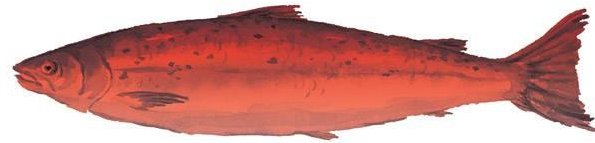


Red Herrings Cause Alzheimer's Disease

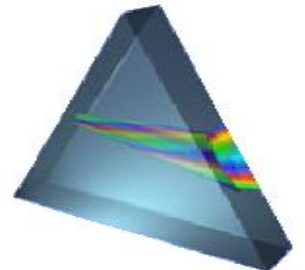


MEDS Conference
January 27th, 2018



UNIVERSITY
OF MANITOBA

Shawn Bugden
College of Pharmacy
Rady Faculty of Health Science
University of Manitoba



Faculty/Presenter Disclosure

- **Relationships with commercial interests:**
 - **No Conflicts to Declare**

Red Herrings



red her·ring

' ,red 'heriNG/

noun

plural noun: **red herrings**

1.

a dried smoked herring, which is turned red by the smoke.

2.

something, especially a clue, that is or is intended to be misleading or distracting.



Red Herrings



red her·ring

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plural noun: **red herrings**



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Red Herrings?



Original Investigation

Association of Proton Pump Inhibitors With Risk of Dementia A Pharmacoepidemiological Claims Data Analysis

Willy Gomm, PhD; Klaus von Holt, MD, PhD; Friederike Thomé, MSc; Karl Broich, MD; Wolfgang Maier, Anne Fink, MSc; Gabriele Doblhammer, PhD; Britta Haenisch, PhD

JAMA Neurol. 2016;73(4):410-416.



CONCLUSIONS AND RELEVANCE The avoidance of PPI medication may prevent the development of dementia.

What does that look like?



The Take Home

An advertisement for Life Matters. The background is a photograph of an elderly couple walking away from the camera on a sandy beach. The woman is on the left, wearing a white long-sleeved shirt and tan pants. The man is on the right, wearing a white long-sleeved shirt and blue pants. They are walking towards the ocean under a clear blue sky. The text is overlaid on the right side of the image.

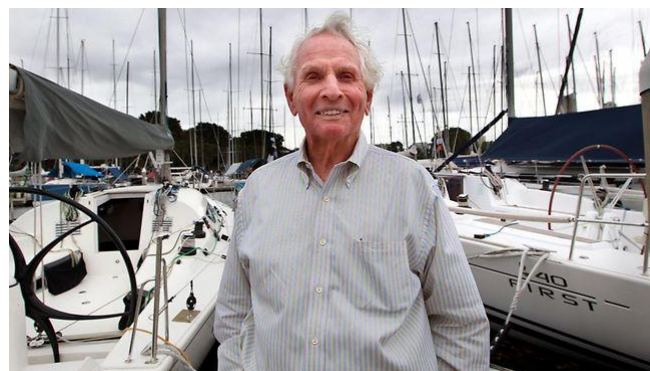
PROTON PUMP INHIBITORS
CAN INCREASE RISK OF
DEMENTIA
BY **44%**

 LIFE MATTERS

Consequences



- TB is an octagenarian who is a regular user of PPIs for Stage C Reflux
- His PPI is stopped by his family doctor in response to family concerns about cognitive decline



Consequences



- ❑ A few months later TB presents with heartburn and difficulty swallowing
- ❑ Endoscopy reveals stricture
- ❑ Harmed by “fake news”



Fake News?



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JAMA Neurol. 2016;73(4):410-416.

Risk Factor	Risk of Incident Dementia	
	HR (95% CI)	P Value
PPI use calculated ^a		
With potential confounding factors	1.44 (1.36-1.52)	<.001



Fake News?



Original Investigation

Association of Proton Pump Inhibitors With Risk of Dementia A Pharmacoepidemiological Claims Data Analysis

Willy Gomm, PhD; Klaus von Holt, MD, PhD; Friederike Thomé, MSc; Karl Broich, MD; Wolfgang Maier, MD;
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JAMA Neurol. 2016;73(4):410-416.

**Observational
Studies**



Meta-analysis of RCTs



Individual RCT



Observational Studies (Patient Important Outcomes)



Basic Research
(Test tube, animal/human physiology)



Clinical Experience
(Non-systematic clinical observation)

Sir Austin Bradford Hill



Validate cause and effect

1. Biologically Plausible
2. Be Strong
3. Reflect a biological gradient – dose response relationship
4. Be found consistently
5. Hold over time – temporal incidence of the disease should reflect prevalence of offending agent
6. Confirmed by experiment



Sir Austin Bradford Hill

Sir Austin Bradford Hill



Validate cause and effect

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Sir Austin Bradford Hill

Biologically Plausible?

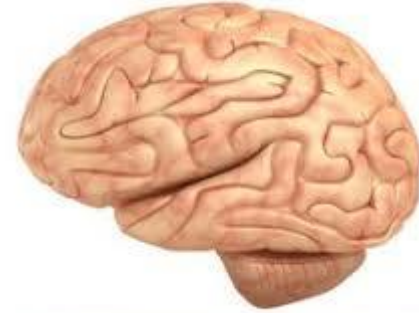


ONCE
upon a
TIME

Biologically Plausible?



- PPIs cross BBB so could directly effect brain



Biologically Plausible?



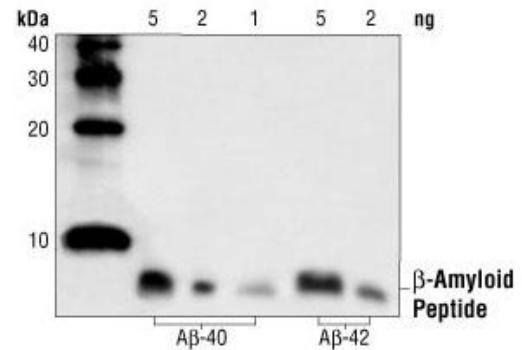
- Increased A β levels in amyloid cell model in mice brains.
- Inverse γ -secretase modulation in combination with augmented β -secretase BACE1 activity leads to accumulation of A β peptides which are a major pathological sign of dementia



Biologically Plausible?



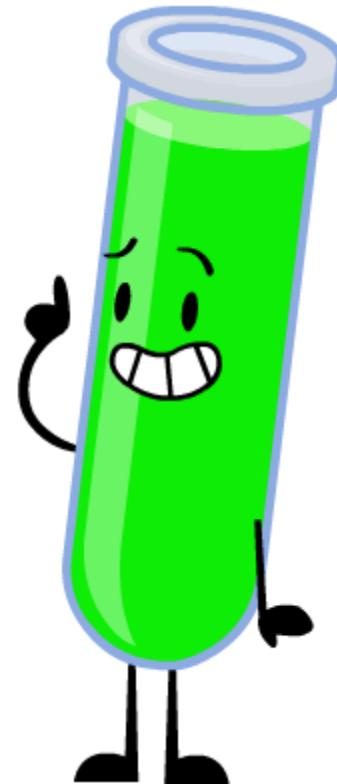
- Modulation of degradation of A β by lysosomes in microglia
Fibrillar A β clearance is pH dependent. So the vacuolar—type H⁺ ATPase mediate this acidification.
- PPIs inhibit V-ATPase.
Reduce A β degradation and increase A β levels



Biologically Plausible?



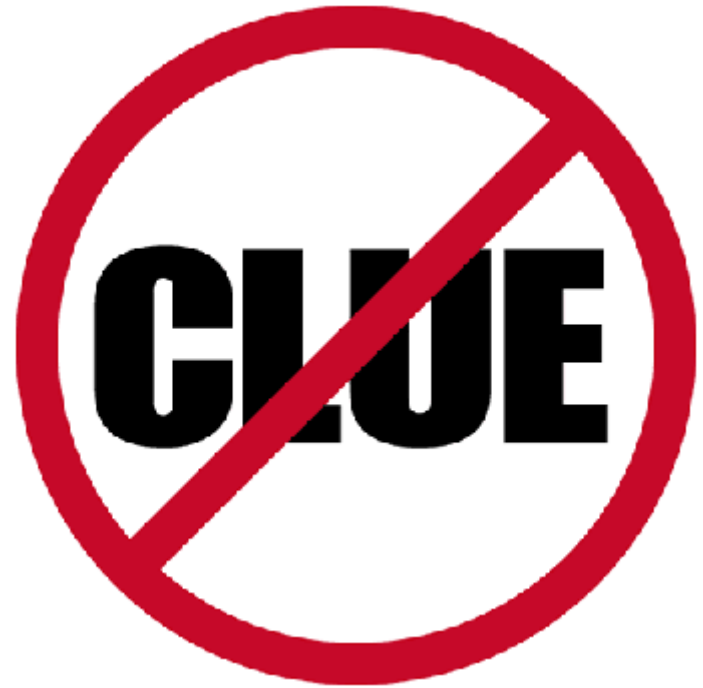
- PPIs associated with vitamin B12 deficiency which is associated with lower cognition and neurological damage via impaired DNA synthesis and methylation



Biologically Plausible?



