



Questionable Thoughts about Meta-analysis and Rare Events

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“Suicidality”

For the purpose of this talk:

Any suicide-related phenomena of interest.



Caveat Aggregator

- n Non-Random Acts of Withdrawal
- n In the Long Run, We're All Dead
- n Models by the Pool(ing of Data)
- n Zen and the Art of Zero Event Trials



Non-Random Acts of Withdrawal

n Revealed Confounding


- .. Propensity to withdraw affected by
 - n Susceptibility to AE (including lack of effect)
 - n Tolerance of AE
 - n Ability/Desire to adhere to protocol
 - .. Personality
 - .. Lifestyle
 - .. Life events
- .. May correlate with propensity or detectability of suicidality



Non-Random Acts of Withdrawal

n Informative Censoring

- Withdrawal may be prodrome for suicidality
- Or, conceivably, be a sign of remission with good prognosis



In the Long Run, We're All Dead

- n Any study of sufficient length will have a mortality ratio of one and a mortality risk difference of zero.
- n Models make particular assumptions about how and when events occur



In the Long Run, We're All Dead

Measure	Background Rate Relationship	Subject Observation Period	Drug Effect	Background Rate
Incidence Rate Ratio (Poisson)	Multiplicative	Variable	Constant	Constant
Incidence Rate Difference	Additive	Variable	Constant	Constant
Risk (Odds) Ratio	Multiplicative	Constant	Constant	Variable
Risk Difference	Additive	Constant	Variable	Variable



