



Epidemiological Ideas

Richard Rosenbaum, M.D.



Epidemiological Ideas

- Incidence v. prevalence
- Case-Control Study
- Prospective Cohort Study
- Consistency of Association
- Dose-Response Relationship
- Biases
- Direct causation
- Indirect causation
- Confounding
- Reverse causation
- Temporal relationship
- Biological plausibility

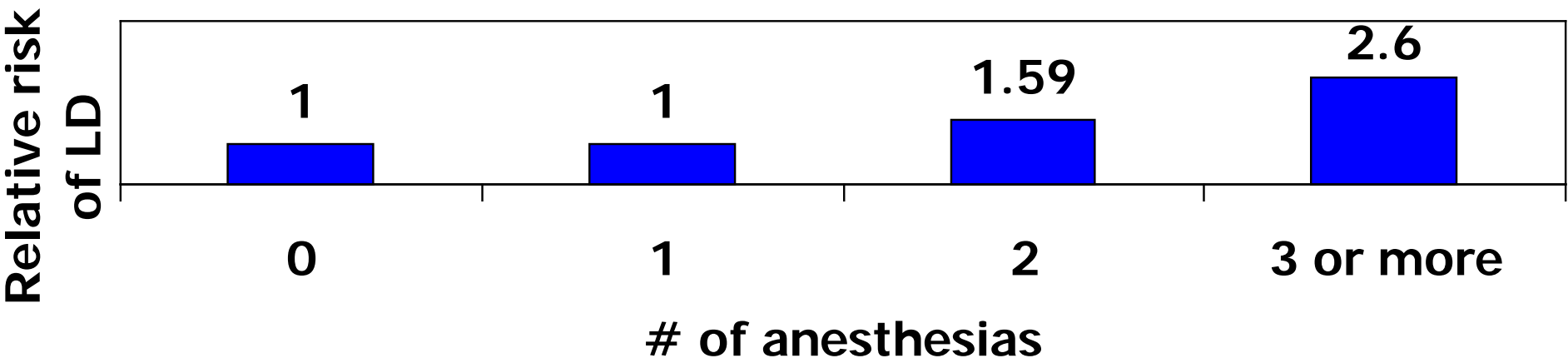


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Early exposure to anesthesia and learning disabilities in a population-based birth cohort.

- Cohort all children born in Olmstead County 1976-1982 = 5,537
- Outcome: incidence of learning disability
 - Wilder et al Anesthesiology. 2009 Apr;110(4):796-804



Strengths

Weaknesses

Observational study

- Can involve large numbers of typical patients in settings of routine care
- Can focus on specific vulnerable populations
- Can be performed relatively quickly and at modest cost
- Can identify rare adverse events
- Can follow patients over many years
- Can compare outcomes of several treatment alternatives

- Susceptible to confounding caused by underlying differences among patients treated with different drugs
- Confounding (especially due to patient selection and differences in compliance) can generate drug–outcome associations that are not truly causal
- Methodologically difficult to do well
- Difficult to identify selective reporting of findings
- Difficult to require registration

Avorn **In Defense of [Pharmacoepidemiology](#) — Embracing the Yin and Yang of Drug Research** N Engl J Med. 2007 Nov 29;357(22):2219-21





Strengths of Observational Study

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Hypotheses: Early exposure to anesthesia and learning disabilities in a population-based birth cohort.

- **Direct causation:** Anesthetics damage the brain
- **Indirect causation:** Other effects of surgery damage the brain

