Applying Hypothesis-Testing Methods to Help Inform Causality Conclusions from Epidemiology Studies

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Outline

- Background – Interpreting epidemiology studies
- Case study concept – Patterns in epidemiology study results
- Theoretical basis – evidence for expected patterns
- Positive control – lung cancer and tobacco smoke
- Negative control – cancer and dietary constituents
- Conclusions and future work

Specific requests for input from panelists and audience members will be distributed throughout

Background – Epidemiology Studies

- Epidemiology (or observational) studies provide important information for understanding the relationship between a stressor and an adverse effect that is a crucial first step in a risk assessment

- Often provide information that cannot be obtained using any other research design – at low concentrations, in vulnerable populations, etc

- Epidemiology studies are associational by design – that is, they provide information about the *association* between a stressor and an effect, and not about the *causation* (or even necessarily the direction of the relationship) between the stressor and the effect

Interpreting Epidemiology Studies

- Because of the association/causation issue, epidemiological studies can be difficult to interpret, particularly in isolation

- What do we do with epidemiology study results?
  - Interpret carefully: e.g. only trust what is corroborated in randomized controlled trial or other experimental studies
  - Conduct meta-analyses: useful, but can only be done on studies with similar methods and results, and they don't address underlying flaws (i.e. combining many flawed results doesn't produce an unflawed effect estimate)
  - Use a somewhat subjective weight-of-evidence framework for determining validity of conclusions
  - **Hypothesis-test: if there is some sort of causal relationship, there should be an identifiable pattern in the epidemiology study results**

Case-Study Concept

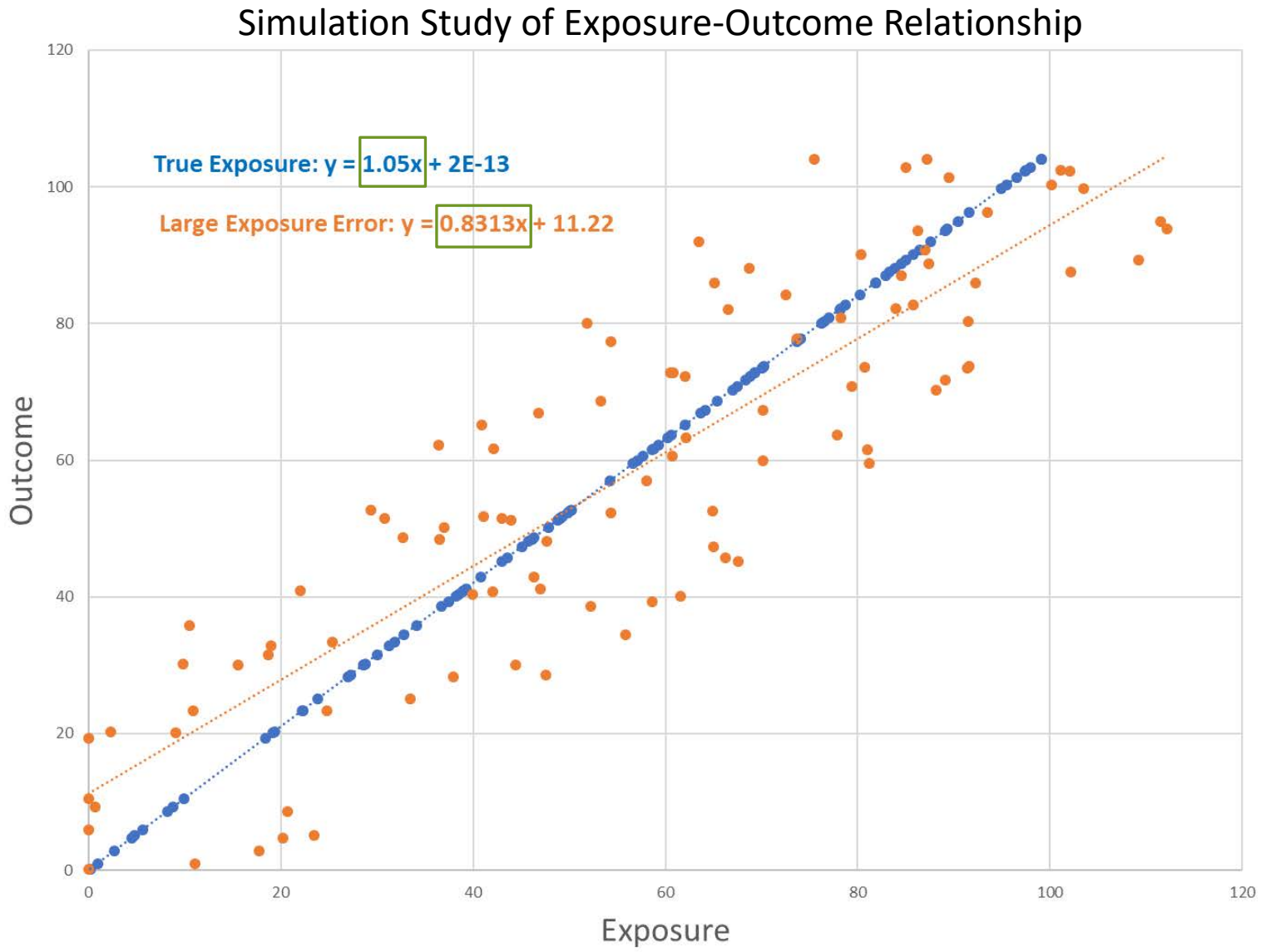
- Using the full literature of observational studies, if a true causal relationship exists between an exposure and a health effect, then we might expect patterns in the study results based on:
  - Exposure and outcome variability
  - Exposure concentration (i.e. dose-response)
  - Specificity of the health effect
  - Severity of the health effect
- This case study tests this idea through:
  - Literature review and simple simulations
  - Positive control – smoking and lung cancer
  - Negative control – nutrient supplementation and cancer
- Food for Thought: If the idea of the patterns is technically sound, but the patterns aren't as expected in the positive and negative controls, then what is the explanation?

Literature Review and Simple Simulations

Theoretical Basis: Exposure Variability

- **Concept**: It is often stated that when there is an increase in the random variability or mis-classification of an exposure estimate, then the effect estimate will be biased towards the null (attenuated)

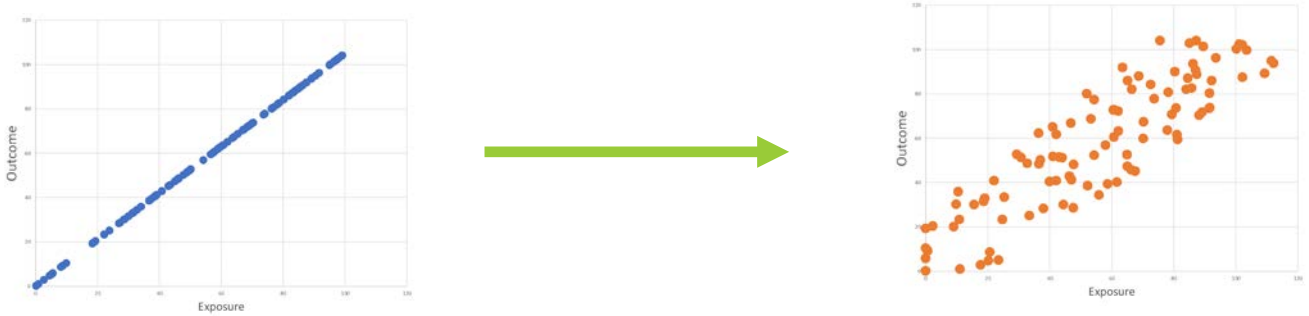
- **Hypothesis**: **in two similar studies, the one with the more precise exposure estimate would be expected to have a higher effect estimate**



Theoretical Basis: Exposure Variability

Classical Error – the exposure estimate varies randomly around the true value and has a greater variation than the true exposure (e.g. instrument error). Expected to bias effect estimate towards the null

- Hausman (2001), Zeger et al. (2000), Hutcheon et al. (2010), Szipiro et al. (2011), Goldman et al. (2011)