ONCE
upon a
TIME



Sir Austin Bradford Hill



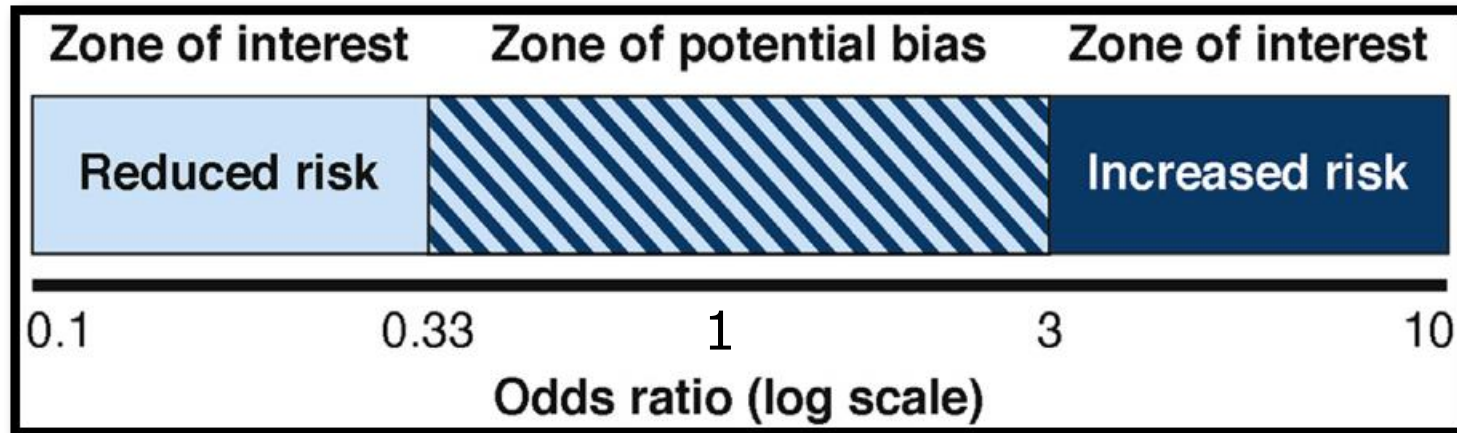
Validate cause and effect

1. Biologically Plausible
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3. Reflect a biological gradient – dose response relationship
4. Be found consistently
5. Hold over time – temporal incidence of the disease should reflect prevalence of offending agent
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Sir Austin Bradford Hill

Strong?



No difference



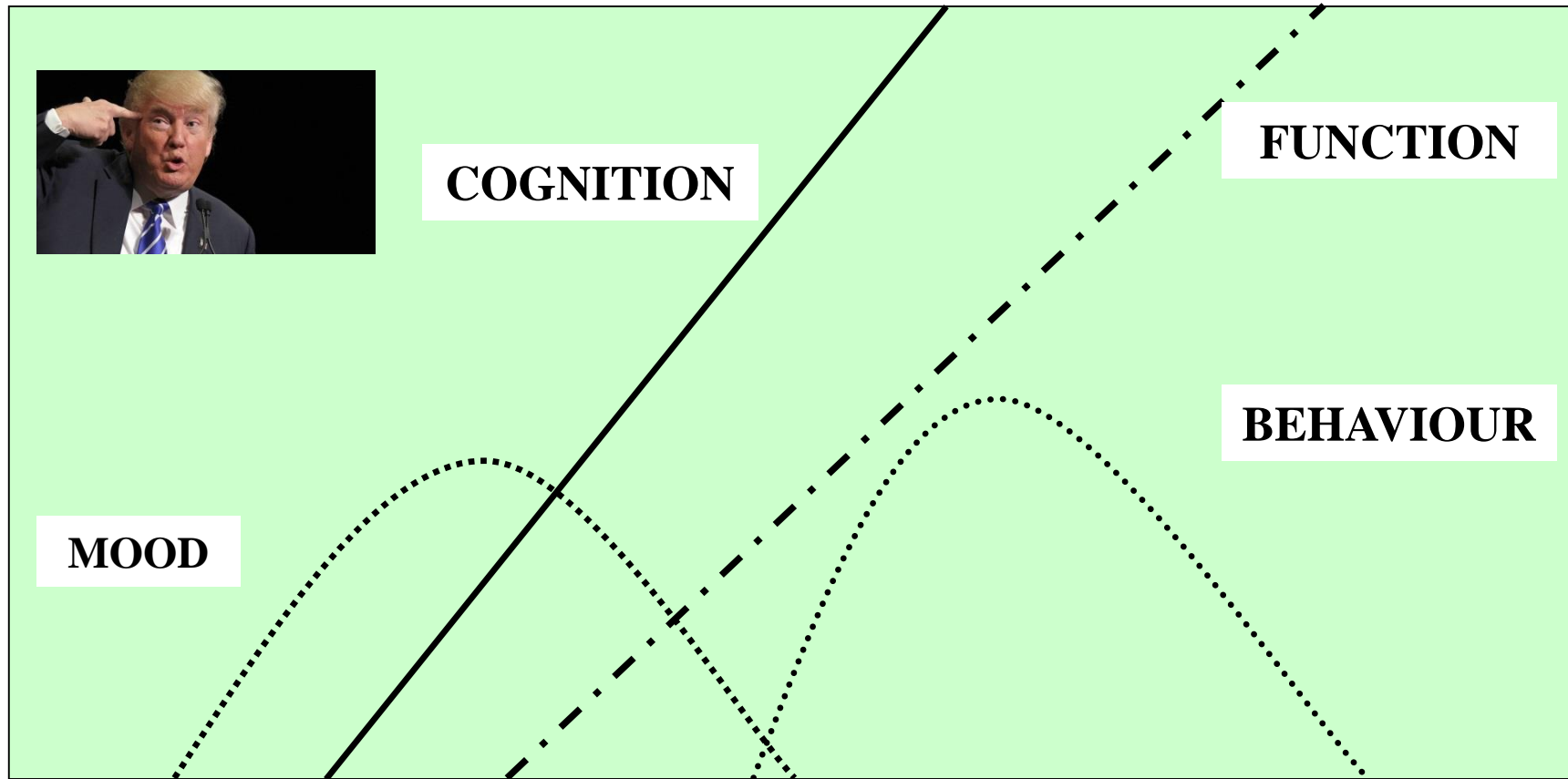
1.44
95% CI
1.36 to 1.52

Data base
Large Number
Greater Precision
BUT Not Greater Validity
Precisely Wrong Answer
Selection Bias
Inadequate Control of
Confounding

