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Estrogen Therapy and Risk of AD in the Baltimore Longitudinal Study of Aging

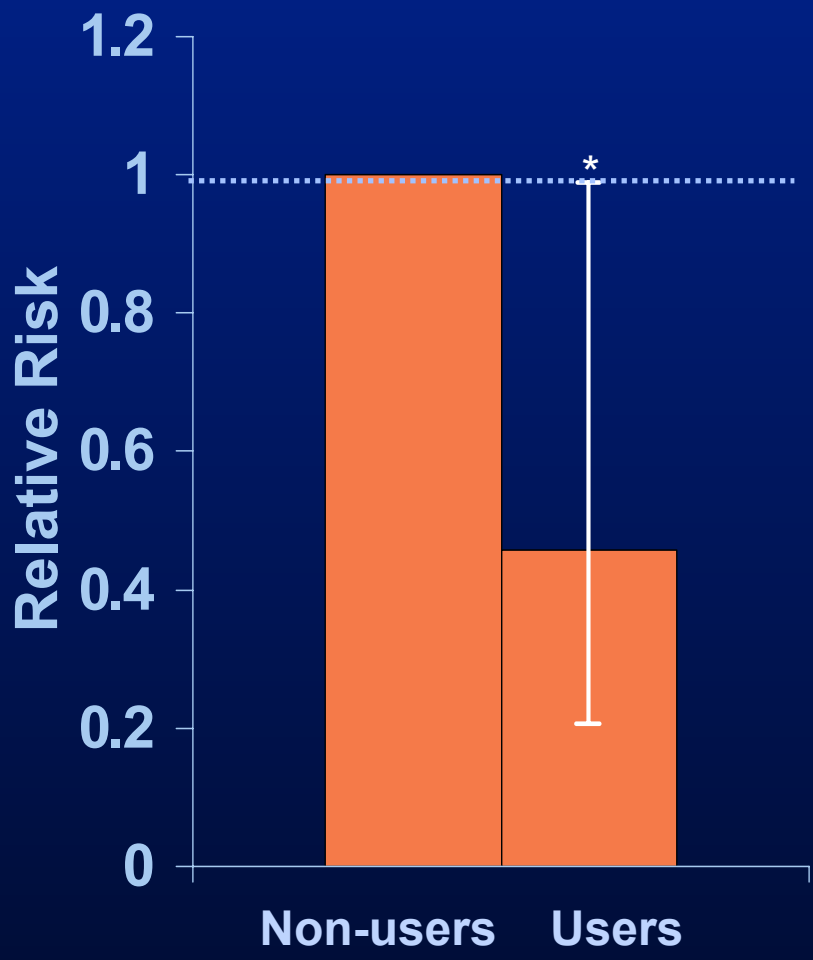
Estrogen and Survival to Age 90 in the Leisure World Cohort Study

Benefits and Pitfalls of Observational Research and Randomized Clinical Trials

Prospective Study of ET and the Risk of Developing AD in the BLSA

- 472 post or peri-menopausal women including 34 AD cases
- Up to 16 years follow-up
- Cox proportional hazards regression
  - Age used as time scale
  - Adjusted for education

RR = 0.457
95% CI = 0.209 - 0.997



Kawas, et al. Neurology, 1996

Prospective Study of ET and the Risk of Developing AD in the BLSA

Variables that did not affect risk of AD

- Dose
- Duration
- Route of administration
- Age at menopause or menarch
- Years of natural estrogen
- Surgical menopause

Strengths and Weaknesses of Study

Strengths

- Prospective investigation with exposure ascertained directly from subject before development of the outcome

Weaknesses

- Predominantly white, well-educated women
- Potential unknown confounders inherent in all observational research