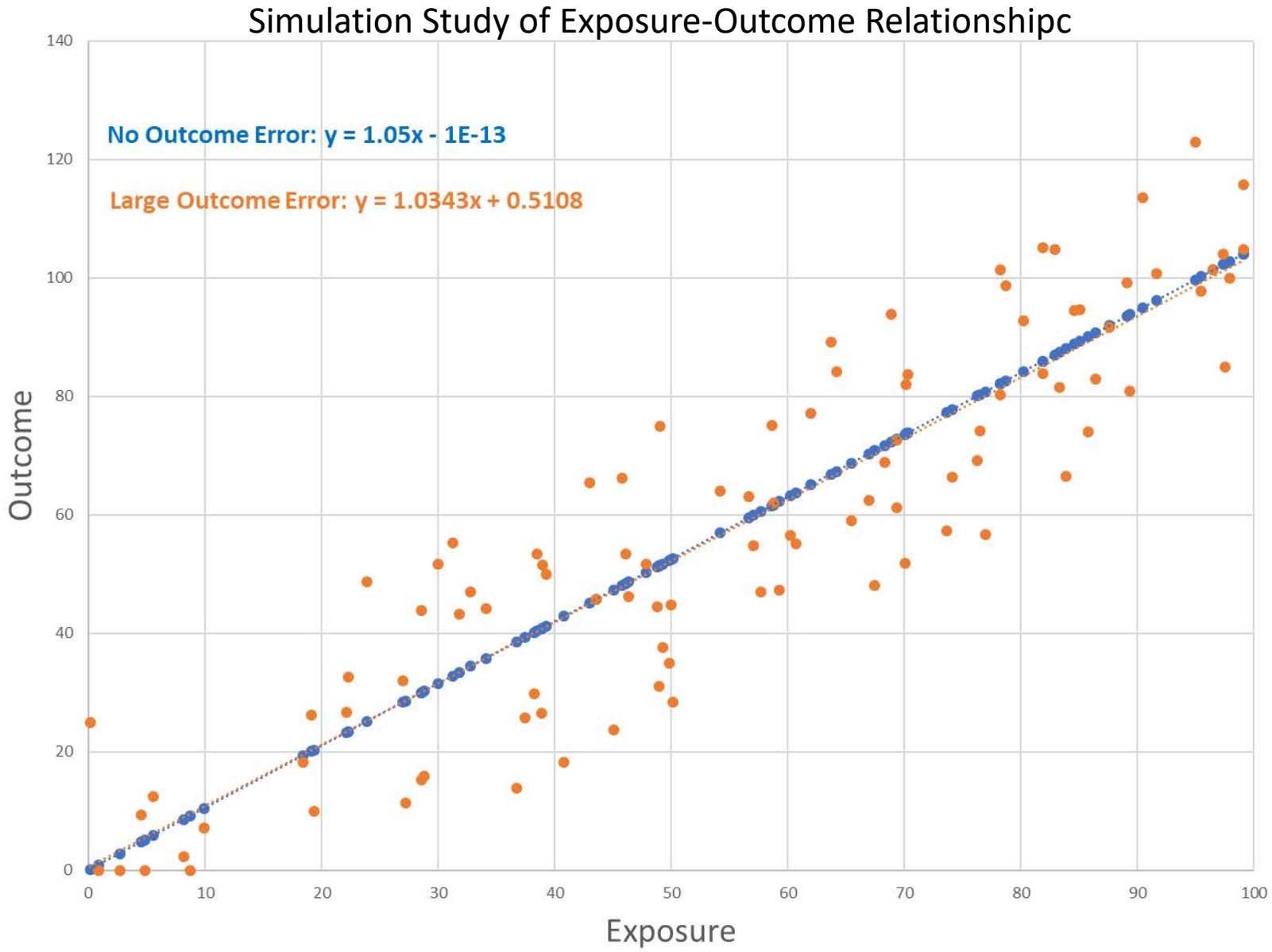


Berkson Error – the true exposure varies randomly around the estimated exposure and has greater variation than the estimated values (e.g. using the average of monitored concentrations from many monitors around a city). Not expected to bias the effect estimate, but will increase the width of the confidence interval

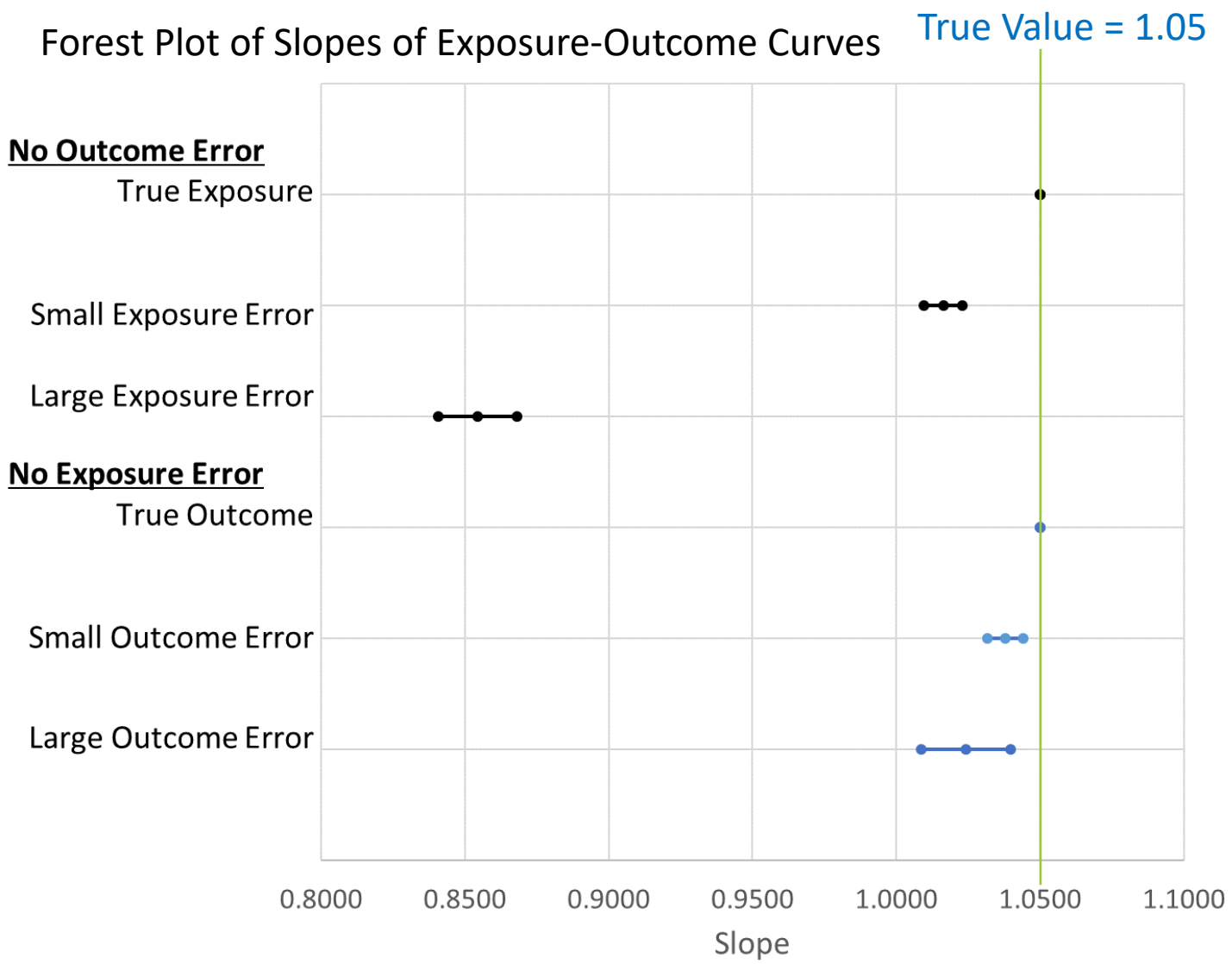
- Zeger et al. (2000), Szipiro et al. (2011), Goldman et al. (2011)

Theoretical Basis: Outcome Variability

- Generally outcome measurement error will not bias the effect estimate but will increase the width of the error bars. (Hausman 2001, Hutcheon et al. 2010)

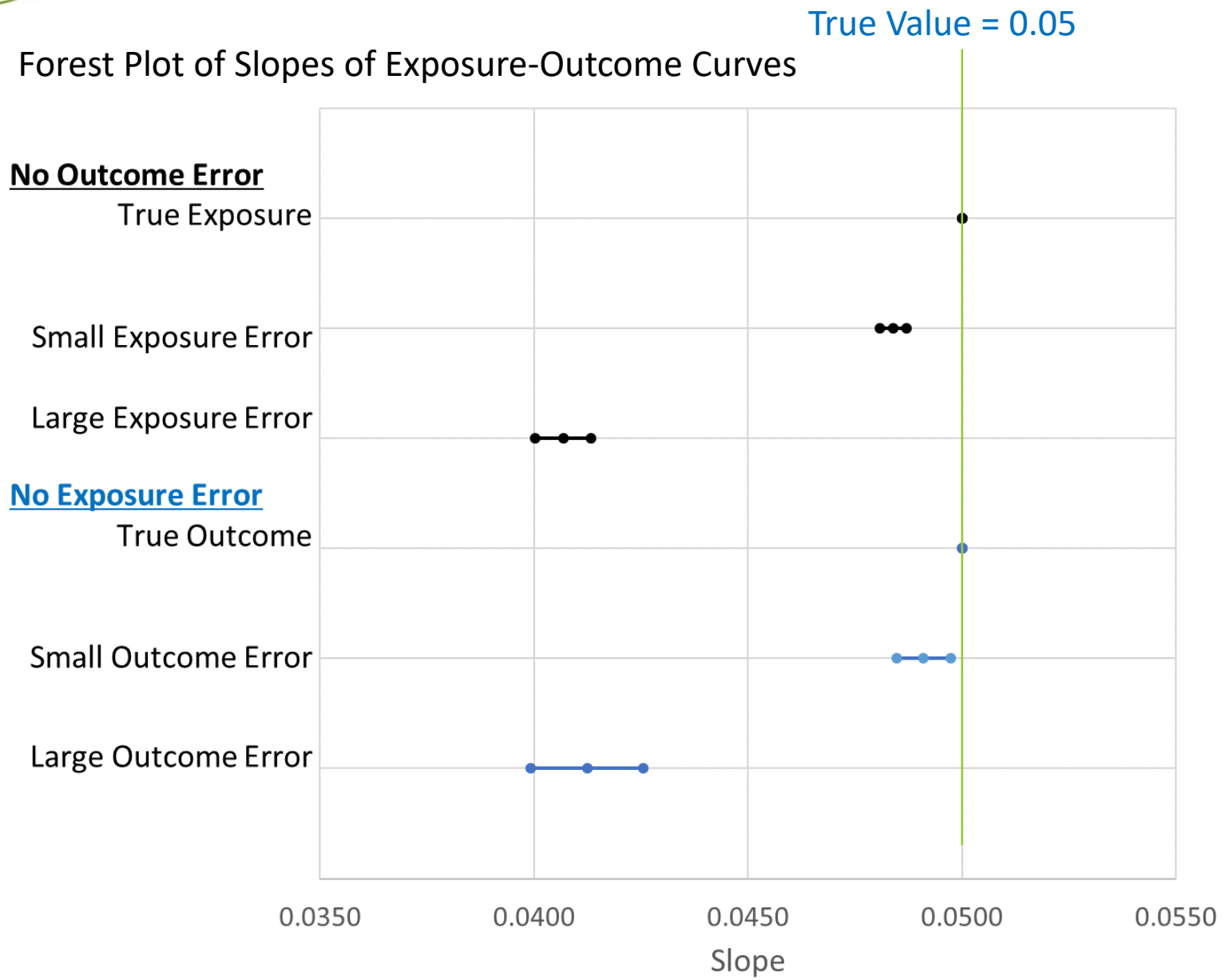


Exposure vs Outcome Error – Linear Regression



- Exposure error has a far greater impact on the magnitude of the slope than does outcome error
- Both exposure and outcome error cause a similar magnitude increase in the width of confidence intervals around the slope estimate