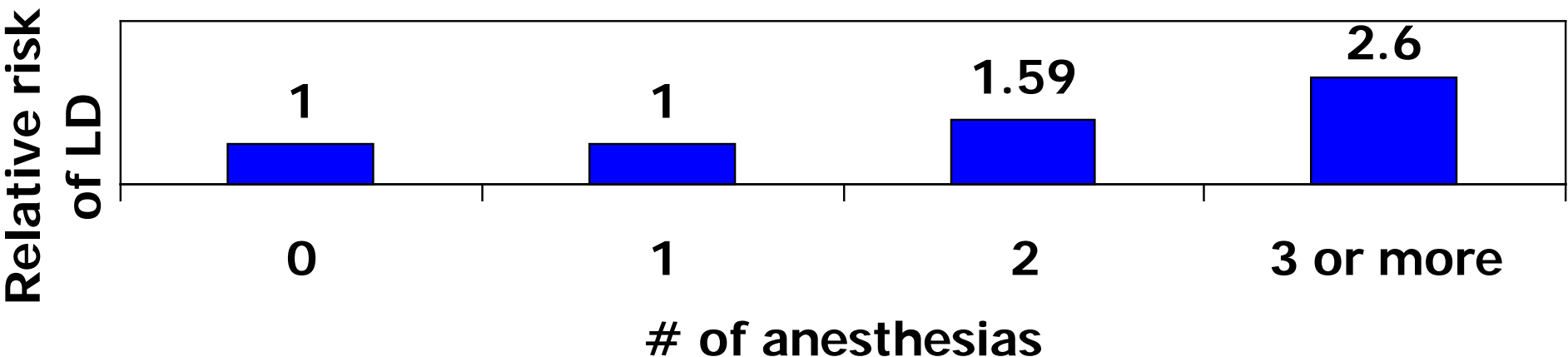


Epidemiology

Association Does
Not Prove Causation

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Weakness of Observational Study

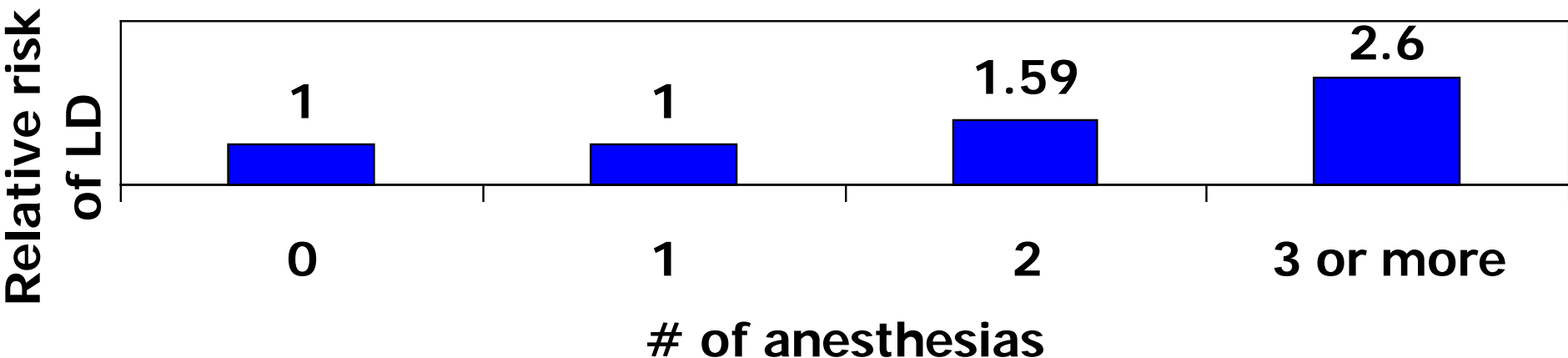
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Early exposure to anesthesia and learning disabilities in a population-based birth cohort.

- Cohort all children born in Olmstead County 1976-1982 = 5,537
- Outcome: incidence of learning disability
- Possible confounders?
- "These data cannot reveal whether anesthesia itself may contribute to learning disability or whether the need for anesthesia is a marker for other unidentified factors that contribute to learning disability."
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Hypotheses: Early exposure to anesthesia and learning disabilities in a population-based birth cohort.

