20-29	33/1349	1.8	1.0-3.3
30-39	17/401	2.6	1.3-5.2
≥40	8/201	2.3	0.9-5.3
Sex			
Male†	32/2025	1.0	. . .
Female	43/1102	2.2	1.4-3.5

Table 3. Independent Relative Risk Estimates for Suicide or Attempted Suicide in Isotretinoin Users and in Patients With Acne Treated With Antibiotics by Exposure Status, Sex, and History of Depression or Psychosis (Saskatchewan Health Data)*

	All Subjects		Subjects With No Psychiatric History	
Variable	No. of Cases/ Person-years	Adjusted Relative Risk Estimate (95% Confidence Interval)	No. of Cases/ Person-years	Adjusted Relative Risk Estimate (95% Confidence Interval)
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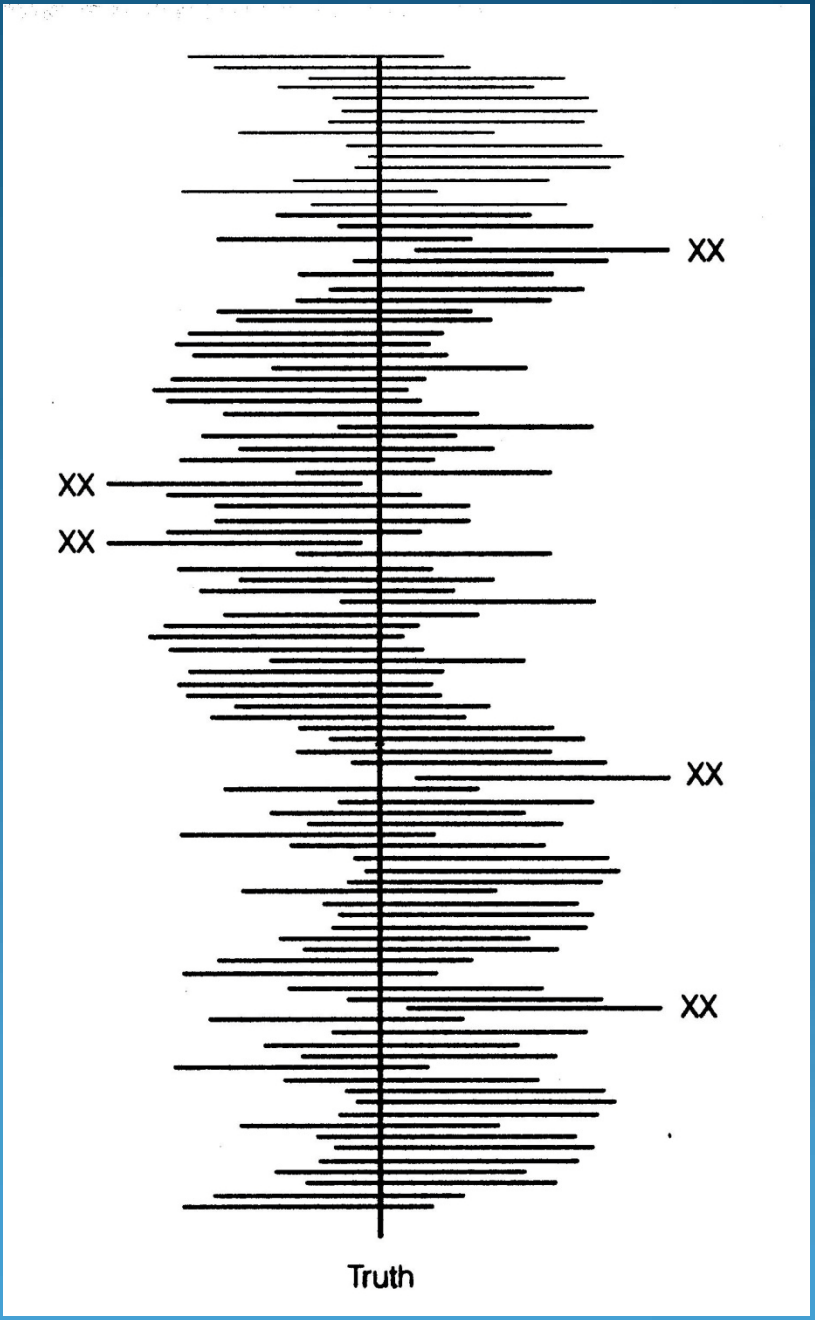
Current isotretinoin use	4/4003	0.9 (0.3-2.4)	4/3553	1.3 (0.3-4.6)
Current acne with antibiotic use	11/11 051	0.8 (0.4-1.7)	3/9617	0.5 (0.1-1.6)
Recent isotretinoin use	2/1678	1.1 (0.2-3.7)	1/1499	1.0 (0.1-5.7)
Recent acne with antibiotic use	3/5133	0.5 (0.1-1.4)	2/4433	0.7 (0.1-2.7)
Sex				
Male†	14/16 510	1.0	8/15 101	1.0
Female	24/19 247	1.2 (0.6-2.5)	10/16 136	1.4 (0.5-3.8)
Previous depression or psychosis				
No†	18/31 237	1.0	. . .	. . .
Yes	20/4520	8.0 (4.1-15.5)	. . .	. . .