Exposure vs Outcome Error – Log-Linear Regression



- Exposure error has a similar impact on the magnitude of the log-linear slope compared to outcome error
- Exposure error causes a somewhat greater increase in the CI around the slope, compared to outcome error

Exposure Variability - Requirements

- Studies have shown that the relationship between exposure error and the exposure-response estimate can be quite complicated (Brakenhoff et al., 2018; Hausman, 2001; Jurek et al., 2008, 2005; Loken and Gelman, 2017)

- Requirements for classical error biasing towards null, and Berkson error generating no bias but increasing confidence intervals:
  - The underlying concentration-response is linear (Zeger et al 2000, Fuller et al. 1987)
  - The exposure estimate is a good surrogate (well-correlated) for the true exposure (Zeger et al 2000)
  - Differences between the exposure estimate and the true exposure are constant (Zeger et al 2000)
  - Other variables in the regression are measured without error (Szpiro et al. 2011, Corrothers & Evans 2000, Cefalu & Dominici 2014, Brakenhoff et al. 2018)
  - There is no correlation between the exposure measurement error and the true exposure (Hausman 2001)
  - There is no correlation between the exposure measurement error and other error terms in the regression (Hausman 2001)

Theoretical Basis: Outcome and Exposure Variability

Exposure measurement error – may bias an effect estimate towards the null, but this rule can only be applied to simple regressions with single predictor variables. Should not be applied if the regression is more complex

Outcome measurement error – Depends on a simple system and how the outcome is modeled – e.g. if the outcome is limited such as in a logit or probit system (with an all or none response), then this could bias the effect estimate or make it inconsistent (Hausman 2001)

<u>Conclusion</u>: Unless the study has a very simple, one-variable linear analysis one should not make an assumption of effect estimate attenuation with increasing exposure error, or about effect estimate changes (or lack thereof) with outcome error

Request for Input

- Your thoughts about how exposure or outcome error can bias (or not bias) effect sizes?

- Is there value in continuing to pursue exposure and outcome error in this case study? (e.g. applying it to the positive and negative controls?)

Theoretical Basis: Dose (Exposure)-Response

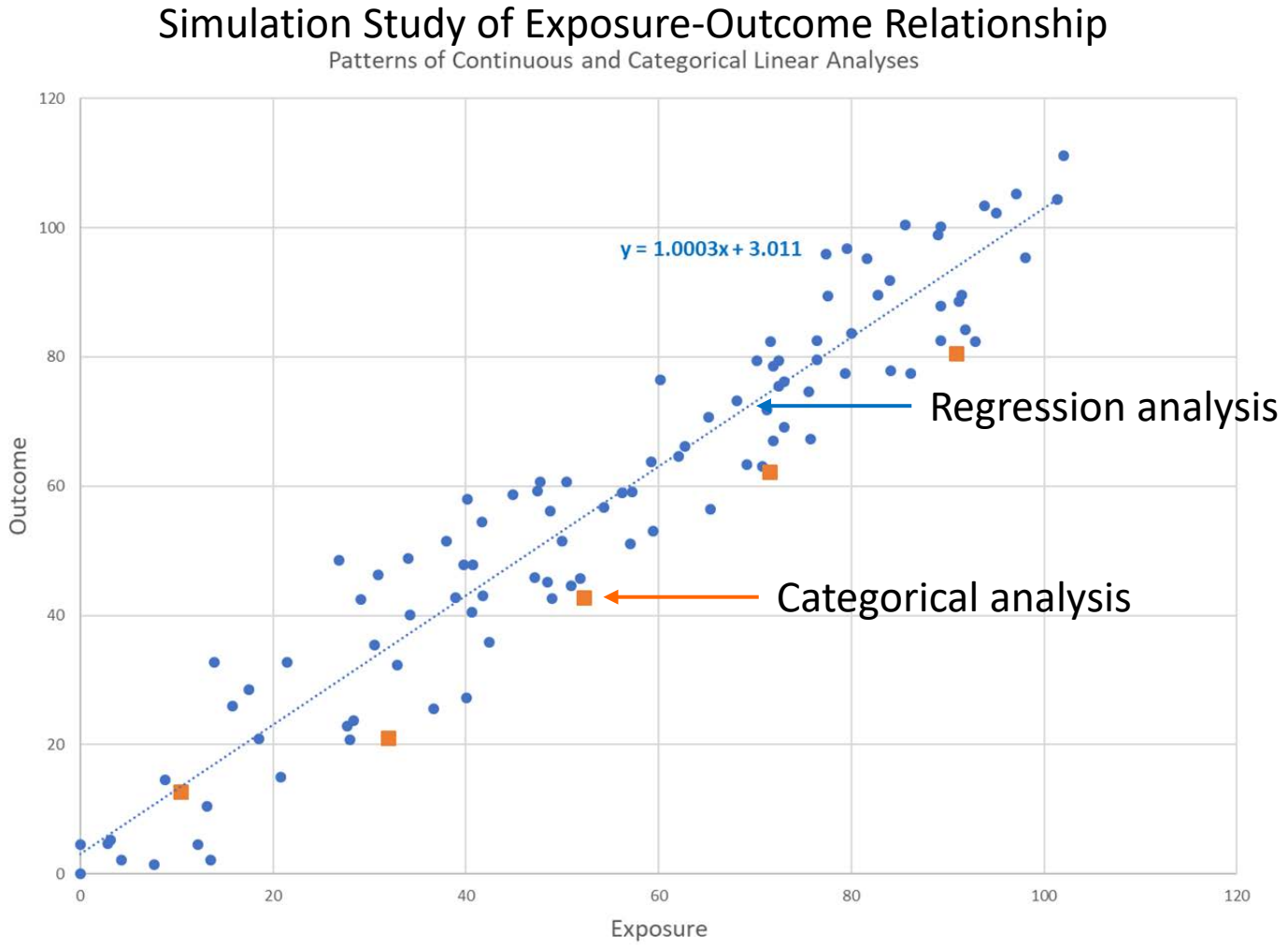
Concept: Based on toxicological theory, higher exposure concentrations should produce greater effect estimates, and more severe health effects.

Often epidemiology studies present a single effect estimate (a slope, relative risk, odds ratio, hazard ratio, etc) to represent the relationship between exposure and outcome. From a dose-response (or exposure-response) standpoint, there are several ways to interpret this:

- If the effect estimate is statistically significant, there is a dose-response between exposure and outcome
- In the absence of the primary data, dose-response cannot be assessed because the model assumes a certain shape and a constant increase in outcome with dose

Theoretical Basis: Dose (Exposure)-Response

- One way to test for the presence of a dose (exposure)-response is to look at categorical results – there should be an increasing effect estimate with increasing dose, relative to a single reference group
- This is true for both linear and log-linear relationships, and with exposure and/or outcome error in the data
- Blue dots are the continuous data (with the equation for the relationship)
- Orange squares are the categorical data points showing increasing effect (compared to the first quintile) with increasing dose quintile