- **Direct causation:** Anesthetics damage the brain
- **Indirect causation:** Other effects of surgery damage the brain
- **Confounding:** Socioeconomic or other environmental or genetic factors influence need for surgery and incidence of learning disabilities
- **Reverse causation:** Children with learning disabilities need more surgery

Hypotheses

Parkinson's disease and smoking, alcohol, and coffee

- Life habits may be markers of an underlying premorbid personality manifesting early in life and characterized by reduced novelty seeking. (**Indirect causation**)
- Patients avoid coffee or smoking because they are intolerant to their pharmacologic stimulating effects. (**Confounding**)
- Smoking is more common due to an underlying olfactory deficit occurring in the preclinical phase of PD. (**Reverse causation**)
- Smoking has a direct pharmacological action. (**Direct causation**)



Publication Types

- Case report
- Clinical trial
- Meta-Analysis
- Editorial
- Letter
- Review
- Randomized controlled trial
- Practice Guideline



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Anti-inflammatory drugs and risk of Parkinson disease

A meta-analysis



Gagne JJ, Power MC

Neurology. 2010;74:995-1002

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Nonsteroidal anti-inflammatory drugs: aspirin, Advil, Aleve, and many others



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Cancer Prevention Study II Nutrition Cohort (US)	146,948	Cohort
Nurses' Health Study and Health Professionals Follow-up Study (US)	142,902	Cohort
Group Health Cooperative (US)	589 (206/383)	Case-control
General Practice Research Database (UK)	7,896 (1,258/6,638)	Case-control
Rochester Epidemiology Project (US)	392 (196/196)	Case-control
Three rural California counties: Fresno, Tulare, Kern (US)	579 (293/286)	Case-control
NeuroGenetics Research Consortium (US)	2,114 (1,186/928)	Case-control



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Two kinds of epidemiological studies

- Case-control

- Match subjects with condition to controls
- Retrospective

- Cohort

- Prospective
- Follow a large group



Case-control studies

Advantages

- Good for rare diseases
- Relatively inexpensive

Disadvantages

- Potential biases
 - Recall
 - Selection
- Lack information on incidence and prevalence
- Possible confounding or reverse causation