Natural History of ALZ



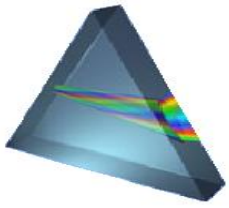
Deterioration



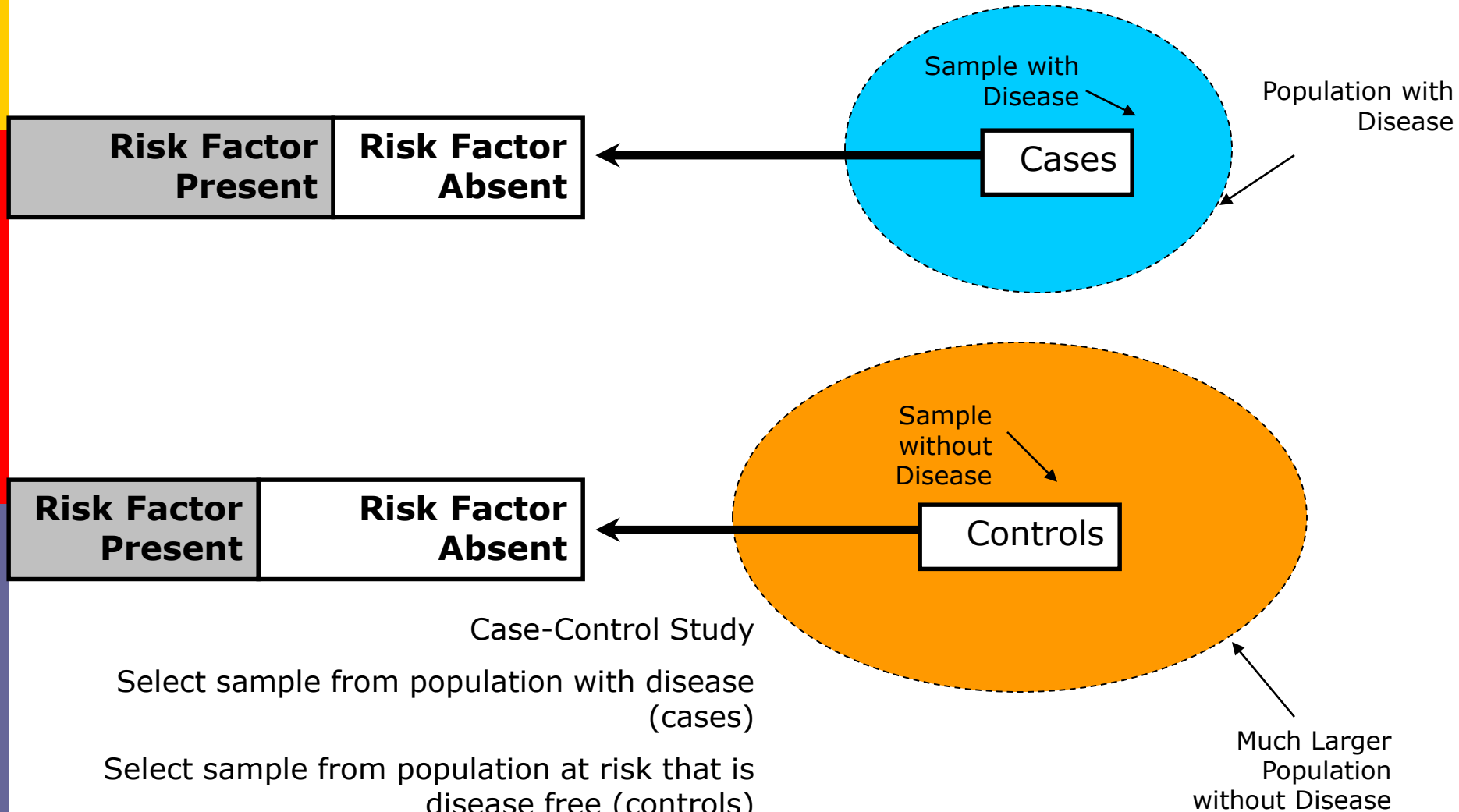
TIME

Brody et al. 2003. J. Clin Psychiatry 64:36.

<http://www.ucc.ie/en/>



Protopathic Bias

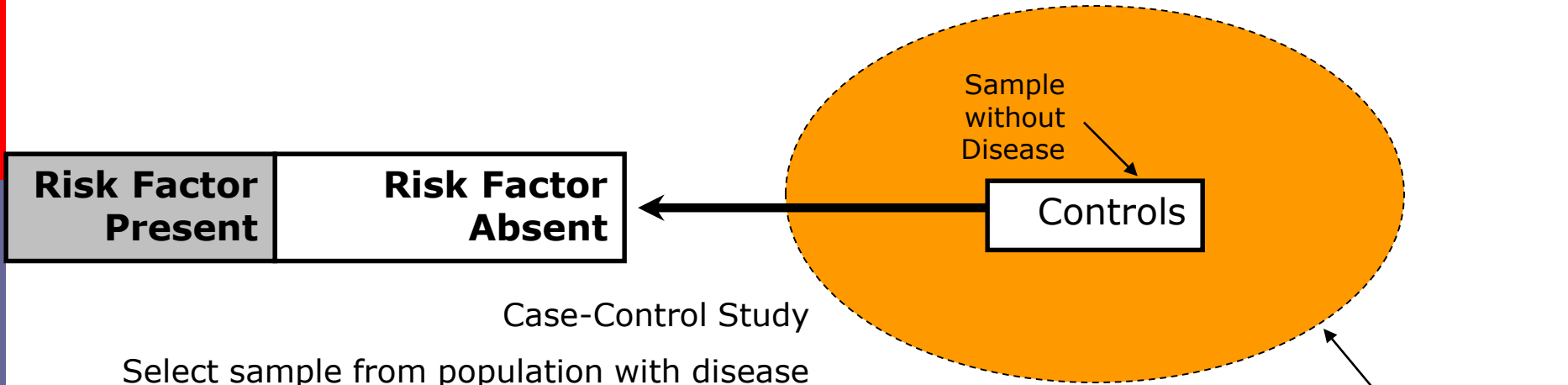
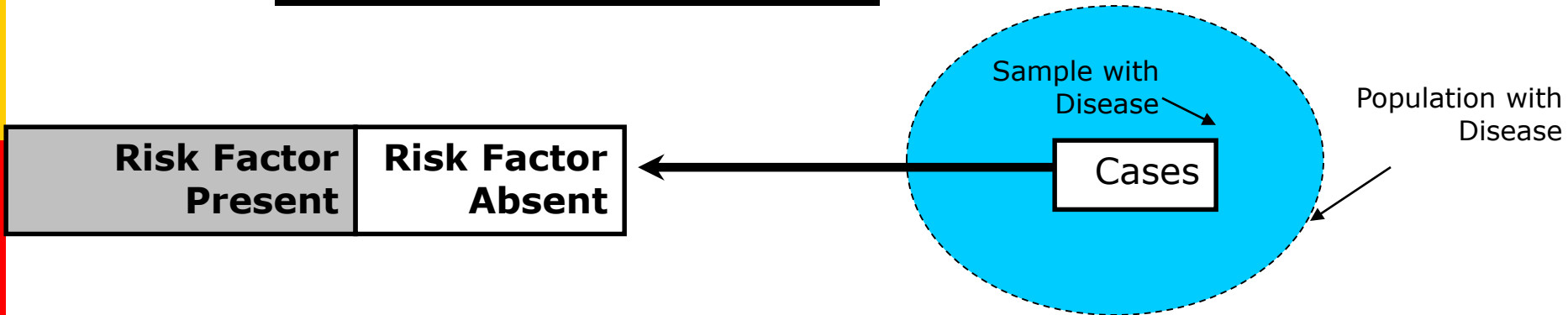


Case-Control Study

Select sample from population with disease (cases)

Select sample from population at risk that is disease free (controls)

Measures Predictor variables



Case-Control Study

Select sample from population with disease (cases)

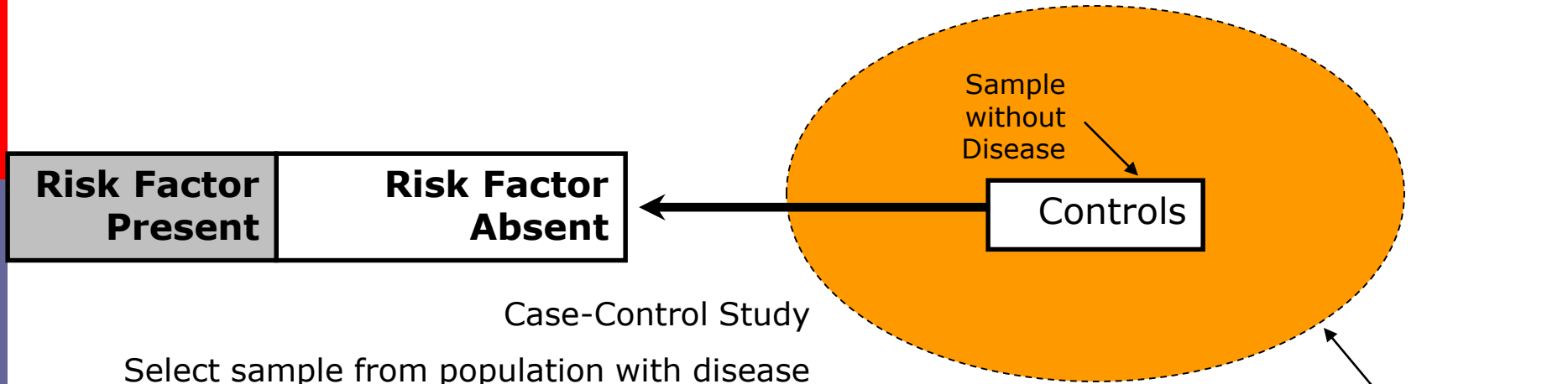
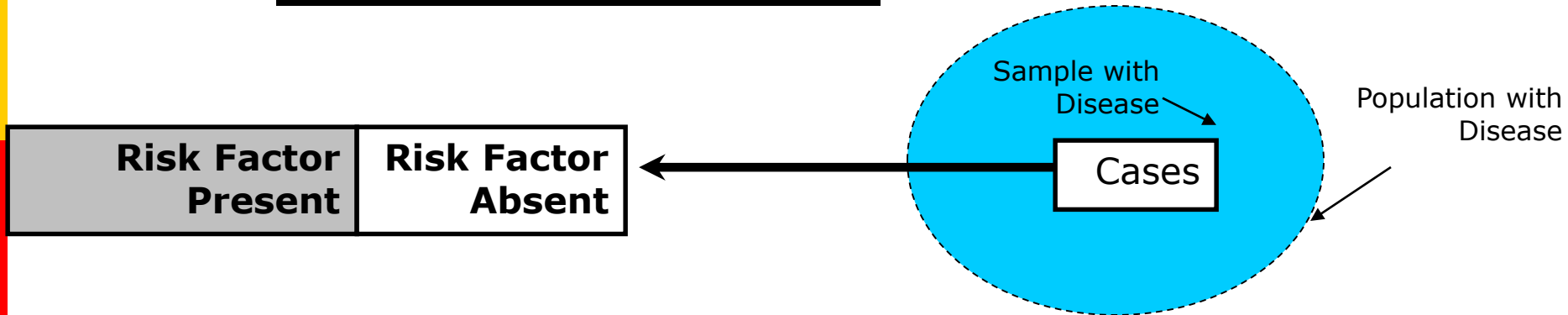
Select sample from population at risk that is disease free (controls)