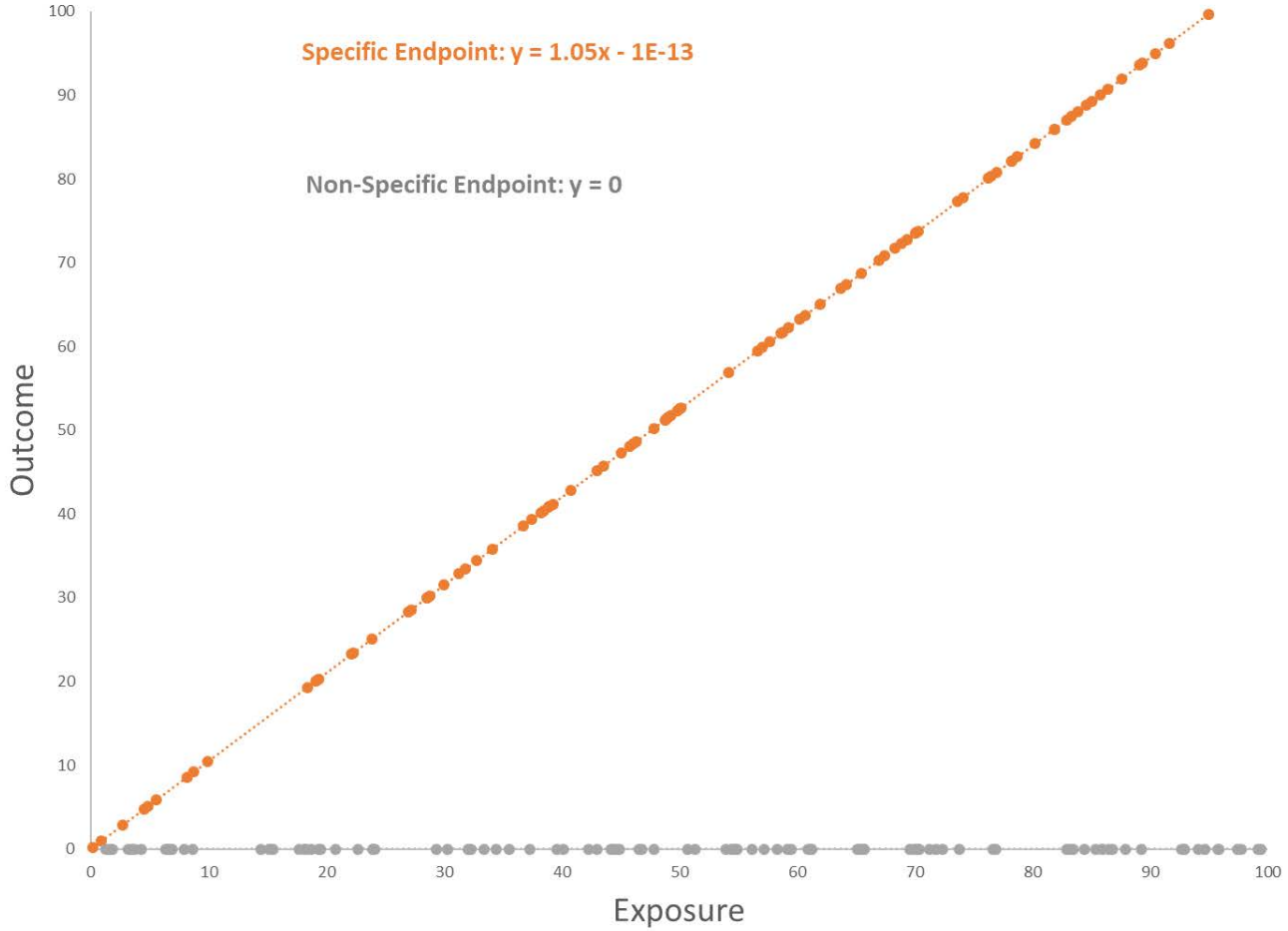
Request for Input

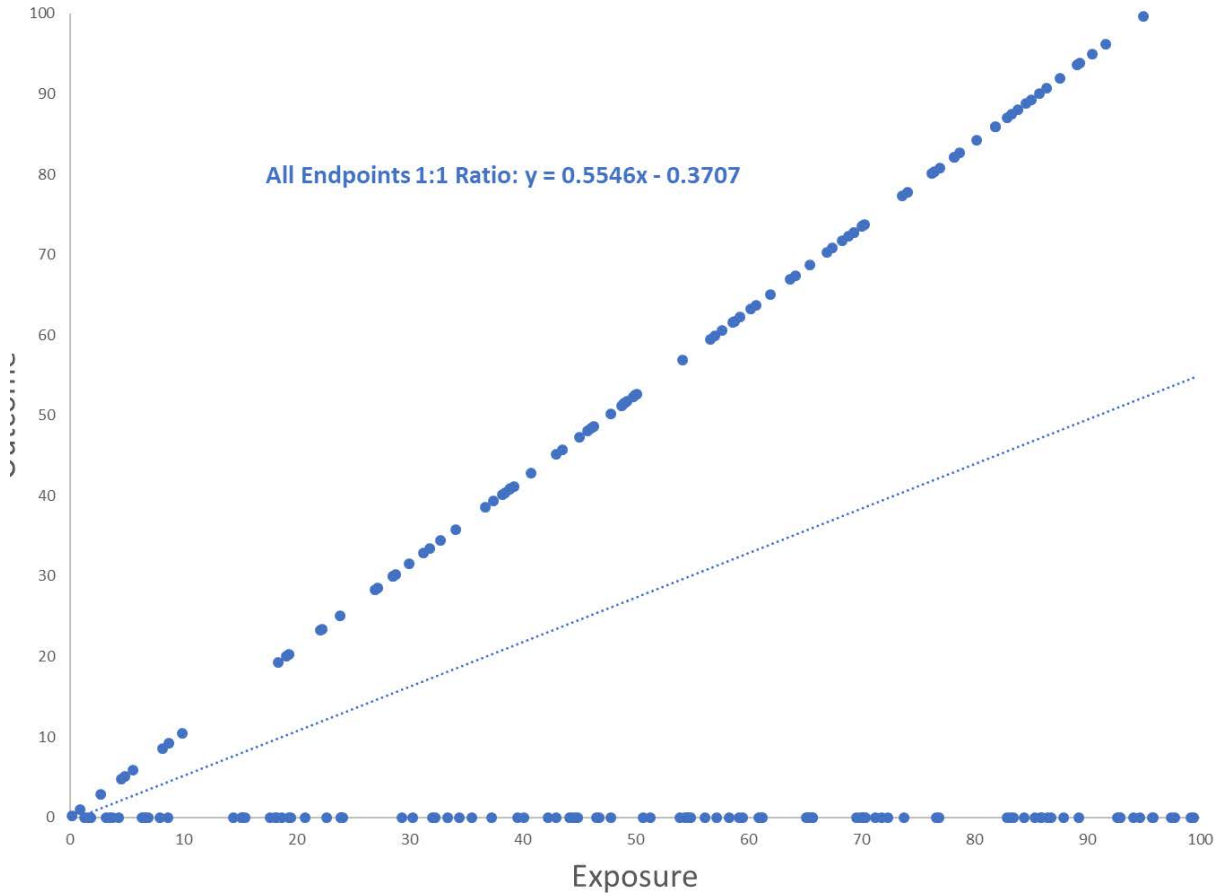
- Your thoughts about using categorical analyses (and not relying on slopes) for dose (exposure) – response assessment?

Theoretical Basis: Specificity

Concept: More specific health effects (that are causally-related to an exposure) should have greater effect estimates than less specific health effects because of less noise in the data (assuming that an agent is not associated with all health effects)

Simulation Studies of Exposure-Outcome Relationship





Theoretical Basis: Specificity

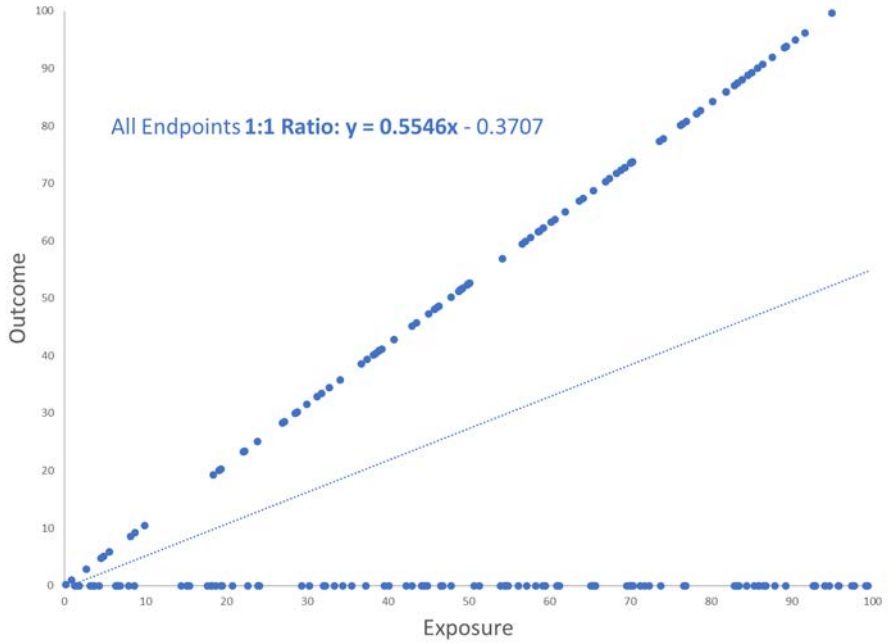
- The principle should be a straight-forward signal-to-noise problem. If there is only one causal relationship in a subset of a dataset, but many other data points are included that are not causally related to the exposure, then there will be a diminishment of the signal from the subset of data.

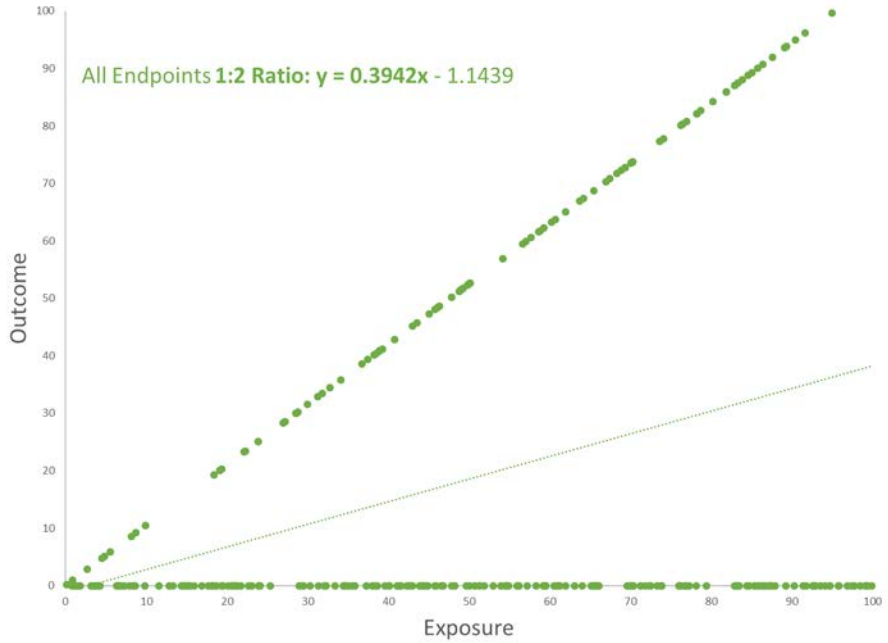
- Similar, but not the same as exposure or outcome measurement error, because this is variability in the effect estimate (β/slope), not in the predictor or the outcome