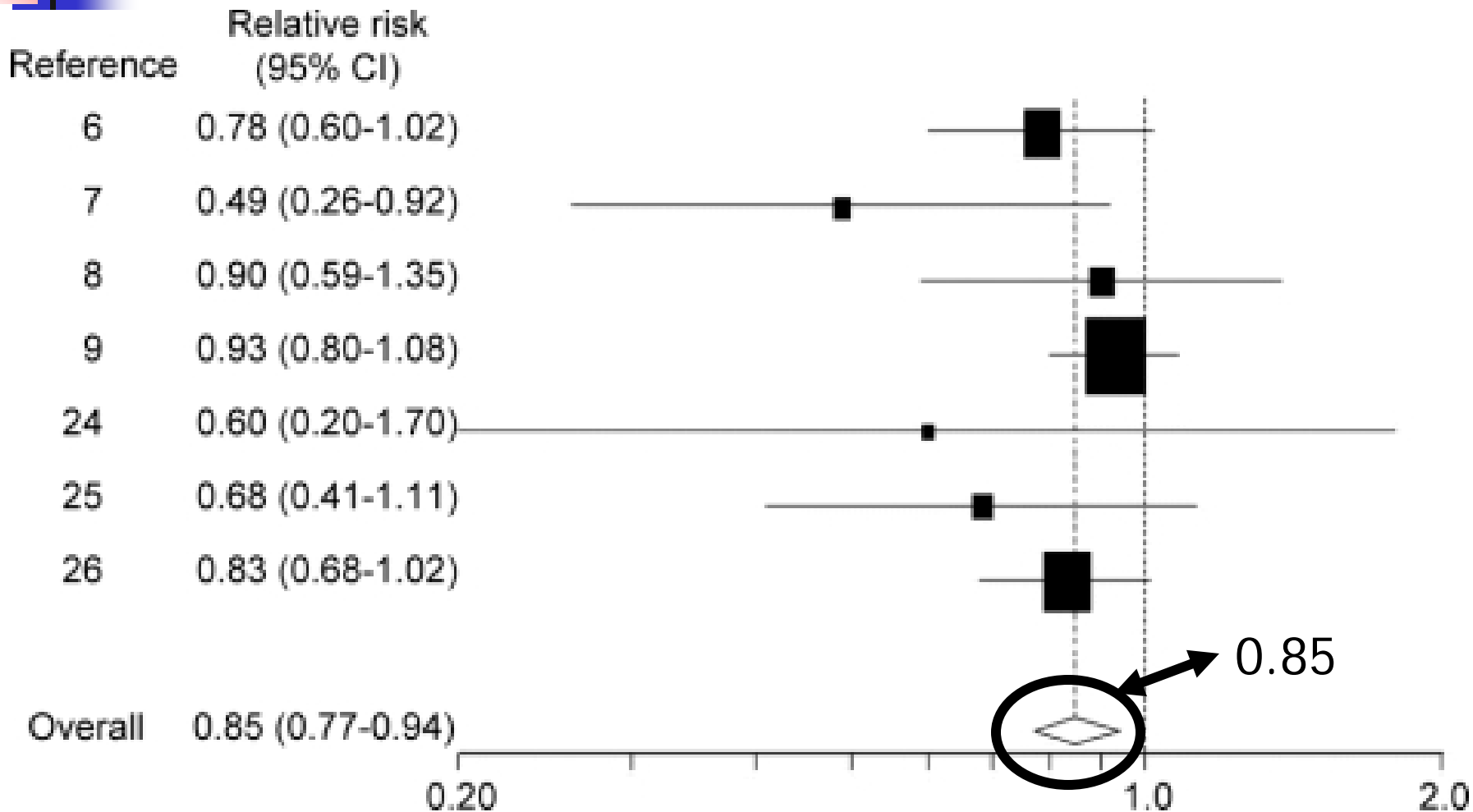


Cohort studies

- Detect temporal relationships
- Direct measurement of incidence
- Time consuming
- Expensive
- Higher risk of confounding