Measures Predictor variables

Pre - ALZ symptoms sleeping pills – benzodiazepines, PPIs?

Diagnosis of ALZ

15 Plus Years



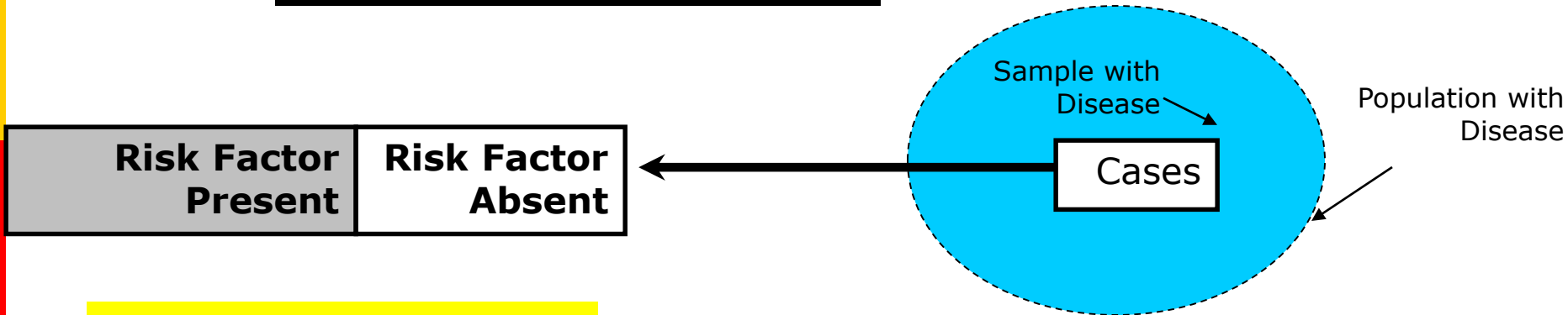
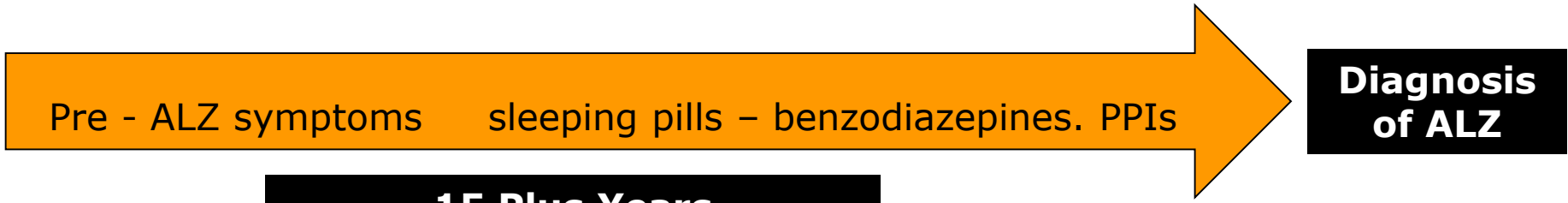
Case-Control Study

Select sample from population with disease (cases)

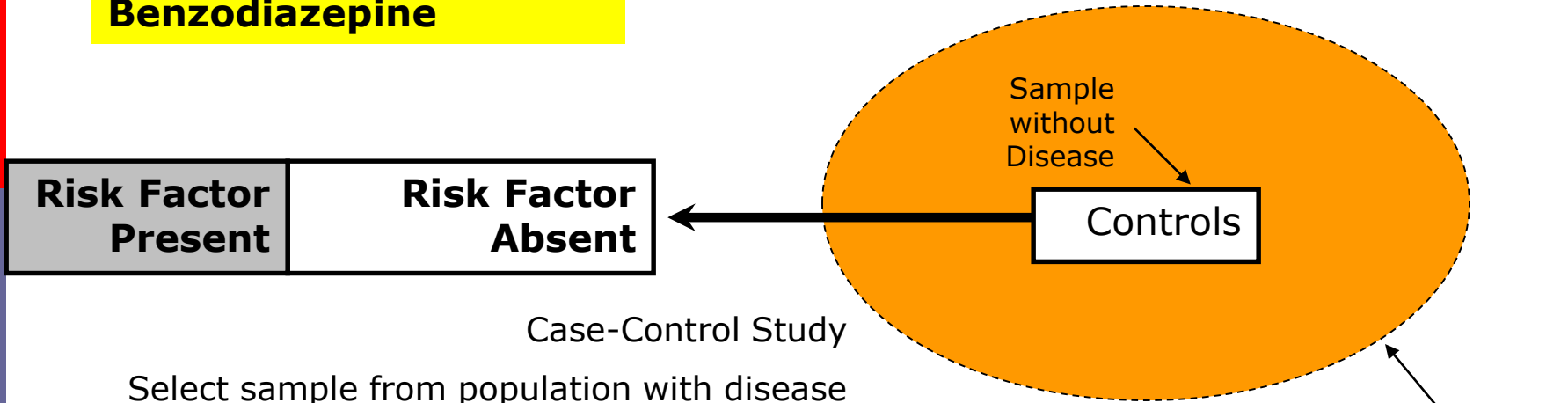
Select sample from population at risk that is disease free (controls)

Measures Predictor variables

Much Larger Population without Disease



Benzodiazepines +++
Benzodiazepine



Case-Control Study

Select sample from population with disease (cases)

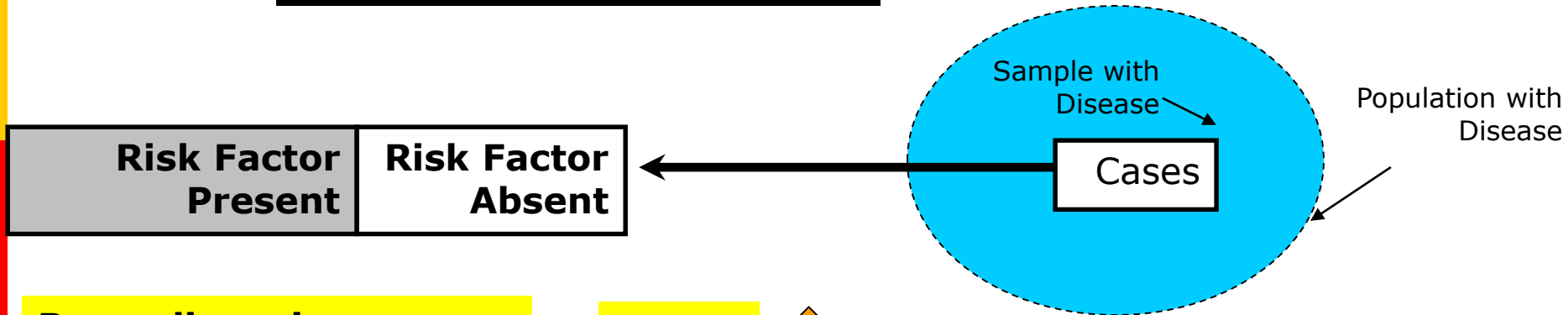
Select sample from population at risk that is disease free (controls)