Models by the Pool

*Gratuitous photo of gorgeous people
in swim suits*

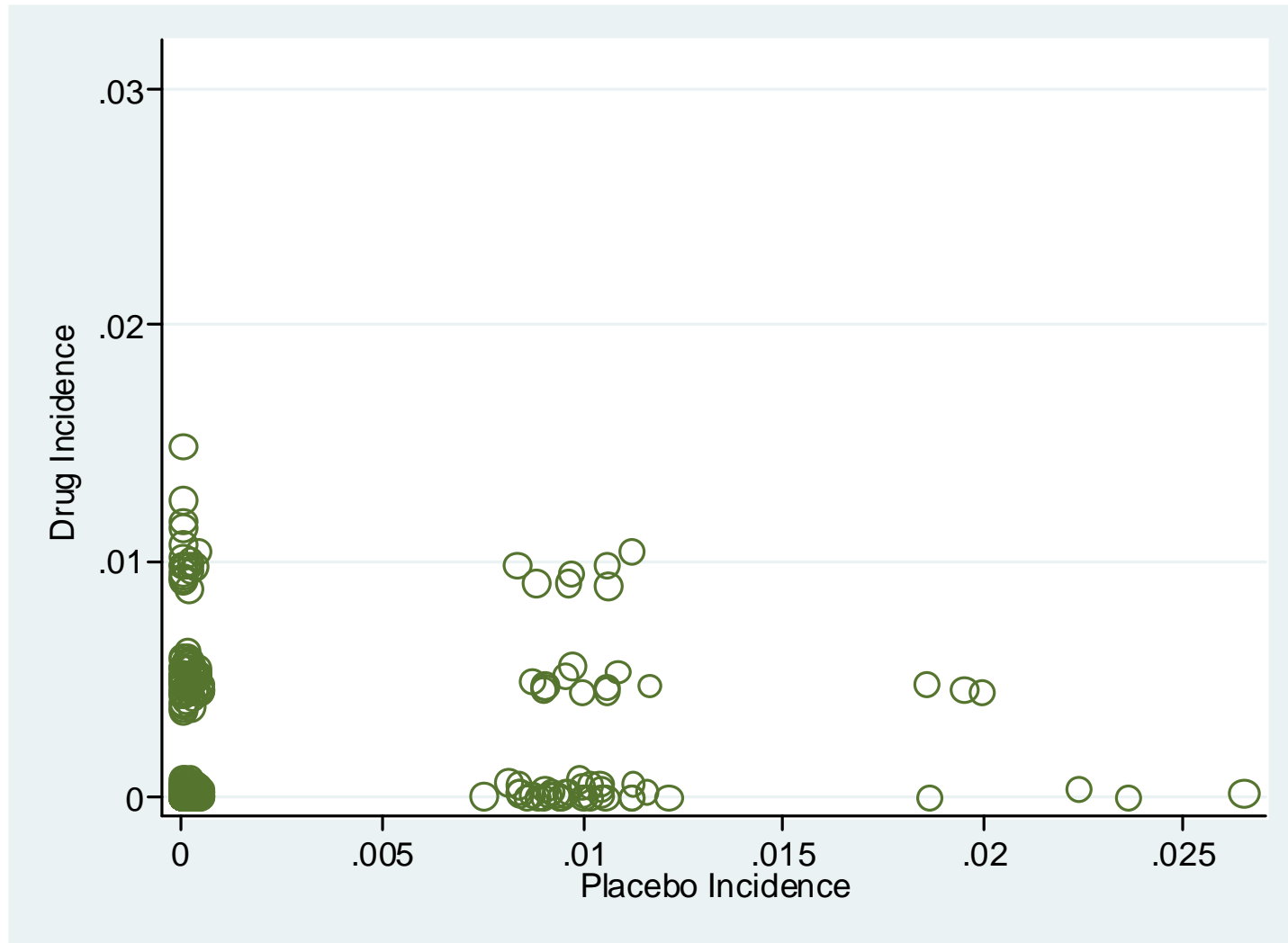


Models by the Pool

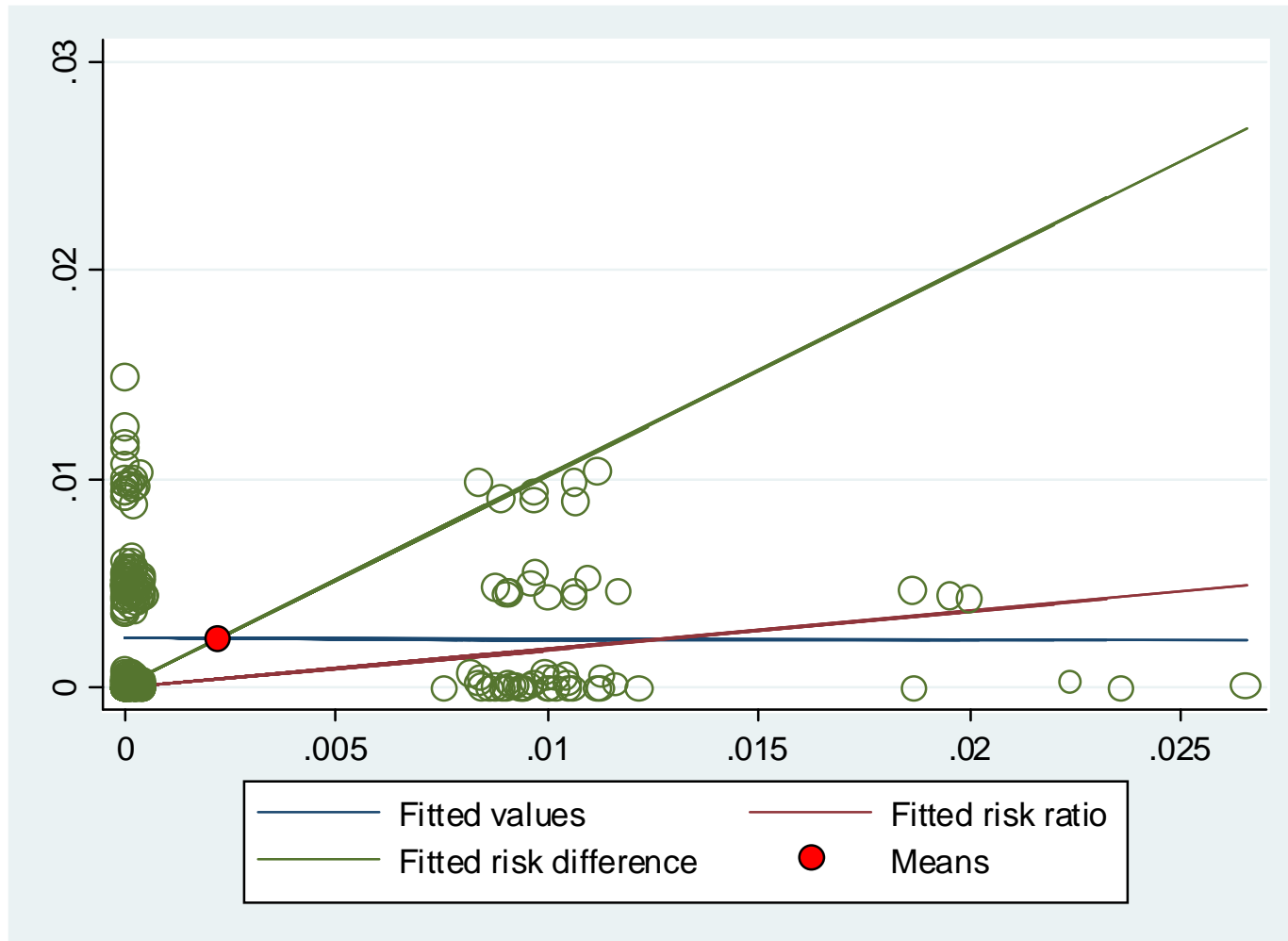
A Simulation

- n 300 clinical trials
- n Approx. 300 subjects per trial (256-359)
- n Randomized 2:1 drug:placebo
 - 159-241 subjects in drug arm
 - 75-142 subjects in placebo arm