Anti-inflammatory drugs and risk of Parkinson disease

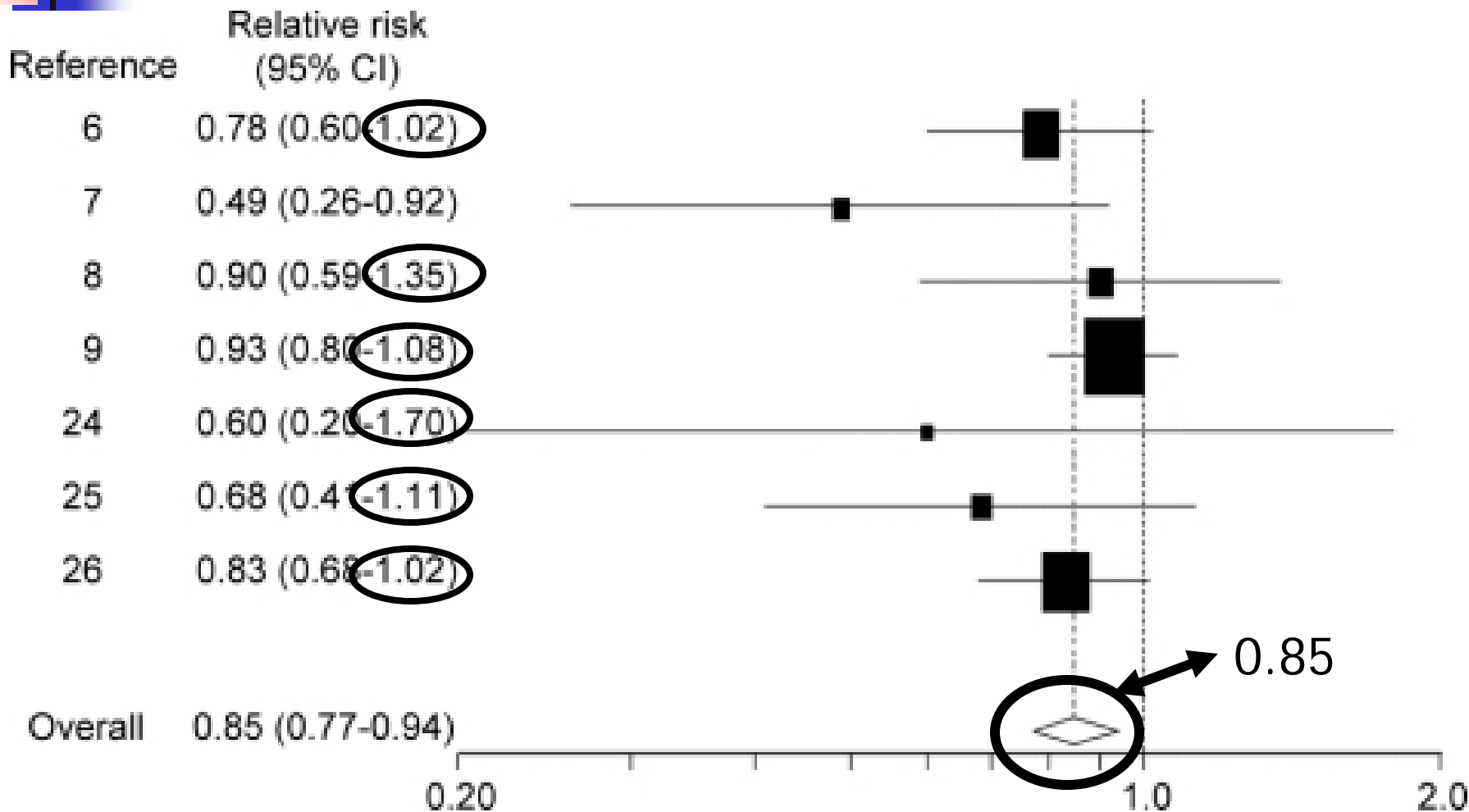
A meta-analysis



Anti-inflammatory drugs and risk of Parkinson disease

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If Confidence Interval (CI) crosses 1.0, result is not statistically significant!





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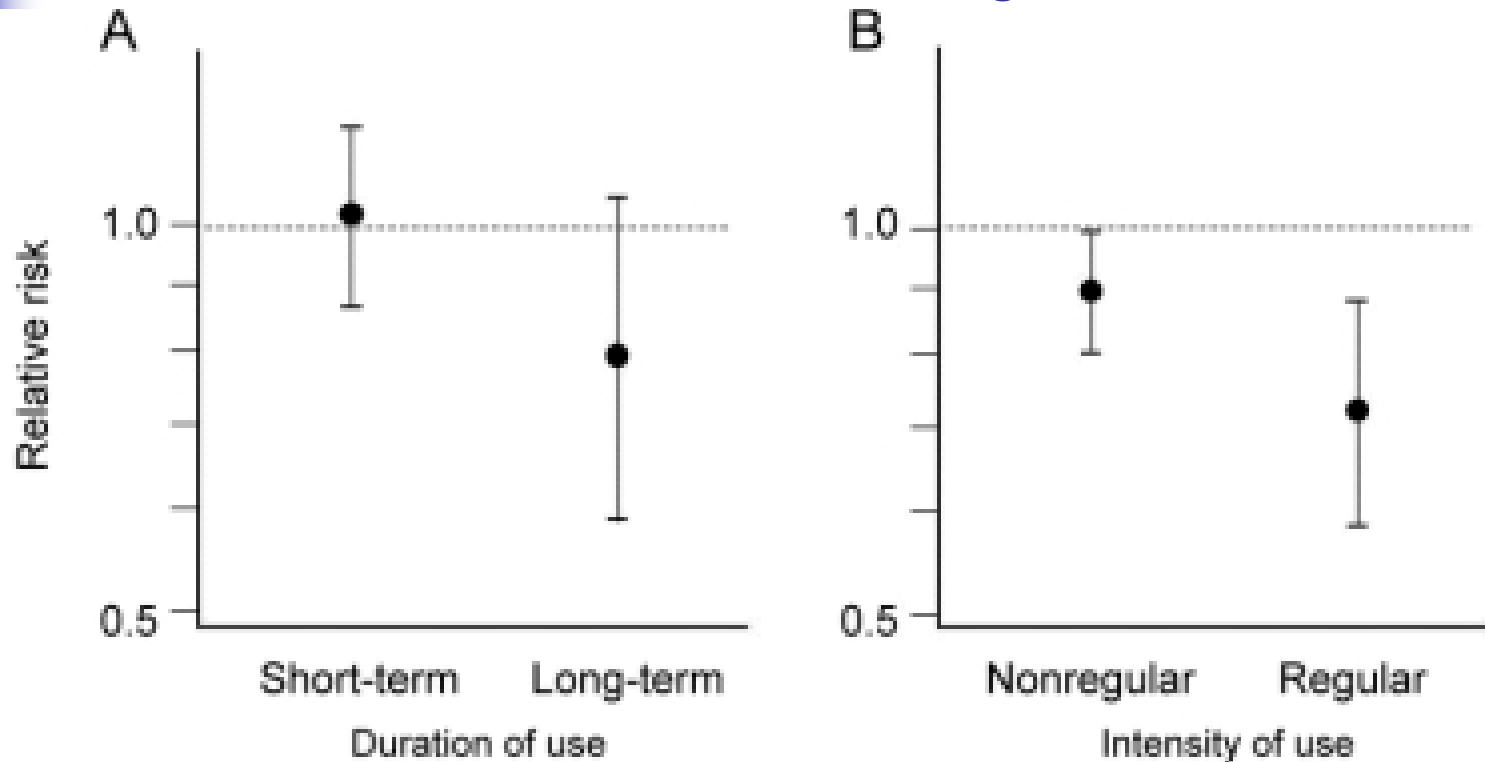