Measures Predictor variables

Pre - ALZ symptoms sleeping pills – benzodiazepines, PPIs

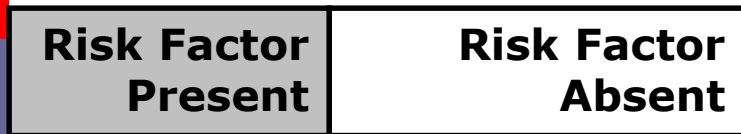
Diagnosis of ALZ

15 Plus Years



Benzodiazepines +++
Benzodiazepine

RISK



Case-Control Study

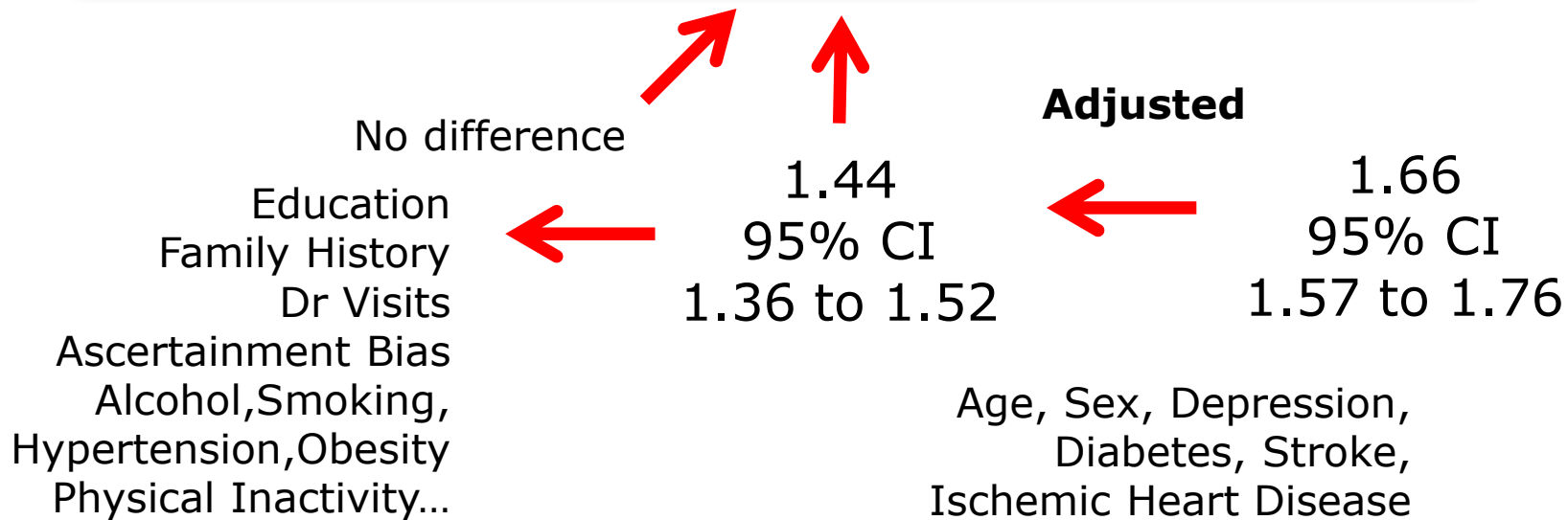
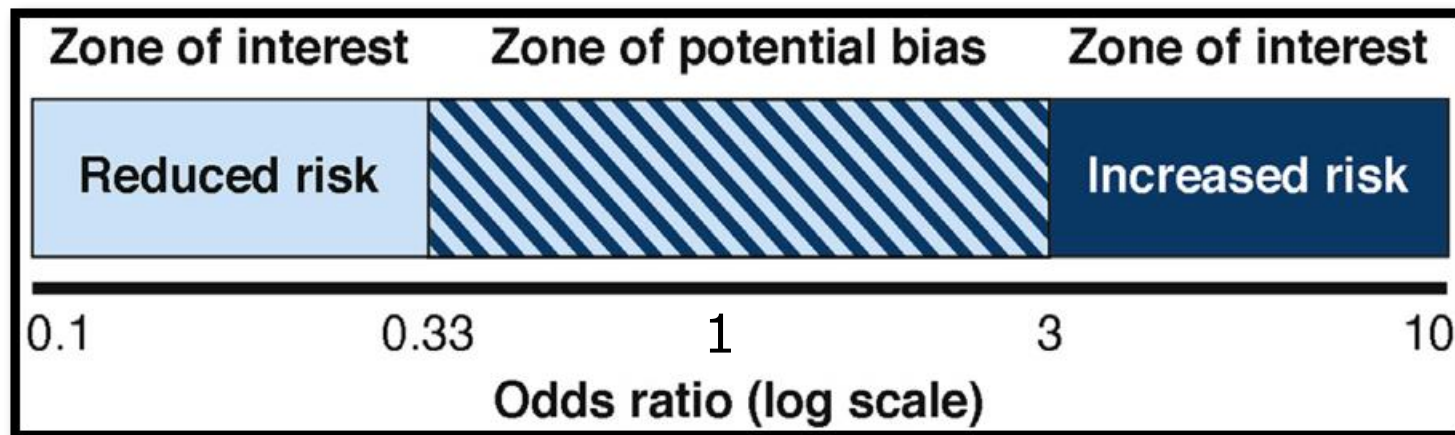
Select sample from population with disease (cases)

Select sample from population at risk that is disease free (controls)

Measures Predictor variables

Much Larger Population without Disease

Strong?



Sir Austin Bradford Hill



Validate cause and effect

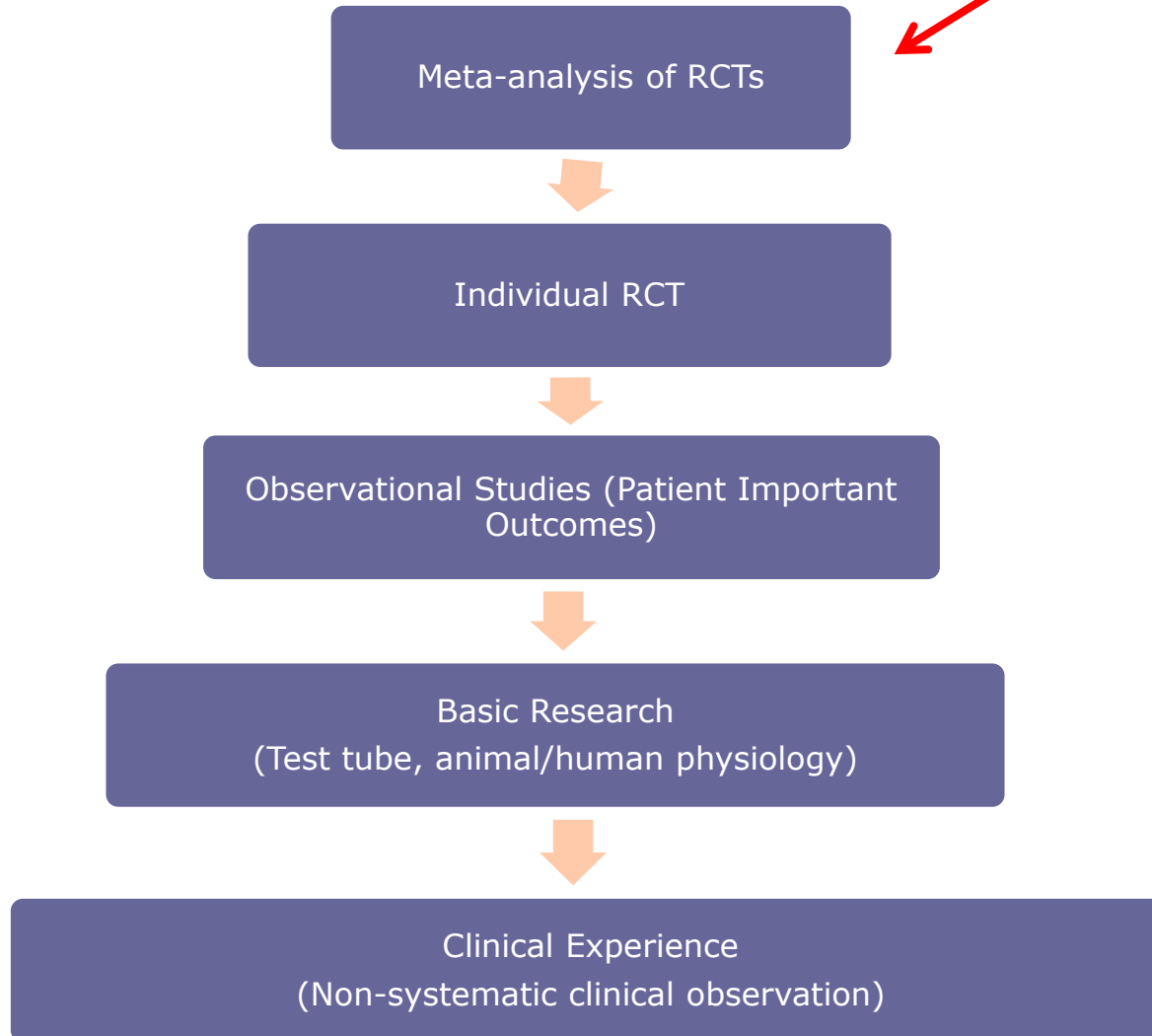
1. Biologically Plausible
2. Be Strong
3. Reflect a biological gradient – dose response relationship
4. **Be found consistently**
5. Hold over time – temporal incidence of the disease should reflect prevalence of offending agent
6. Confirmed by experiment