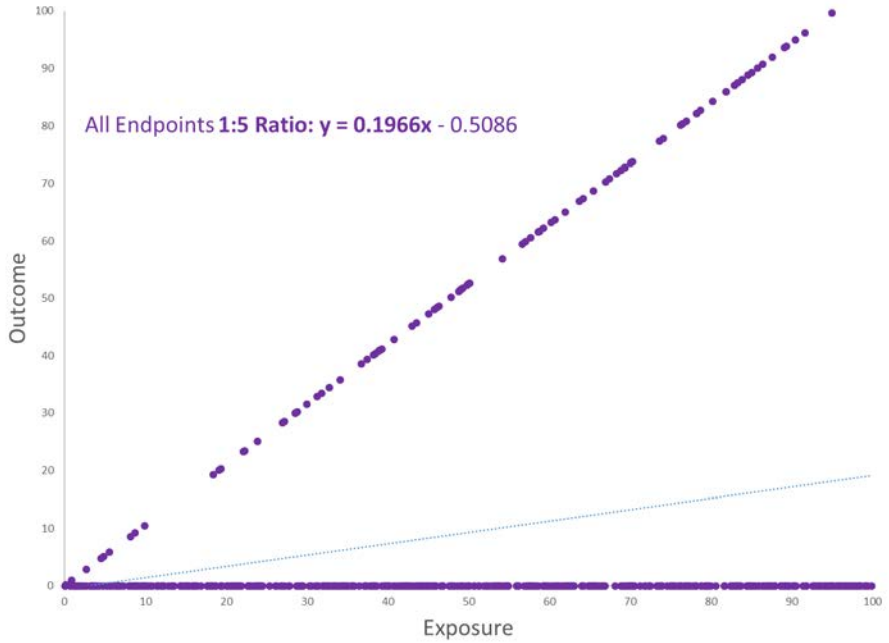
Specificity - Ratios

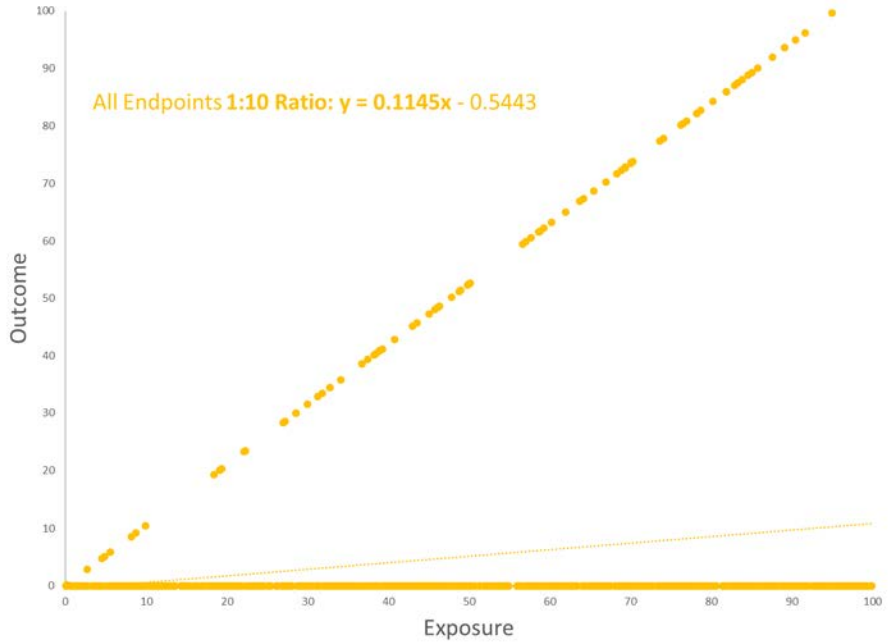
The higher the number of non-specific outcome endpoints, the greater the difference between specific and non-specific effect estimates.

Simulation Studies of Exposure-Outcome Relationship



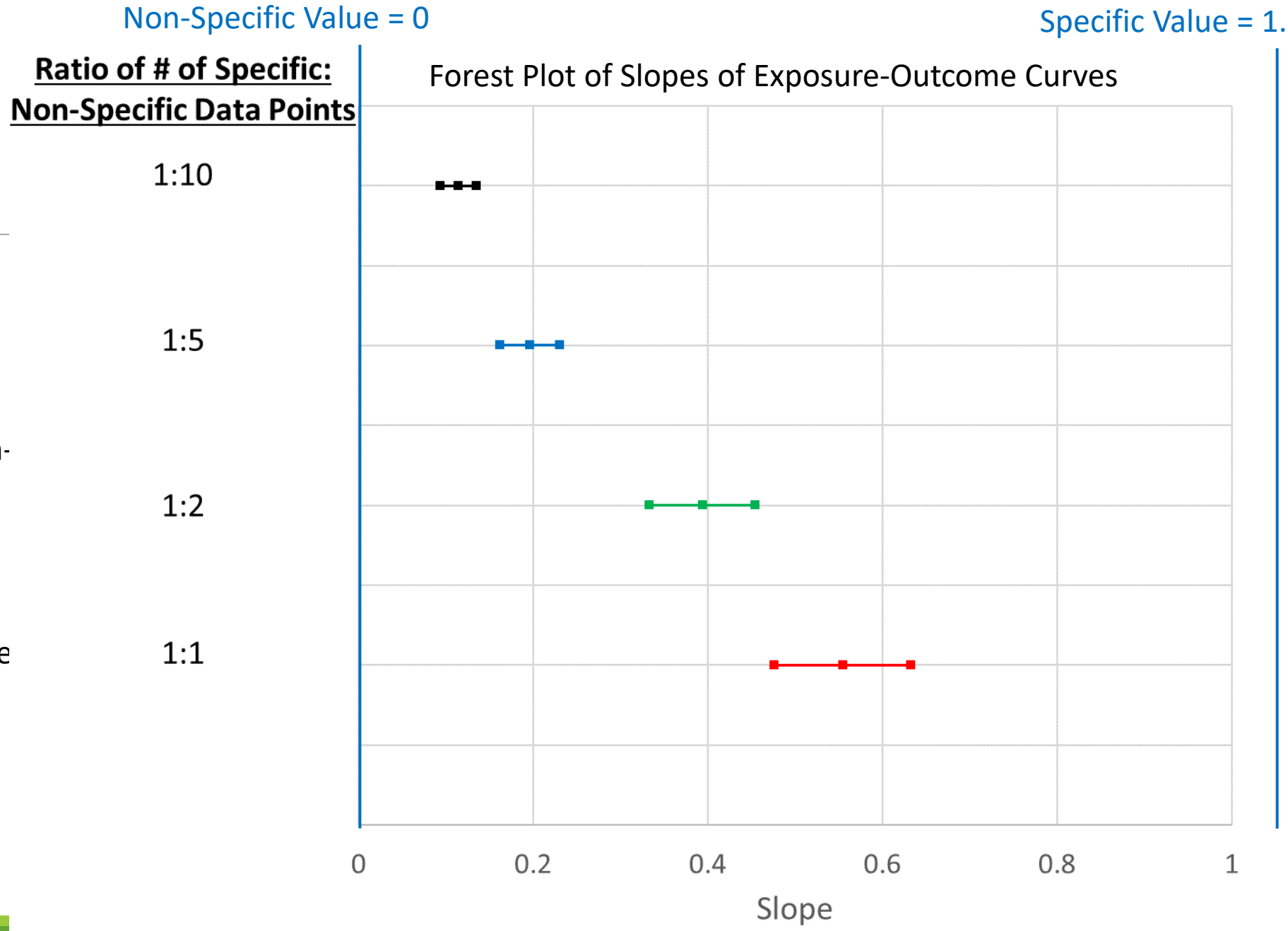






Specificity - Ratios

The higher the number of non-specific outcome endpoints, the greater the difference between specific and non-specific effect estimates, and the smaller the std error of the association.



Specificity: Application of Ratios?

- According to the simulations:

  Total Effect Estimate = Specific Effect Estimate x Non-Specific Effect Estimate x (Specific sample size/total sample size)

- Can we quantitatively use the observation that the greater the number of non-specific compared to specific endpoints, the greater the difference between the total and the specific effect estimates?