a picture is worth 1000 words…



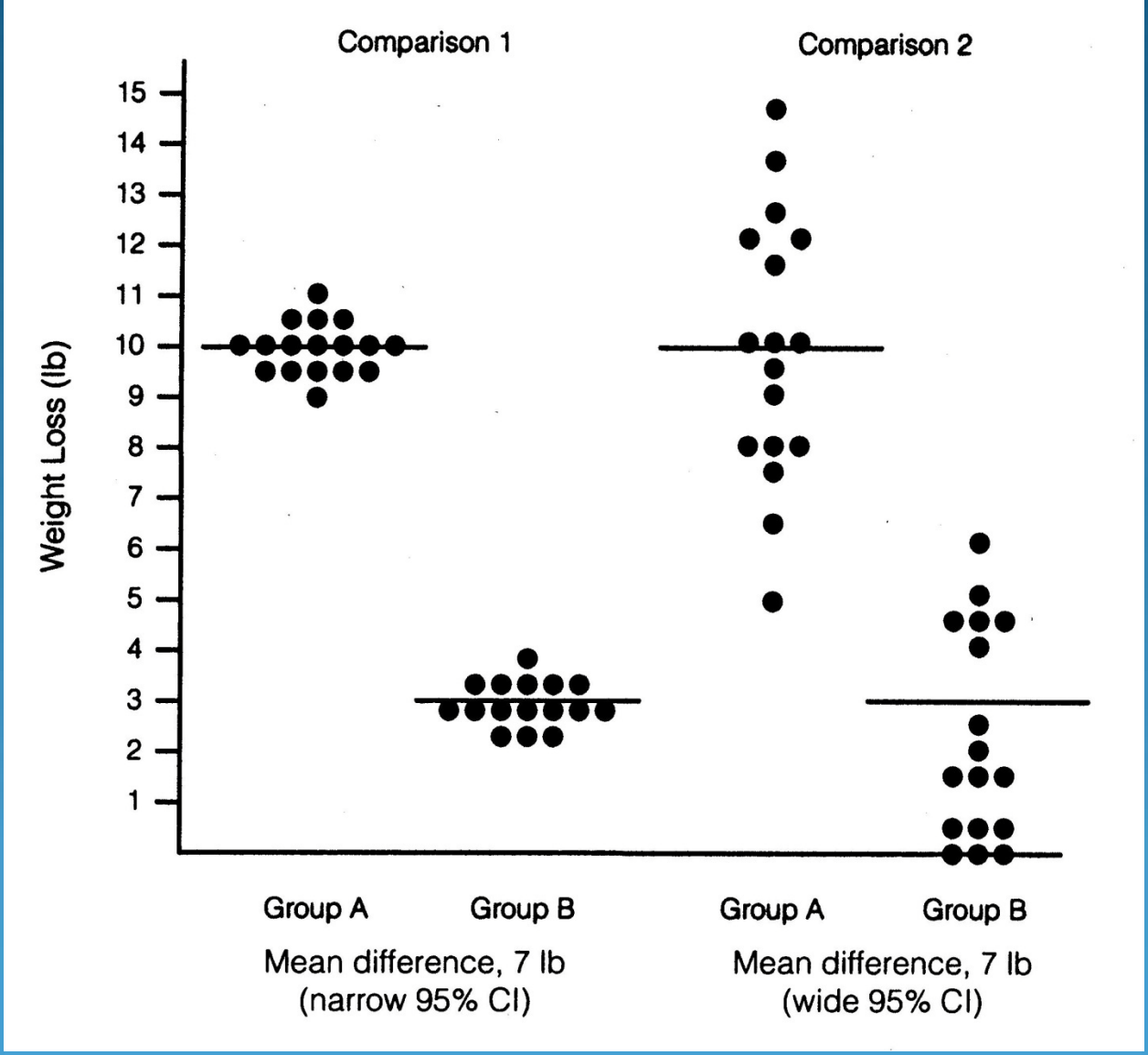
Primer on 95% Confidence Intervals. *Effective Clinical Practice* 2001; 229-231.

Width of CIs

- As with other things, skinny is better
- Does this yield any useful information?

  RR = 12.3 (95% CI: 1.2-99.8), p = 0.042
- Factors that affect width of CIs:
  - sample size
  - variability (stdev)
  - degree of confidence

How stdev affects CI width



Primer on 95% Confidence Intervals. *Effective Clinical Practice* 2001; 229-231.

CI vs. p

- The range of a CI can tell you whether or not the given result is stat sig, though it doesn't tell you the exact p value
- If a 95% confidence interval excludes the 'no difference between groups' option, then p will be <0.05 (note that CI+p = 1)
- For a difference in means or proportions, the CI must exclude 0
- For OR/RR, the CI must exclude 1