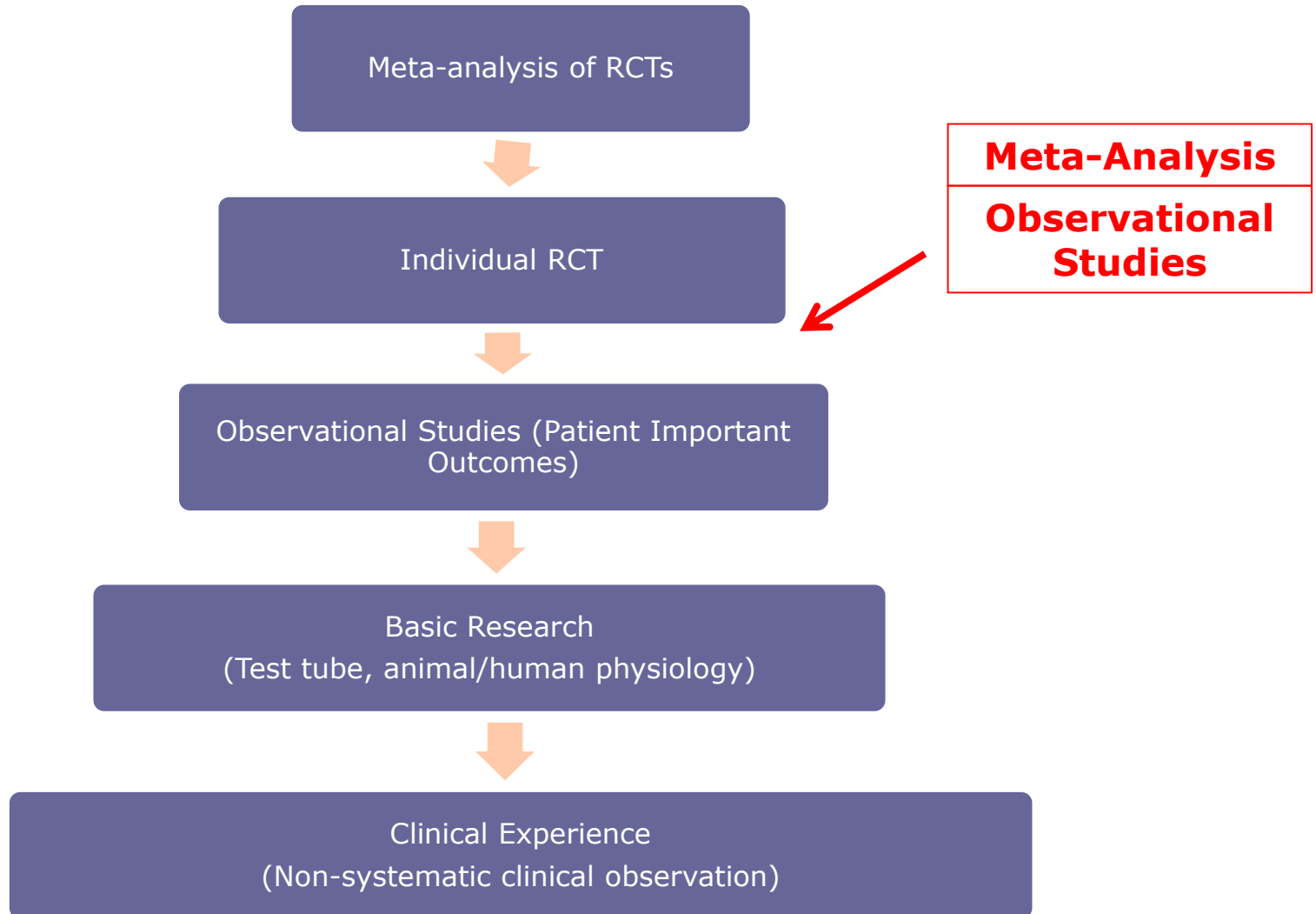
Sir Austin Bradford Hill

Hierarchy of Evidence

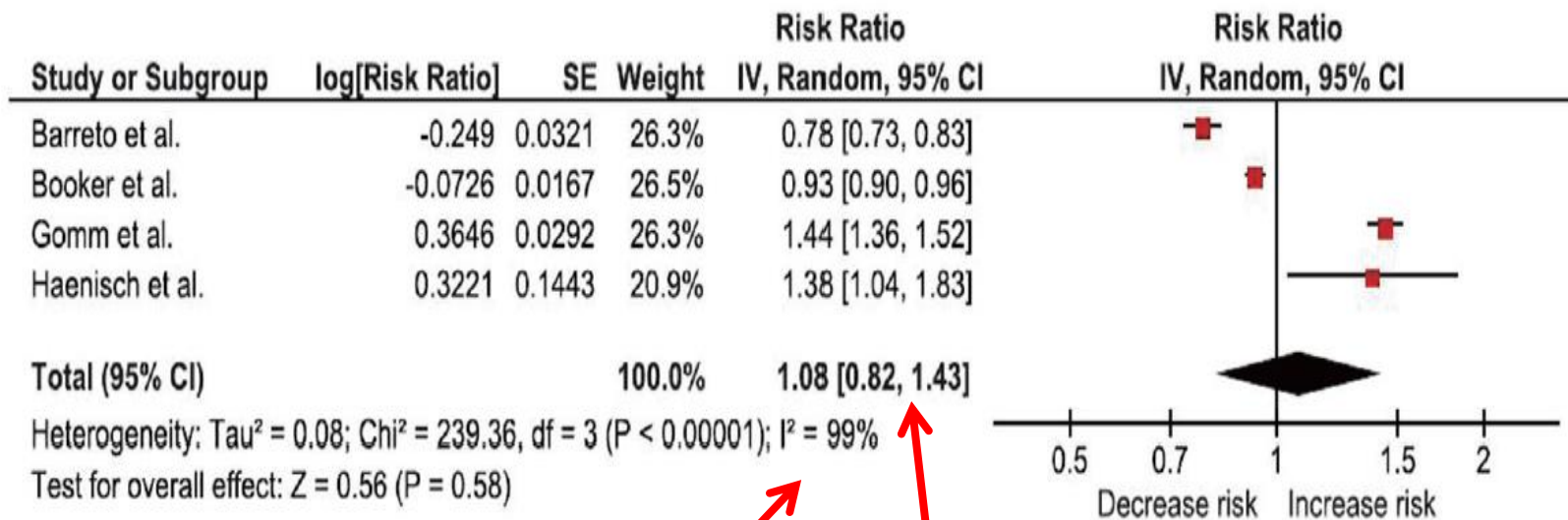
Meta-Analysis



Hierarchy of Evidence



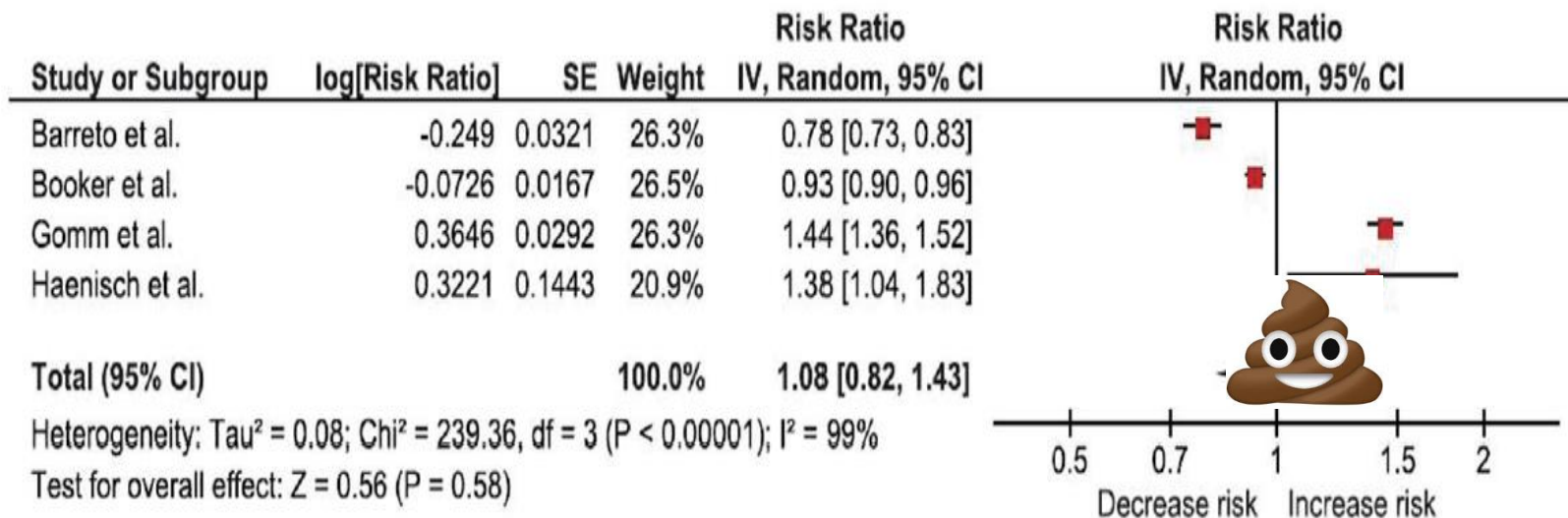
Consistent?



Heterogeneity

Not Significant

Consistent?



Consistent?



Composite score	No PPI use	1–4 y	5–8 y	9–14 y
Psychomotor speed, attention (n)	(9235)	(2328)	(1181)	(1094)
Model 1 ^b	ref	–0.02 (–0.06 to 0.02)	–0.05 (–0.11 to 0.00)	–0.10 (–0.15 to –0.04)
Model 2 ^c	ref	–0.01 (–0.05 to 0.03)	–0.04 (–0.09 to 0.02)	–0.06 (–0.12 to –0.01)
Model 3 ^d	ref	0.00 (–0.04 to 0.04)	–0.03 (–0.08 to 0.03)	–0.06 (–0.11 to 0.00)
Learning to working memory (n)	(9248)	(2334)	(1181)	(1095)
Model 1 ^b	ref	–0.02 (–0.05 to 0.01)	–0.03 (–0.07 to 0.02)	–0.08 (–0.12 to –0.03)
Model 2 ^c	ref	–0.01 (–0.04 to 0.02)	0.00 (–0.04 to 0.05)	–0.03 (–0.08 to 0.01)
Model 3 ^d	ref	0.00 (–0.04 to 0.03)	0.01 (–0.03 to 0.05)	–0.03 (–0.07 to 0.02)
Overall cognition (n)	(9231)	(2328)	(1181)	(1092)
Model 1 ^b	ref	–0.02 (–0.05 to 0.01)	–0.04 (–0.08 to 0.00)	–0.08 (–0.13 to –0.04)
Model 2 ^c	ref	–0.01 (–0.04 to 0.02)	–0.02 (–0.06 to 0.02)	–0.05 (–0.09 to 0.00)