The Data

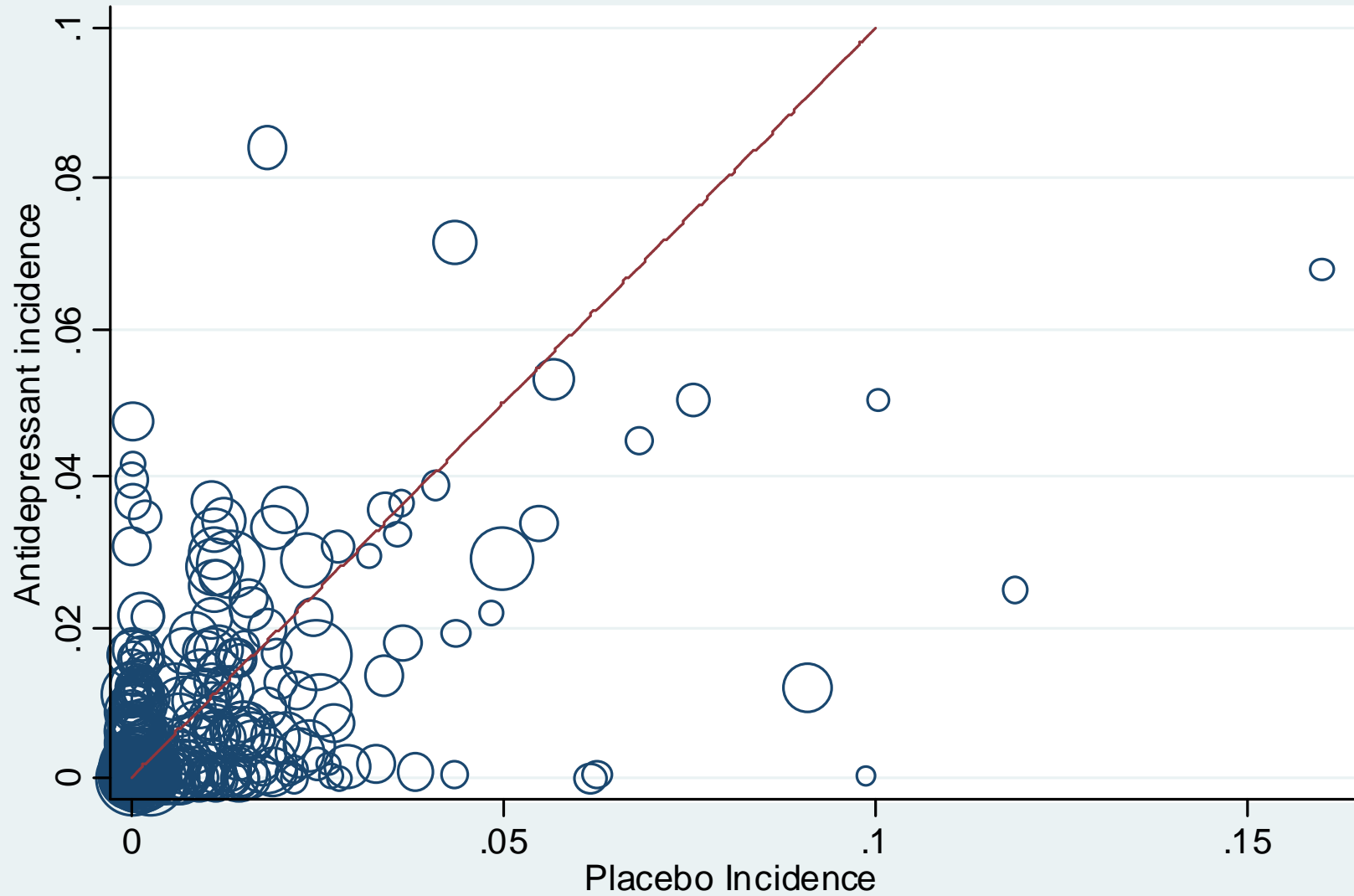


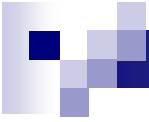
Visualizing Models



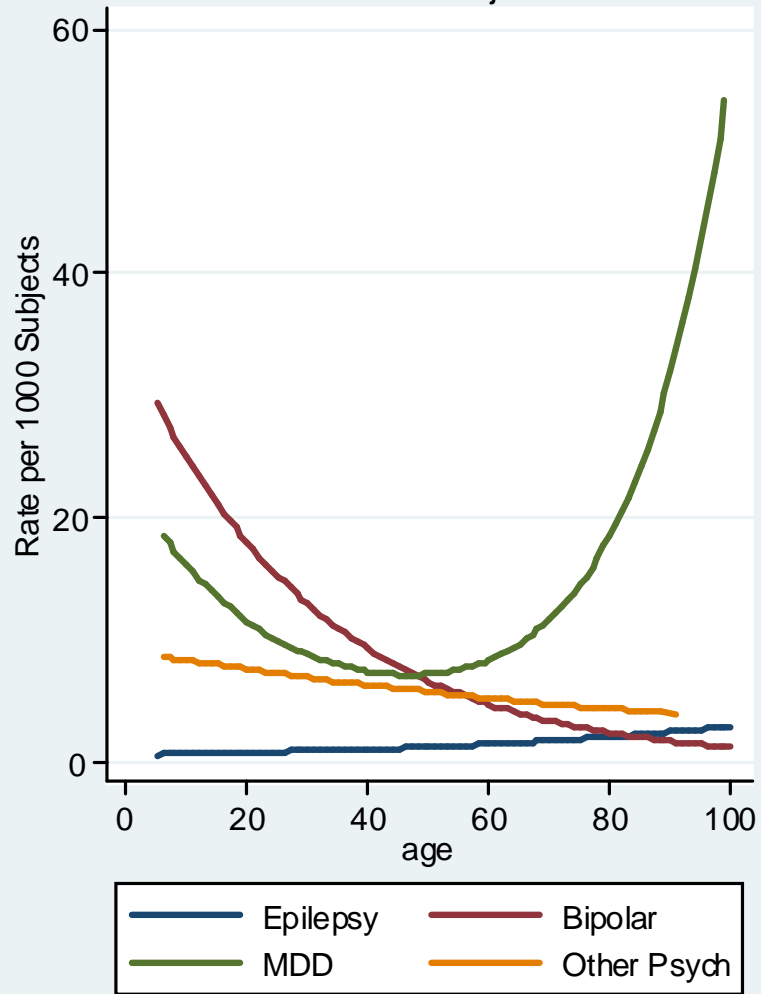


Suicidal behavior or ideation