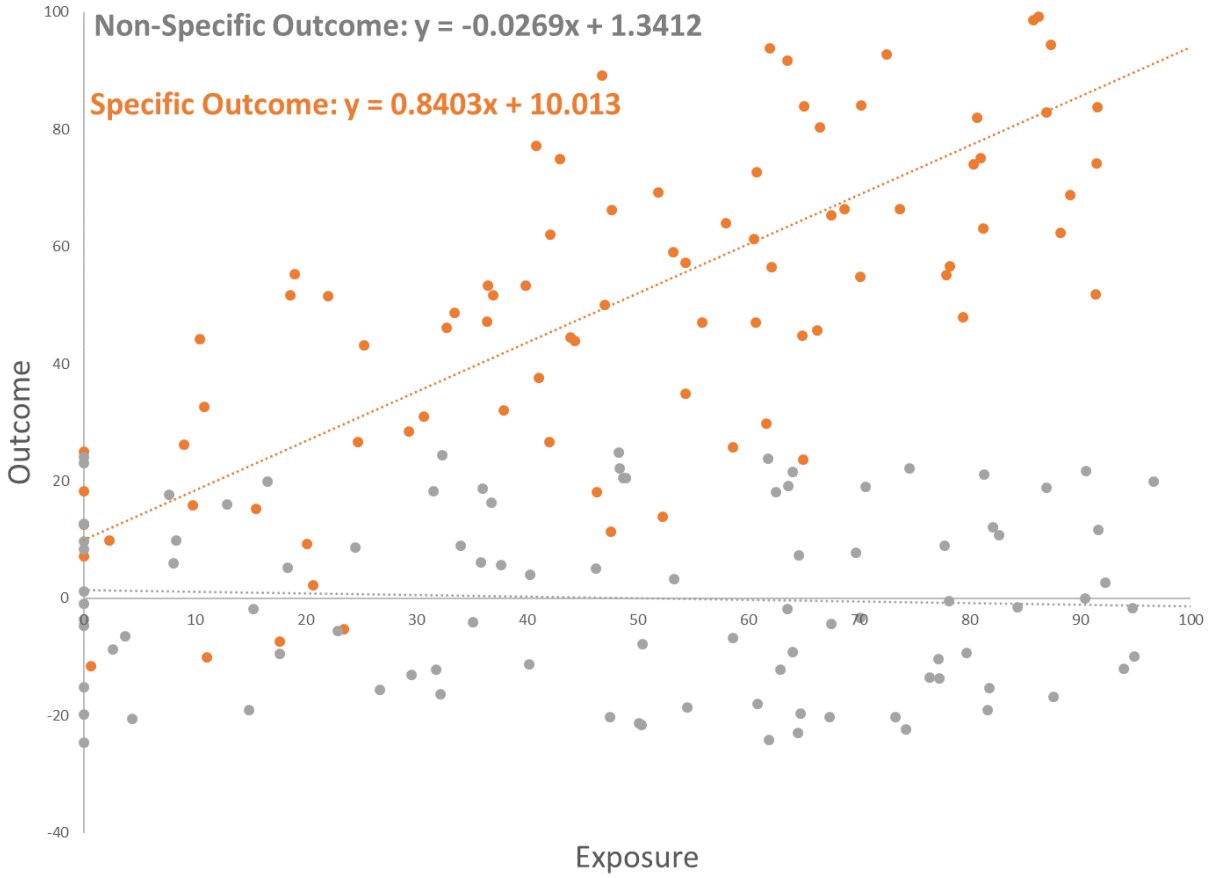
- E.g. 160 cancer cases, 60 lung cancer cases; lung cancer RR = 10

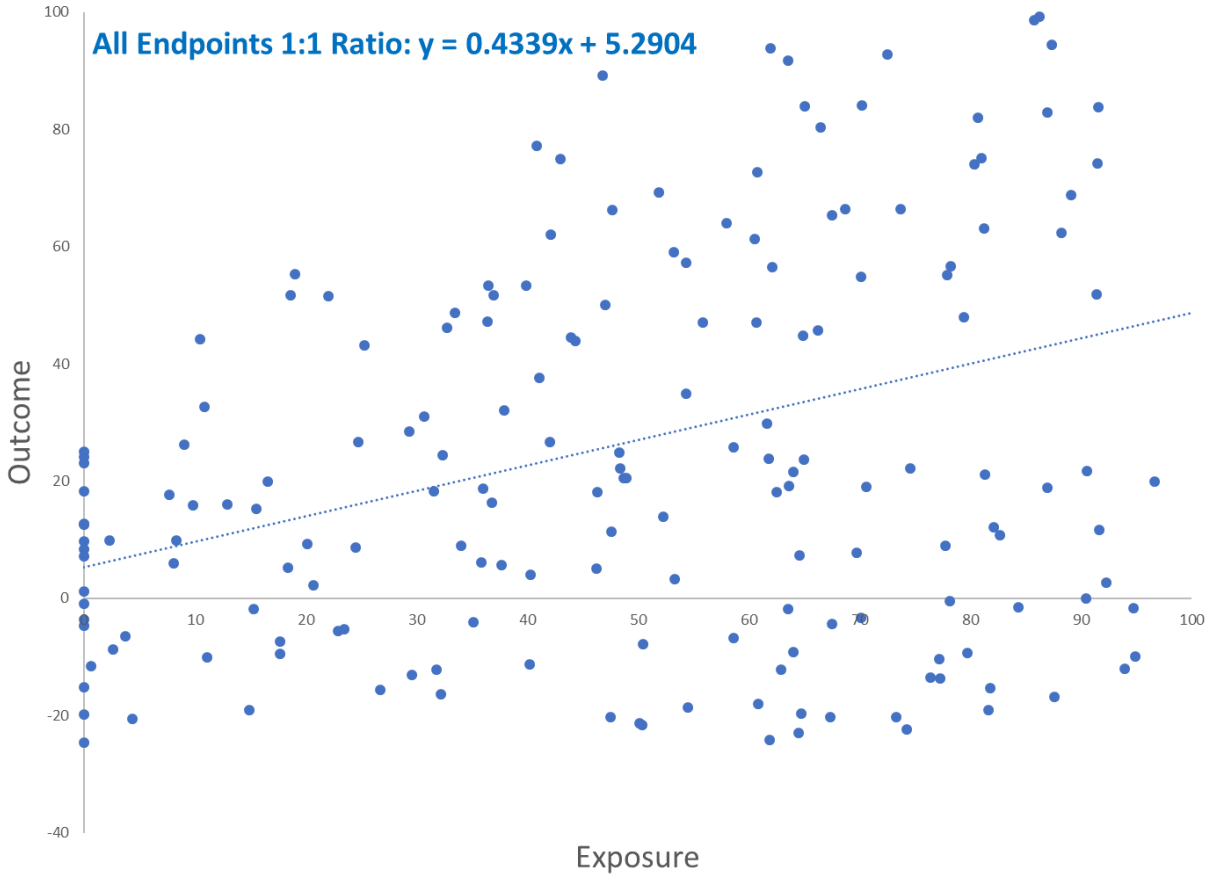
Assuming non-specific RR = 1: Total Effect Estimate = 10 x 1 x (60/160) = RR 3.75

Assuming non-specific RR = 1.5 (average): Total Effect Estimate = 10 x 1.5 x (60/160) = RR 5.625

Specificity – With Exposure & Outcome Error

Simulation Studies of Exposure-Outcome Relationship





Theoretical Basis: Specificity

- Patterns of effects of outcome specificity:
  - Added exposure error or outcome error doesn't change the difference between total and specific outcome
  - Having a small effect estimate does not seem to decrease the difference between the total and specific outcome
  - Higher number of non-specific outcome endpoints, the greater the difference between specific and non-specific effect estimates
  - All of these patterns are true for both linear and log-linear regression analyses
- What to look for:
  - Studies that investigate both more and less specific endpoints in the same group (e.g. all cancer and lung cancer, all mortality and CVD mortality, etc)
  - Based on this hypothesis, we would expect that if a specific endpoint is genuinely causally related to the exposure, that it should have a higher effect estimate compared to the less-specific endpoint group
  - In addition, the less common the specific outcome, the greater the expected differential compared to the effect estimate for the larger endpoint group

Request for Input

- Your thoughts about the utility of investigating patterns of outcome specificity in epidemiology studies?

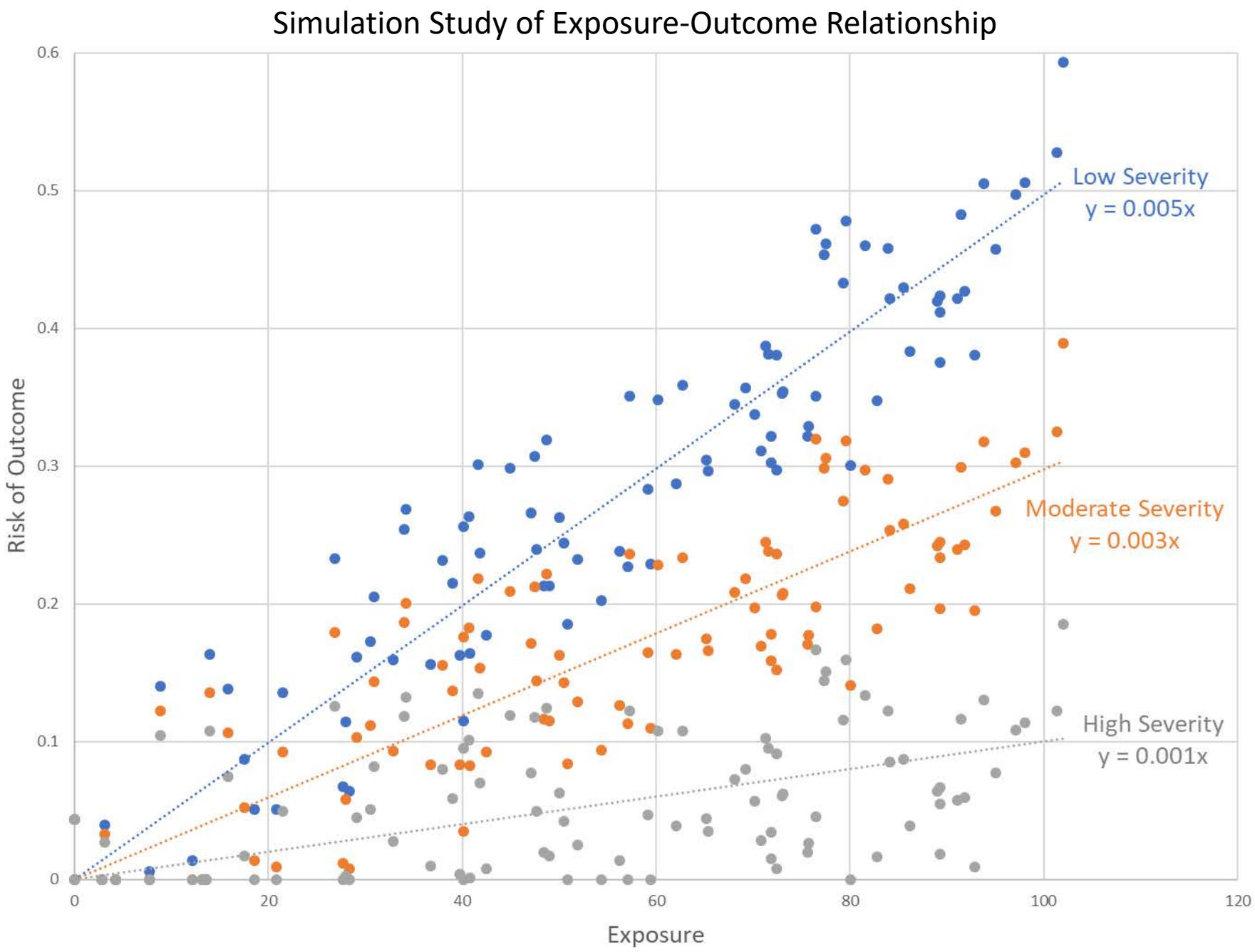
- Can the phenomenon of the ratios of specific to non-specific outcome data points affecting the magnitude of the difference in specific to total effect estimates be used as a predictive pattern?