Model 3 ^d	ref	0.00 (–0.03 to 0.03)	–0.01 (–0.05 to 0.03)	–0.04 (–0.08 to 0.00)

Not Significant

CONCLUSIONS: In an analysis of data from the Nurses' Health Study II, we did not observe a convincing association between PPI use and cognitive function. Our data do not support the suggestion that PPI use increases dementia risk.

Consistent?



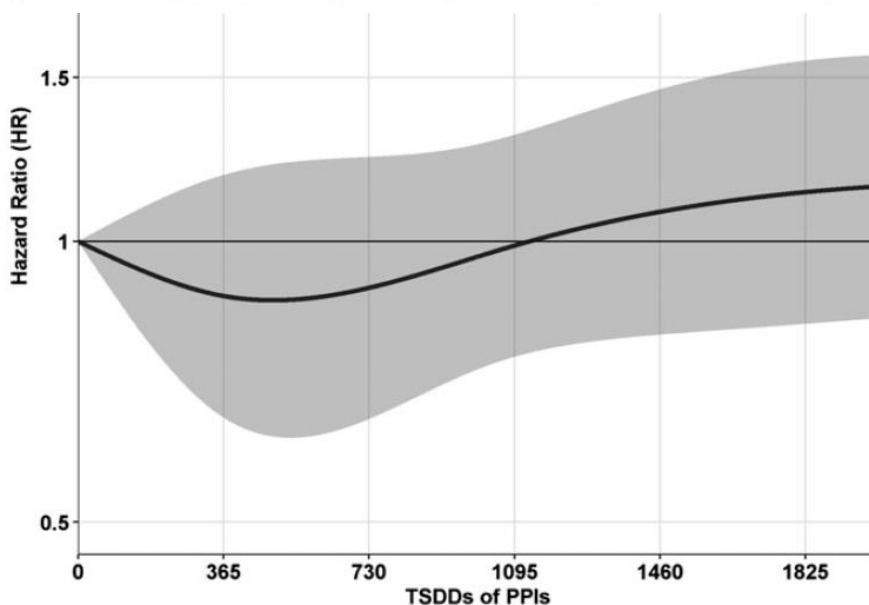
Proton Pump Inhibitor Use and Dementia Risk: Prospective Population-Based Study

Shelly L. Gray, PharmD, MS, Rod L. Walker, MS,[†] Sascha Dublin, MD, PhD,^{†‡} Onchee Yu, MS,[†] Erin J. Aiello Bowles, MPH,[†] Melissa L. Anderson, MS,[†] Paul K. Crane, MD, MPH,[§] and Eric B. Larson, MD, MPH^{†§}*

Consistent?



Adjustment	365 TSDDs	730 TSDDs	1095 TSDDs	1460 TSDDs	1825 TSDDs
Minimal	1.04 (0.77, 1.39)	1.11 (0.81, 1.52)	1.19 (0.91, 1.56)	1.26 (0.94, 1.70)	1.31 (0.95, 1.81)
Primary	0.87 (0.65, 1.18)	0.89 (0.65, 1.23)	0.99 (0.75, 1.30)	1.08 (0.80, 1.46)	1.13 (0.82, 1.56)



All-cause dementia HR (95% CI) comparing given level of PPI exposure to no exposure (0 TSDDs)

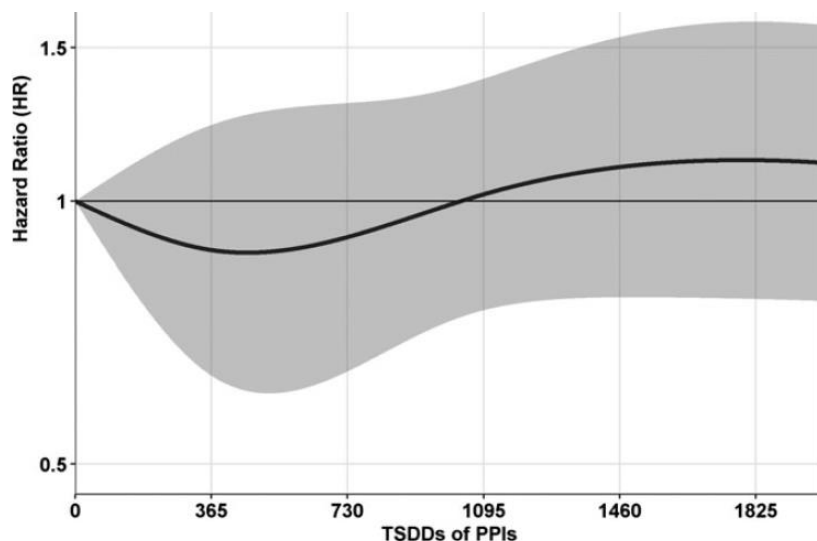
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Consistent?