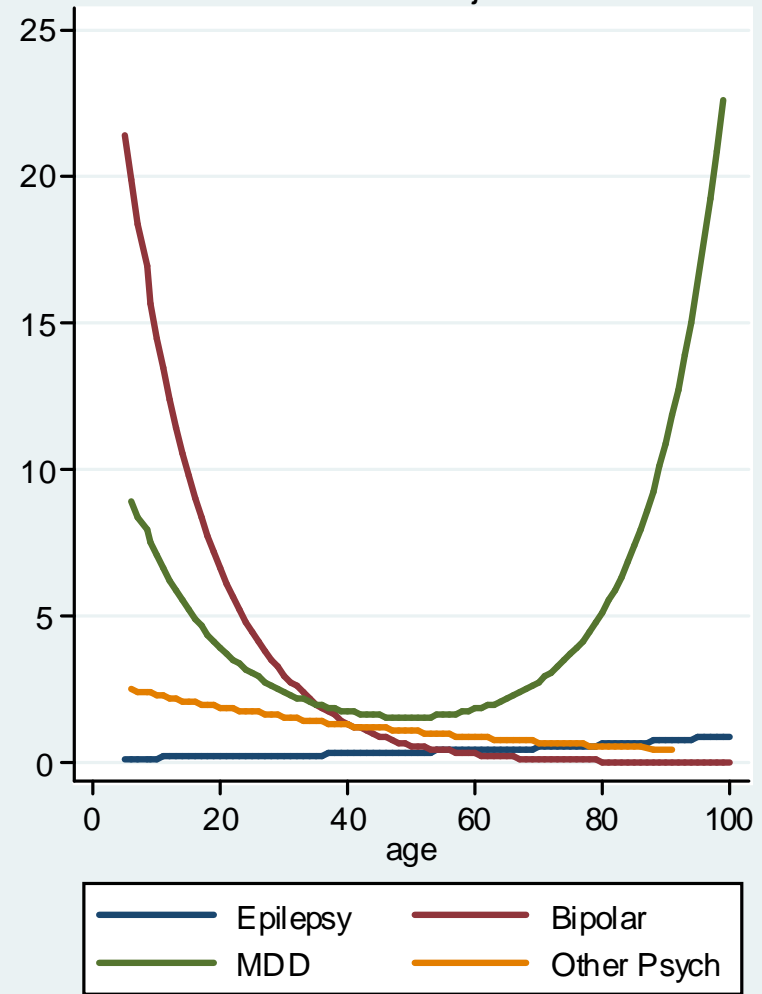




Suicidal Behavior or Ideation Placebo Subjects



Suicidal Behavior Placebo Subjects

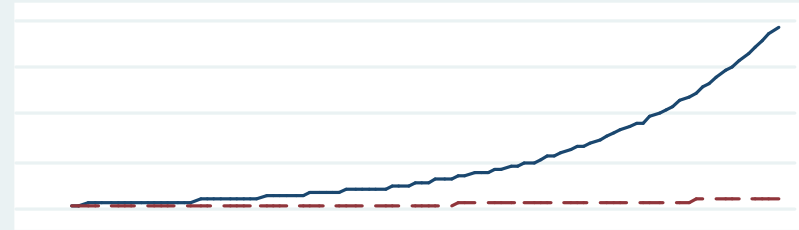
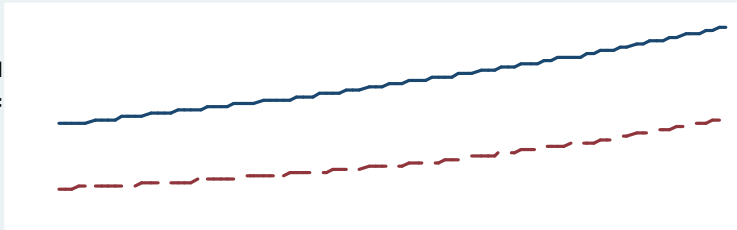