Evidence of causation from epidemiological studies (Hill)

- 1) A strong and consistent **statistical association** between the reputed cause (such as smoking) and the reputed effect (such as lung cancer)
- 2) A **dose-response relation** between reputed cause and effect,
- 3) A **temporal relation** between reputed cause and effect (Innumerable statistical associations would be unconvincing if the smokers did not start smoking until after they developed cancer), and
- 4) **Biologic plausibility** supporting the causal nature of the association.

Anti-inflammatory drugs and risk of Parkinson disease

A meta-analysis



No. data points:	4	4	3	4
Relative risk:	1.02	0.79	0.89	0.71
95% CI:	0.87-1.20	0.59-1.07	0.80-1.00	0.58-0.89

Long-term and regular use effect suggest dose response



Evidence of causation from epidemiological studies (Hill)

- 1) A strong and consistent **statistical association** between the reputed cause (such as smoking) and the reputed effect (such as lung cancer)
 - **Meta-analysis of 7 studies**
- 2) A **dose-response relation** between reputed cause and effect,
 - **More effect with regular or long term users**
- 3) A **temporal relation** between reputed cause and effect (Innumerable statistical associations would be unconvincing if the smokers did not start smoking until after they developed cancer), and
 - **Examined use at least a year before diagnosis of Parkinson's**
- 4) **Biologic plausibility** supporting the causal nature of the association.
 - **Is inflammation part of the cause of cell loss in Parkinson's disease?**



Potential Confounders

- Age
- Arthritis
- Coffee
- Vitamins
- Other analgesics
- Gender
- Smoking
- Diabetes
- Race
- Stroke
- Heart Disease
- High blood pressure
- And so on



Hypotheses: **Anti-inflammatory drugs and risk of Parkinson disease**

A meta-analysis

- **Direct causation:** Anti-inflammatory drugs protect nerve cells
- **Reverse causation:** Patients with early Parkinson's disease take pain medication
- **Confounding:** Socioeconomic or other environmental or genetic factors influence use of anti-inflammatory drugs and risk of Parkinson's disease

Association Does Not Prove Causation

Anti-inflammatory drugs and risk of Parkinson disease A meta-analysis



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**Should there be a randomized controlled trial
of use of anti-inflammatory drugs in early
Parkinson's disease?**