Alzheimer's Disease HR (95% CI) comparing given level of PPI exposure to no exposure (0 TSDDs)

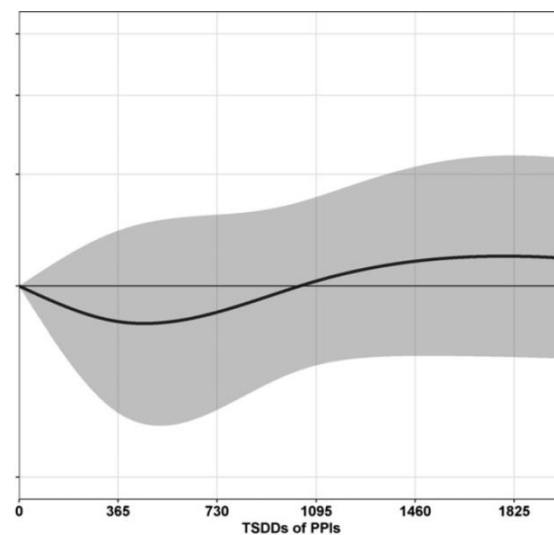
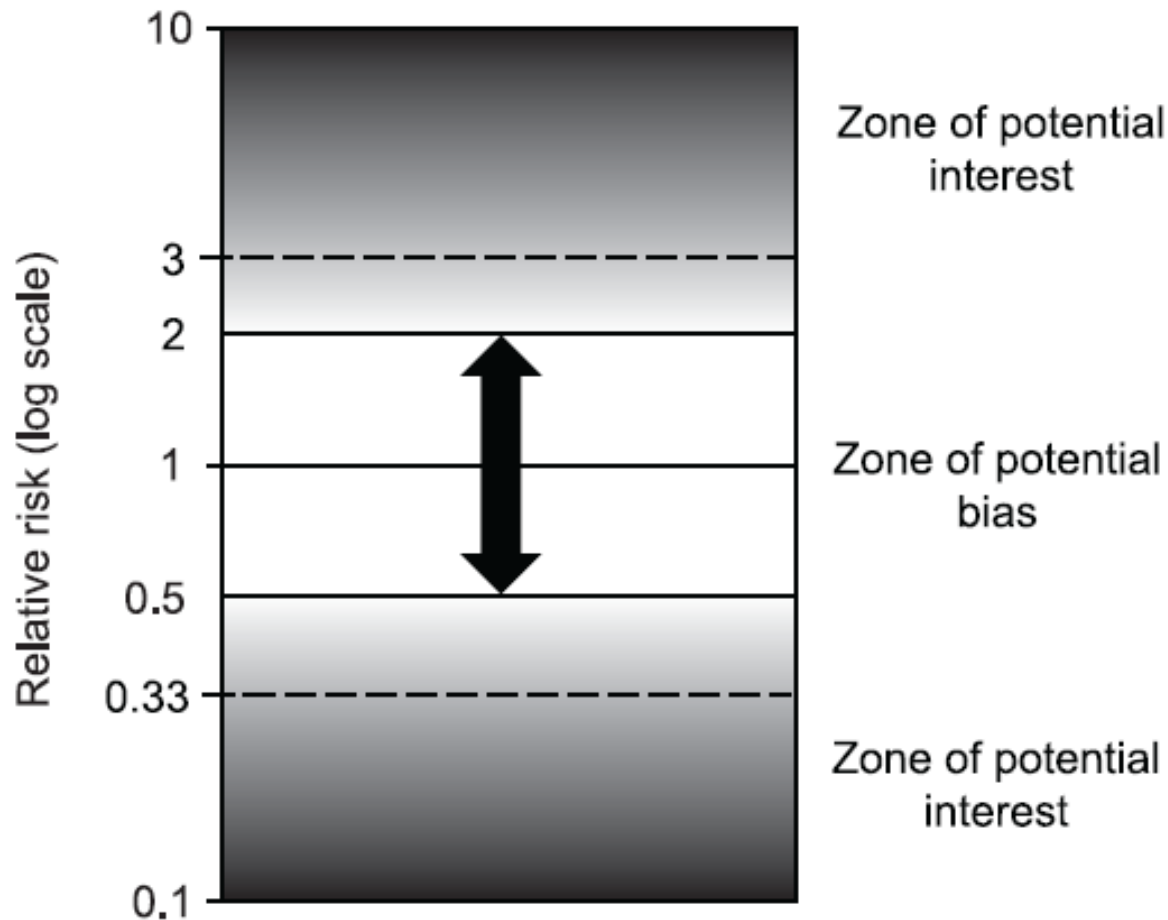
Adjustment	365 TSDDs	730 TSDDs	1095 TSDDs	1460 TSDDs	1825 TSDDs
Minimal	1.01 (0.73, 1.39)	1.08 (0.77, 1.52)	1.18 (0.88, 1.59)	1.25 (0.89, 1.75)	1.26 (0.88, 1.81)
Primary	0.88 (0.63, 1.22)	0.91 (0.64, 1.30)	1.02 (0.75, 1.38)	1.09 (0.78, 1.54)	1.11 (0.77, 1.61)



Alzheimer's Disease HR (95% CI) comparing given level of PPI exposure to no exposure (0 TSDDs)

Adjustment	365 TSDDs	730 TSDDs	1095 TSDDs	1460 TSDDs	1825 TSDDs
Minimal	1.01 (0.73, 1.39)	1.08 (0.77, 1.52)	1.18 (0.88, 1.59)	1.25 (0.89, 1.75)	1.26 (0.88, 1.81)
Primary	0.88 (0.63, 1.22)	0.91 (0.64, 1.30)	1.02 (0.75, 1.38)	1.09 (0.78, 1.54)	1.11 (0.77, 1.61)

Consistent?



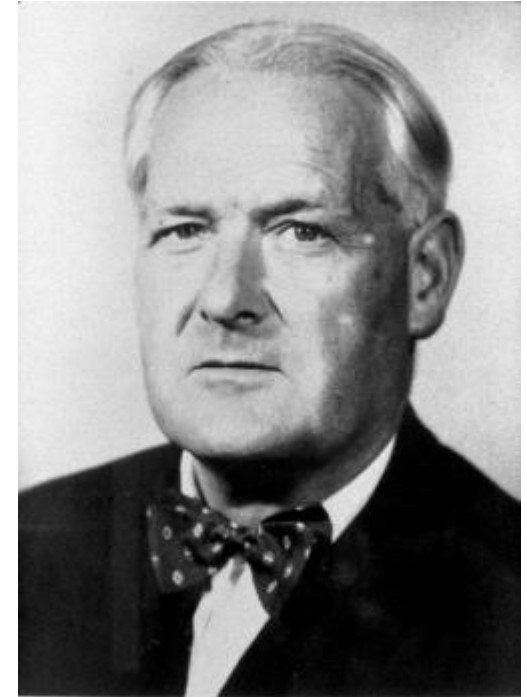
Alzheimer's Disease HR (95% CI) comparing given level of PPI exposure to no exposure (0 TSDDs)	365 TSDDs	730 TSDDs	1095 TSDDs	1460 TSDDs	1825 TSDDs
HR	1.01 (0.73, 1.39)	1.08 (0.77, 1.52)	1.18 (0.88, 1.59)	1.25 (0.89, 1.75)	1.26 (0.88, 1.81)
95% CI	0.88 (0.63, 1.22)	0.91 (0.64, 1.30)	1.02 (0.75, 1.38)	1.09 (0.78, 1.54)	1.11 (0.77, 1.61)

Sir Austin Bradford Hill



Validate cause and effect

1. **Biologically Plausible** - **WHO KNOWS**
2. **Be Strong** - **NO**
3. Reflect a biological gradient – dose response relationship
4. **Be found consistently** - **NO**
5. Hold over time – temporal incidence of the disease should reflect prevalence of offending agent
6. Confirmed by experiment



Sir Austin Bradford Hill

And the Winner Is?



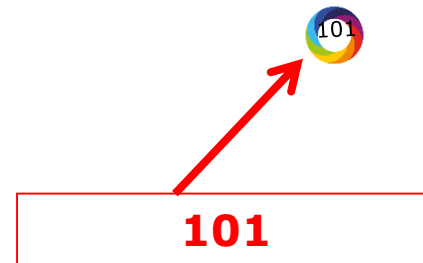
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Association of Proton Pump Inhibitors With Risk of Dementia A Pharmacoepidemiological Claims Data Analysis

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and Eric B. Larson, MD, MPH^{†§}



Red Herrings



red her·ring

' ,red 'heriNG/

noun

plural noun: **red herrings**



1.

a dried smoked herring, which is turned red by the smoke.

2.

something, especially a clue, that is or is intended to be misleading or distracting.



Questions?

A thick, curved line is drawn under the word "Questions?". A black marker is visible in the bottom right corner of the image, with its tip pointing towards the end of the underline.