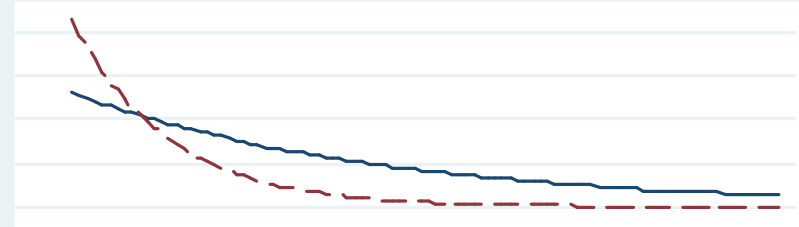
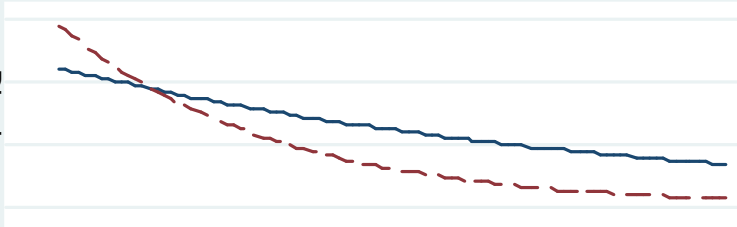
Suicidal Behavior or Ideation

Suicidal Behavior

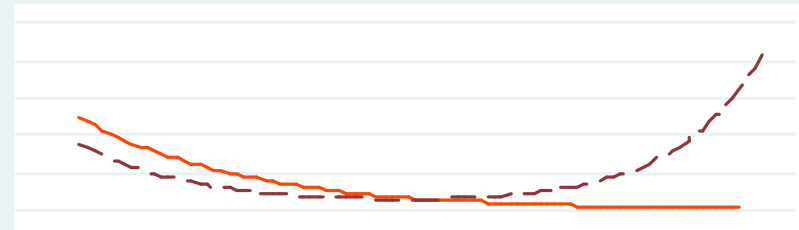
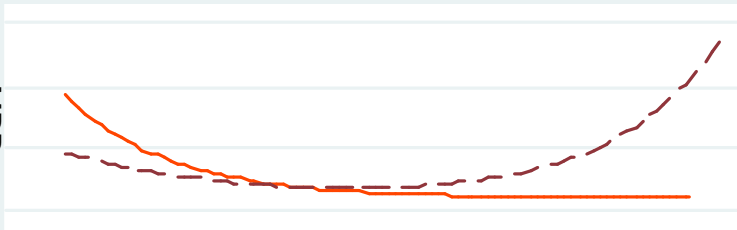
Epilepsy



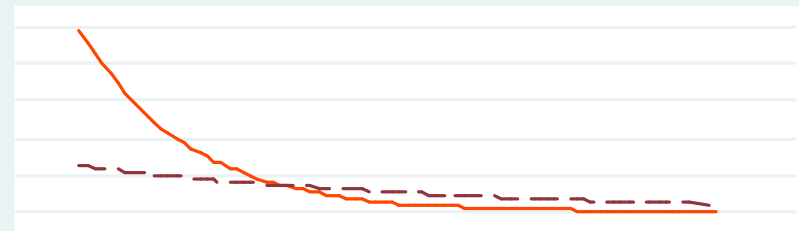
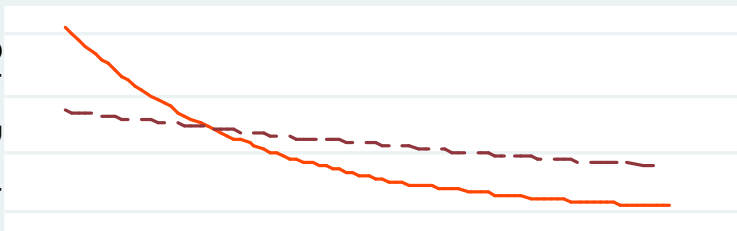
Bipolar



MDD



Other Psych






Models by the Pool

To Meta-analyze is To Model

- n Incidence rate/s in placebo arms across trials (Fixed vs. Random Effects)
- n Relationship between drug effect and placebo incidence *rates*
- n Effect of covariates



Zen and the Art of Zero Event Trials

OR


What is the ratio of one arm eventing?