Theoretical Basis: Severity

- **Concept**: Based on toxicological theory
  - Higher exposure concentrations should produce more severe health effects than lower exposure concentrations.
  - *At the same concentrations*, less severe health endpoints should show larger and less variable effect estimates than more severe health endpoints.
- Based on this theory, for linear and log-linear relationships without modeled thresholds, the slope of the relationship (and therefore the HR or RR) is steeper with less severe effects
- This also holds true with random error incorporated into the exposure or outcome variables
- Because this concept is based on the probability of an effect in the population, the severity hypothesis may not apply to case-control studies (that generates odds and odds ratios) because these studies do not provide probability information about the total population, just for the case and control groups

Severity

- E.g. For 100 units of exposure, the risk of a low severity effect is 0.5, of a moderate severity effect is 0.3, and of a high severity effect is 0.1



Request for Input

- Your thoughts about the utility of investigating patterns of outcome severity in epidemiology studies?

- Do other factors impacting severity (e.g. individual differences, access to health care or screening, etc) decrease the utility of the outcome severity pattern?

Positive and Negative Controls

"In theory, there is no difference between theory and practice. But in practice, there is."
--Jan L. A. van de Snepscheut

Positive Control: Smoking & Lung Cancer

- We tested for the presence of these patterns using a relationship that has been definitively causally established: smoking and lung cancer
- Patterns of dose-response and outcome specificity evaluated in 6 case-control or cohort studies
- Dose-Response: Freedman et al., 2008; Powell et al., 2013; Remen et al., 2018
- Outcome-Specificity: Lewer et al., 2017; Ordóñez-Mena et al., 2016; Thun et al., 2013

Dose-Response: Smoking & Lung Cancer

Exposure Variable	Ref Quantile	Quantile 2	Quantile 3	Quantile 4	Quantile 5	Evidence of Dose-Response?
Powell et al., 2013, Lung Cancer, Odds Ratios (95% CI)						
Smoking Quantity	**Never**	**Light**	**Moderate**	**Heavy**		
	1	9.32 (8.48-10.25)	11.78 (10.79-12.87)	15.02 (13.69-16.48)		✓
Remen et al., 2018, Lung Cancer in Women, Odds Ratios (95% CI)						
Duration of Smoking (yrs)	**Never (0)**	**0-20**	**20-30**	**30-40**	**> 40**	
	1	1.51 (0.74-3.04)	6.37 (3.55-11.41)	13.64 (8.19-22.74)	28.79 (16.86-49.16)	✓
Intensity of Smoking (cig/day)	**0**	**0-20**	**20-30**	**> 30**		
	1	6.05(3.70-9.90)	19.4(11.81-31.86)	18.2(10.10-32.80)		✓
Pack-years	**0**	**0-20**	**20-40**	**40-60**	**> 60**	
	1	2.04 (1.11-3.74)	8.66 (5.10-14.68)	25.48 (15.08-43.04)	37.39 (19.79-70.62)	✓
Cumulative Smoking Index (CSI)	**0**	**0 – 1**	**1 – 2**	**> 2**		
	1	1.25 (0.62-2.51)	11.98 (7.32-19.62)	29.66 (17.67-49.80)		✓

Dose-Response: Smoking & Lung Cancer

Exposure Variable	Ref Quantile	Quantile 2	Quantile 3	Quantile 4	Quantile 5	Evidence of Dose-Response?
Freedman et al., 2008, Lung Cancer in Current Smokers, Hazard Ratios (95% CI)						
Intensity of Smoking (cig/day) in Men	**Never (0)**	**1-10**	**11-20**	**21-30**	**31-40**	
	1	20.7 (16.3- 26.3)	30.5 (24.6-37.9)	35.9 (28.7- 44.8)	42.6 (33.8-53.8)	✓
Intensity of Smoking (cig/day) in Women	1	13.4 (10.9-16.5)	22.5 (18.8-27.1)	25.2 (20.5-31.0)	40.7 (32.3-51.2)	✓

Outcome Specificity: Smoking & Lung Cancer

Exposure Variable	Less Specific Outcome	More Specific Outcomes	
Lewer et al., 2017, Mortality, Ratio of age-adjusted mortality rate per 100,000 person years in smokers : never-smokers			
	Never Smoker	Ex-Smoker	Current Smoker
All-Cause Mortality	1	1.33	1.87
No. Cases	2059	2748	3842
Lung Cancer or COPD	1	5.17 ✓	13.25 ✓
No. Cases	60	310	795

Outcome Specificity: Smoking & Lung Cancer

Exposure Variable	Less Specific Outcome	More Specific Outcomes				
Thun et al., 2013, Mortality, Relative Risk of mortality among those 55-years or older, for current smokers compared to never smokers, 2000-2010 (95% CI)						
	All Cause Mortality	**Lung Cancer**	**COPD**			
Women	2.76 (2.69 -2.84)	25.66 (23.17-28.40)	22.35 (19.55-25.55)			
No. Cases	62965	4785	3034			
Men	2.80 (2.72-2.88)	24.97 (22.20-28.09)	25.61 (21.68-30.25)			
No. Cases	73800	6635 ✓	3478 ✓			
Ordóñez-Mena et al., 2016, Cancer Incidence or Mortality, Hazard ratio of current smokers compared to never-smokers (95% CI)						
	Total Cancer	**Lung Cancer**	**Head and Neck Cancer**	**Colorectal Cancer**	**Breast Cancer**	**Prostate Cancer**
Cancer Incidence	1.44 (1.28- 1.63)	13.1 (9.90- 17.3)	2.89 (1.98-4.21)	1.20 (1.07-1.34)	1.07 (1.00-1.15)	0.81 (0.72-0.91)
No. Cases	26007	6333	1051	2064	2536	3701
Cancer Mortality	2.19 (1.83-2.63)	11.5 (8.21-16.1)	3.74 (2.38-5.89)	1.35 (1.16-1.58)	1.28 (1.06-1.55)	1.26 (0.97-1.64)
No. Cases	13450	6165 ✓	359 ✓	912	466 ✗	589

Summary: Smoking & Lung Cancer

- Dose-Response: Overall ✓ **(evidence for dose-response pattern)**
  - Powell et al., 2013 - ✓
  - Remen et al., 2018 - ✓
  - Freedman et al., 2008 - ✓

- Outcome-Specificity: Overall ✓ **(evidence for outcome-specificity pattern)**
  - Lewer et al., 2017 - ✓
  - Thun et al., 2013 - ✓
  - Ordóñez-Mena et al., 2016 - ✓

Smoking and Lung Cancer – strong evidence of dose-response and outcome specificity patterns

Negative Control: Dietary Constituents & Cancer

- Multiple epidemiology studies conducted in the 1980s and 1990s demonstrated associations between, among others, lower β-carotene serum concentrations and lung cancer, retinol (vitamin A) and lung cancer, and α-tocopherol (vitamin E) and lung and prostate cancer.

- Multiple randomized controlled trials demonstrated that there was no causal relationship between these dietary constituents and cancer:
  - Beta-Carotene and Retinol Efficacy Trial (CARET) – 18,314 men and women randomly assigned placebo or 30 mg β-carotene plus 25000 IU retinyl palmitate (vitamin A) → terminated 21 months early because of an increase in lung cancer in the intervention group
  - Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study – 29,133 male smokers randomly assigned placebo, α-tocopherol (vitamin E), β-carotene, or both → no effect of α-tocopherol on lung cancer (but less prostate cancer → disproved in SELECT trials), β-carotene supplementation increased lung cancer incidence

Negative Control: Dietary Constituents & Cancer

- Patterns of dose-response and outcome specificity evaluated in 9 case-control or cohort studies
- Dose-Response:
  - B-Carotene: Comstock et al., 1991; Connett et al., 1989; Nomura et al., 1985; Wald et al., 1988
  - Retinol: Friedman et al., 1986; Menkes et al., 1986
- Outcome-Specificity:
  - B-Carotene: Wald et al., 1988; Connett et al., 1989; Knekt et al., 1990; Willett et al., 1984
  - Retinol: Connett et al., 1989; Knekt et al., 1990; Willett et al., 1984

Dose-Response: β-Carotene & Lung Cancer

Exposure Variable	Ref Quantile	Quantile 2	Quantile 3	Quantile 4	Quantile 5	Trend p-value	
Comstock et al., 1991, Lung Cancer Incidence (n = 99), Odds Ratio							
Serum Concentration	**1st (Highest)**	**2nd**	**3rd**	**4th**	**5th (Lowest)**	**Trend**	
	1	1.2	1.8	1.7	2.2	0.04	✓
Connett et al., 1989, Lung Cancer Deaths (n = 66), Odds Ratio							
Serum Concentration	**1st (Highest)**	**2nd**	**3rd**	**4th**	**5th (Lowest)**	**Trend**	
B-Carotene	1	2.17	2.72	1.6	2.32	0.08	✗

Dose-Response: β-Carotene & Lung Cancer

Exposure Variable	Ref Quantile	Quantile 2	Quantile 3	Quantile 4	Quantile 5	Trend p-value
Nomura et al., 1985, Lung Cancer Incidence (n = 74), Odds Ratio (95% CI)						
Serum Concentration	**1st (Highest)**	**2nd**	**3rd**	**4th**	**5th (Lowest)**	**Trend**
Unadjusted estimate	1	1.7 (0.6-4.7)	1.5 (0.5 - 4.1)	2.9 (1.1- 7.3)	3.4 (1.4 - 8.4)	0.004
Adjusted estimate	1	1.5 (0.5 - 4.1)	1.2 (0.4 - 3.5)	2.4 (0.9 - 6.2)	2.2 (0.8 - 6)	0.04
Wald et al., 1988, Lung Cancer Incidence (n = 50), Relative Risk compared to 'all' category						
Serum Concentration	**1st (Highest)**	**2nd**	**3rd**	**4th**	**5th (Lowest)**	**Trend**
	0.82	0.35	0.68	0.93	2	0.008

Outcome Specificity: β-Carotene & Lung Cancer

Exposure Variable	Less Specific Outcome	More Specific Outcomes				
Wald et al., 1988, Cancer Incidence, Percent Difference in Serum Concentration between Cases and Controls (Std Error)						
Serum Concentration	**All Cancer**	**Lung**	**Colorectal**	**Stomach**	**Bladder**	**CNS**
	- 10% (4)	- 22% (8)	- 11% (10)	-27 % (17)	- 9% (20)	- 10% (15)
No. Cases	271	50 ✓	30 ✗	13 ✓	15 ✗	17 ✗
Connett et al., 1989, Cancer Deaths, Mean Difference in Serum Concentration between Cases and Controls						
Serum Concentration (µg/dL)	**All Cancer**	**Lung**	**GI Tract**			
B-Carotene	-0.6	-2.70	0.6			
No. Cases	156	66 ✓	28 ✗			

Outcome Specificity: β-Carotene & Lung Cancer

Exposure Variable	Less Specific Outcome	More Specific Outcomes			
Knekt et al., 1990, Cancer Incidence, Mean Difference in Serum Concentration between Cases and Controls (Std Error)					
Serum Concentration (µg/L)	All Cancer	Lung	Stomach	Prostate/ Breast	
Men	-11.8	-17.2 ✓	-7.4 ✗	-0.4 ✗	
No. Cases	453	144	48	37	
Women	-7	-40 ✓	27 ✗	-18.8 ✓	
No. Cases	313	8	28	67	
Willett et al., 1984, Cancer Incidence, Carotenoids, Mean Difference in Serum Concentration between Cases and Controls (Std Error)					
Serum Concentration (µg/L)	All Cancer	Lung	Breast	Prostate	GI
	8.2 (6.4)	9 (16.5)	8.9 (17.2)	4.3 (19.4)	10.5 (19.9)
No. Cases	111	17 ✗	14 ✗	11 ✗	11 ✗

Summary: β-Carotene & Lung Cancer

- Dose-Response: Overall ~ **(equivocal pattern of dose-response)**
  - Comstock et al., 1991 - ✓
  - Connett et al., 1989 - ✘
  - Nomura et al., 1985 - ~ unadjusted & ~ adjusted
  - Wald et al., 1988 - ~
- Outcome-Specificity: Overall ✓ **(evidence for outcome-specificity pattern)**
  - Wald et al., 1988 - ✓
  - Connett et al., 1989 - ✓
  - Knekt et al., 1990 - ✓ men & ✓ women (only 8 cases)
  - Willett et al., 1984 - ✘

Dose-Response: Retinol & Lung Cancer

Exposure Variable	Ref Quantile	Quantile 2	Quantile 3	Quantile 4	Quantile 5	Trend p-value	
Friedman et al., 1986, Lung Cancer Incidence (n = 151), Odds Ratio							
Serum Concentration	**1st (Highest)**	**2nd**	**3rd**	**4th**	**5th (Lowest)**	**Trend**	
Unmatched analysis	1	1.4	1.1	0.9	1.2		✗
Matched analysis	1	1.3	1.1	0.9	1.2		✗
Menkes et al., 1986, Lung Cancer Incidence (n = 99), Odds Ratio							
Serum Concentration	**1st (Highest)**	**2nd**	**3rd**	**4th**	**5th (Lowest)**	**Trend**	
	1	1.62	0.73	0.92	1.13	0.68	✗

Outcome Specificity: Retinol & Lung Cancer

Exposure Variable	Less Specific Outcome	More Specific Outcomes			
Knekt et al., 1990, Cancer Incidence, Mean Difference in Serum Concentration between Cases and Controls (Std Error)					
Serum Concentration (µg/L)	All Cancer	Lung	Rectum	Stomach	Prostate/ Breast
Men	-22	-38 ✓	-41 ✓	-19 ✗	16 ✗
No. Cases	453	144	15	48	37
Women	-17	24 ✗	-30 ✓	4 ✗	-22 ~
No. Cases	313	8	22	28	67
Willett et al., 1984, Cancer Incidence, Mean Difference in Serum Concentration between Cases and Controls (Std Error)					
Serum Concentration (µg/L)	All Cancer	Lung	Breast	Prostate	GI
	-0.6 (2.5)	7.4 (6.3)	5.4 (6.6)	1.7 (7.5)	-18.4 (7.7)
No. Cases	111	17 ✗	14 ✗	11 ✗	11 ✓
Connett et al., 1989, Cancer Deaths, Mean Difference in Serum Concentration between Cases and Controls					
Serum Concentration (µg/dL)	All Cancer	Lung			
	-1	-3.1			
No. Cases	156	66 ✓			

Summary: Retinol & Lung Cancer

- Dose-Response: Overall ✘ **(no dose-response pattern)**
  - Friedman et al., 1986 - ✘ matched & ✘ unmatched analyses
  - Menkes et al., 1986 - ✘
- Outcome-Specificity: Overall ~ **(equivocal pattern of outcome-specificity)**
  - Knekt et al., 1990 - ✓ men & ✘ women (only 8 cases)
  - Willett et al., 1984 - ✘
  - Connett et al., 1989 - ✓

Request for Input

- Your thoughts about interpreting unclear evidence of patterns of dose-response and outcome specificity?

- Your thoughts about integrating the evidence among and between hypothesized patterns?

Summary: Positive and Negative Controls

Lung Cancer	Smoking	β-Carotene	Retinol
Dose-Response	✓	~	✗
Outcome Specificity	✓	✓	~

- Positive Control: Smoking and Lung Cancer – strong evidence of dose-response and outcome specificity patterns
- Negative Control: β-Carotene and Lung Cancer – equivocal evidence of dose-response pattern, evidence of outcome specificity pattern
- Negative Control: Retinol and Lung Cancer – no evidence of dose-response pattern, equivocal evidence of outcome specificity pattern

Conclusions

- Theory and simulation studies demonstrate a basis for patterns of dose-response and outcome specificity in epidemiology study results; possibly show a pattern for outcome severity; and suggest that exposure and outcome error should not be used for predicting patterns of study results
- The patterns of dose-response and outcome specificity are observed in the positive control of smoking and lung cancer
- The pattern of dose-response is equivocal or not present in the negative controls of β-carotene or retinol and lung cancer
- The pattern of outcome specificity is present or equivocal in the negative controls of β-carotene or retinol and lung cancer

Future Work

- Incorporate a study quality component for study inclusion before investigating hypothesized patterns
- Further develop the theory of the outcome severity pattern
- Consider the difference between whether a causal relationship could still exist in the absence of these patterns, or if a non-causal relationship could exist in the presence of these patterns
- Further investigate the positive and negative control scenarios for these patterns, including assumptions about the ratios of specific to non-specific outcomes
- And…?

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Dose-Response: α-Tocopherol & Lung Cancer

Exposure Variable	Ref Quantile	Quantile 2	Quantile 3	Quantile 4	Quantile 5	Trend p-value
Comstock et al., 1991, Cancer Incidence, Odds Ratio						
Serum Concentration	**1st (Highest)**	**2nd**	**3rd**	**4th**	**5th (Lowest)**	**Trend**
Lung (n = 99)	1	1.3	2.2	1.9	2.5	0.04
Prostate (n = 103)	1	1.6	1.4	1.1		0.94

Outcome Specificity: α-Tocopherol & Lung Cancer

Exposure Variable	Less Specific Outcome	More Specific Outcomes			
Willett et al., 1984, Cancer Incidence, Mean Difference in Serum Concentration between Cases and Controls (Std Error)					
Serum Concentration (mg/dL)	**All Cancer**	**Lung**	**Breast**	**Prostate**	**GI**
	-0.05 (0.06)	0.13 (0.15)	-0.16 (0.17)	-0.09 (0.19)	-0.15 (0.2)
No. Cases	111	17 ✘	14 ~	11 ~	11 ~
Connett et al., 1989, Cancer Deaths, Mean Difference in Serum Concentration between Cases and Controls					
Serum Concentration (mg/dL)	**All Cancer**	**Lung**			
	0.03	-0.06			
No. Cases	156	66 ✓			

Summary: α-Tocopherol & Lung Cancer

- Dose-Response: Overall **~ (equivocal pattern of dose-response)**
  - Comstock et al., 1991 - ~
- Outcome-Specificity: Overall **~ (equivocal pattern of outcome-specificity)**
  - Willett et al., 1984 - ✘
  - Connett et al., 1989 - ✓