Zen and the Art of Zero Event Trials

The Same Simulation

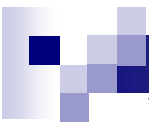
- n 300 clinical trials
- n Approx. 300 subjects per trial
- n Randomized 2:1 drug:placebo
- n AE Rates (Fixed Effects):
 - .. Drug 2.5/1000
 - .. Placebo 2/1000



Zen and the Art of Zero Event Trials

Results

- n 148 trials with no events in either arm
- n 185 trials with no events in drug arm
- n 242 trials with no events in placebo arm
- n 143 AEs in 60,416 drug subjects (0.237%)
- n 66 AEs in 30,251 placebo subjects (0.218%)




What Happens if Zero Event Trials are excluded?

n_i – number of subjects with AEs

Z_i – number of subjects in zero event trials

T_i – total number of subjects

$i = d$ (drug) or p (placebo)




What Happens if Zero Event Trials are excluded?

Risk Ratio

— X — vs. — X —

— X .5007

— X 5024



What Happens if Zero Event Trials are excluded?

Risk Difference

— — — VS. — — —

———— — ————— ————— —————

What Happens if Zero Event Trials are excluded?

Standard Error (Binomial)

$$\sqrt{\frac{x}{n} \left(\frac{n-x}{n} \right)} \quad \text{vs.} \quad \sqrt{\frac{x}{n-x} \left(\frac{n-x}{n} \right)}$$

$$\sqrt{\frac{x}{n}}$$

$$\sqrt{\frac{x}{n}}$$



Risk Difference

Events per 1000 Subjects (Expected Value 0.500)

Method	Estimate	95% CI		p value
Pooled Sample	0.185	-0.468	0.838	0.578
Nonzero Only	0.379	-0.901	1.659	0.562
Mantel - Haenszel	0.177	-0.898	1.252	0.747
DerSimonian - Laird	0.780	-0.215	1.775	0.124



Risk Ratio

(Expected Value 1.250)

Method	Estimate	95% CI		p value
Pooled Sample	1.085	0.811	1.452	0.608
Nonzero Only	1.089	0.814	1.456	0.607
Mantel – Haenszel (No CC, NZ Only)	1.081	0.807	1.449	0.601
Mantel – Haenszel (CC 0.5, NZ Only)	0.796	0.640	0.990	0.041



Risk Ratio

(Expected Value 1.250)

Method	Estimate	95% CI		p value
Pooled Sample	1.085	0.811	1.452	0.608
Nonzero Only	1.089	0.814	1.456	0.607
DerSimonian – Laird (No CC, NZ Only)	0.576	0.329	1.008	0.053
DerSimonian – Laird (CC 0.5, NZ Only)	0.805	0.628	1.031	0.086



Odds Ratio

(Expected Value 1.251)

Method	Estimate	95% CI		p value
Pooled Sample	1.085	0.811	1.452	0.582
Nonzero Only	1.089	0.814	1.457	0.566
Mantel - Haenszel	0.795	0.639	0.990	0.041
DerSimonian - Laird	0.804	0.626	1.031	0.085

Odds Ratio

(Expected Value 1.251)

Method	Estimate	95% CI		p value
Pooled Sample	1.085	0.811	1.452	0.582
Nonzero Only	1.089	0.814	1.457	0.566
Peto's Method (NZ Only)	1.080	0.809	1.441	0.600
Exact LR (NZ Only)	1.081	0.802	1.471	0.657



Odds Ratio

(Expected Value 1.251)

Method	Estimate	95% CI		p value
Pooled Sample	1.085	0.811	1.452	0.582
Nonzero Only	1.089	0.814	1.457	0.566
Maximum Likelihood LR	1.085	0.810	1.453	0.584
Nonzero Only	1.089	0.813	1.459	0.567

Odds Ratio

(Expected Value 1.251)

Method	Estimate	95% CI		p value
Pooled Sample	1.085	0.811	1.452	0.582
Nonzero Only	1.089	0.814	1.457	0.566
Population Averaged LR	1.085	0.810	1.454	0.585
Nonzero Only	1.096	0.770	1.559	0.611



Odds Ratio

(Expected Value 1.251)

Method	Estimate	95% CI		p value
Pooled Sample	1.085	0.811	1.452	0.582
Nonzero Only	1.089	0.814	1.457	0.566
Mixed Effects REML LR	1.085	0.810	1.453	0.584
Nonzero Only	1.089	0.813	1.459	0.567