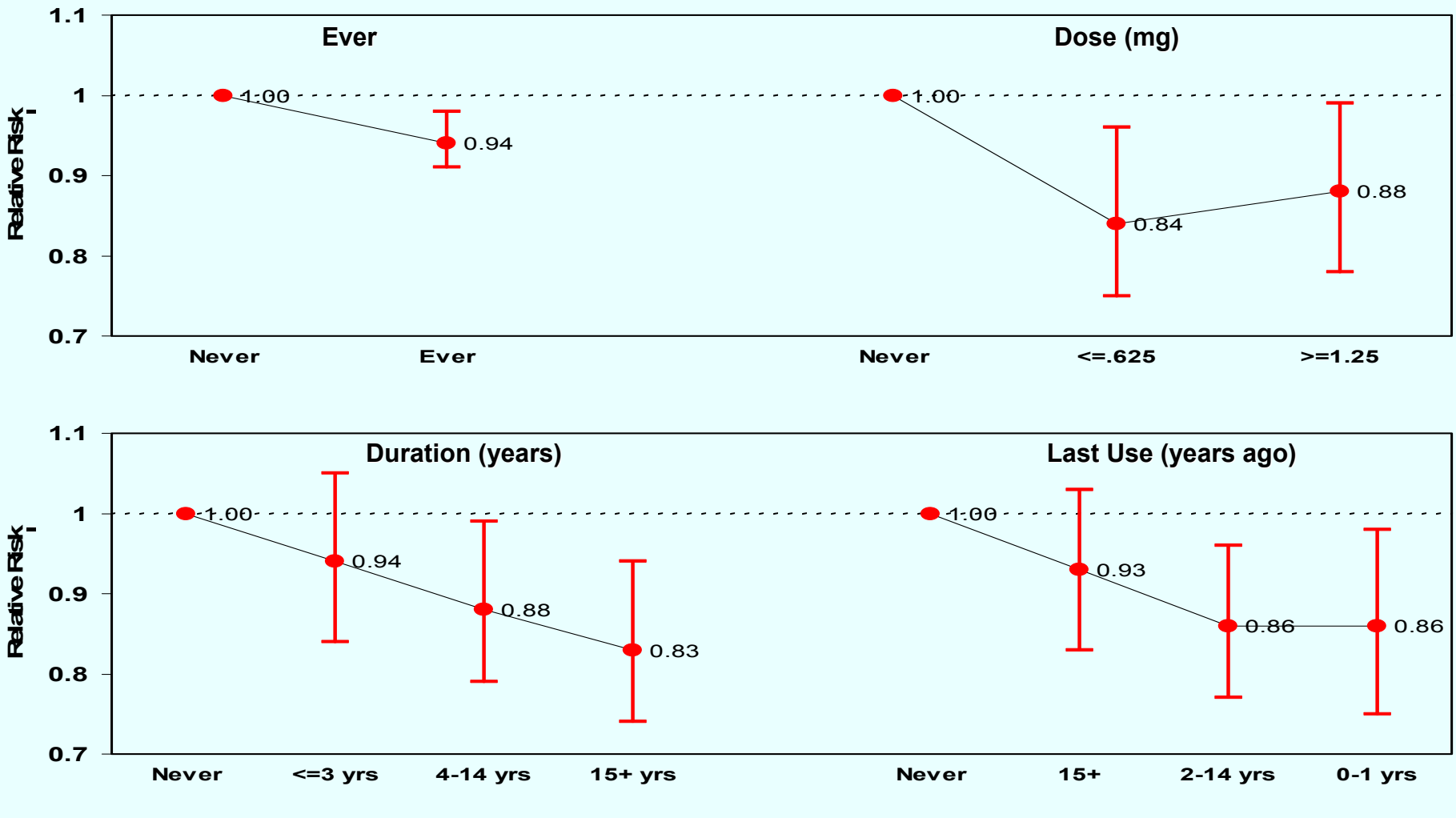
ET and Survival to Age 90 Leisure World Cohort: 1981-2002

A. Paganini-Hill, M. Corrada, C. Kawas

- **Objective**
  - To study the association between menstrual and reproductive factors and the risk of dying before age 90 in a prospective cohort study of older women
- **Subjects**
  - 5,827 (3,562 died < 90 years & 2,265 alive > 90 years)
  - Mean baseline age: 74 years (52-89)
  - Mean follow-up: 11 years
- **Analysis - Logistic regression adjusted for:**
  - Baseline age
  - Smoking
  - History of hypertension, angina, heart attack, stroke, diabetes, fracture after age 40, cancer
  - $p < 0.001$ selected apriori

ET and Mortality
Leisure World Cohort: 1981-2003

A. Paganini-Hill, M. Corrada, C. Kawas



Paganini-Hill et al, AAN 2003

The 90+ Study

The New York Times Magazine / MARCH 16, 2003

Medicine's Progress, One Setback at a Time

The history of medicine is a long, serpentine narrative of the death of old ideas giving way to the birth of new ones. And this cycle is moving faster than ever. **BY LISA SANDERS, M.D.**

A decade ago, I stood alongside my 99 fellow freshmen as we were welcomed into the ranks of medicine in a "white coat ceremony." Here, on our first day of med school, we were presented with the short white coats that proclaimed us part of the mystery and the discipline of medicine. During that ceremony, the dean said something that was repeated throughout my education: half of what we teach you here is wrong — unfortunately, we don't know which half.

At the time it was hard to believe. Within those walls, in the anatomy lab, in the lecture hall, you feel that you are being shown the secrets of how the body is put together, how it lives, how it works, how it dies. It has the feel of authority and certainty. Like math, it has a feeling of inevitability.

But now, as a practicing doctor and teacher of residents, I relive that dean's aphorism daily. Medicine is, and always has been, an evolving discipline. And this necessarily means that what we know about medicine is constantly changing; that medicine is forever putting forth, and simultaneously upending, assumptions (as can be seen in the accompanying chart). This is particularly true at this moment. Virtually all of our

Definitions

Observational Studies

Observe the occurrence of outcome in people who are already grouped on the basis of some exposure; allocation into groups is not controlled by investigator

- Case Control or Cohort
- Retrospective or Prospective

Randomized Clinical Trials (RCT's)

Prospective experimental approach where the investigator studies the impact of a factor that s/he controls by random assignment

Advantages of Observational Studies

- Lower cost
- Time efficient
- Fewer and broader range of patients
- Useful
  - to identify risk factors and prognostic indicators
  - in situations in which RCT's would be impossible or unethical
  - as guides to the design of new controlled trials

Pitfalls of Observational Studies

- Unrecognized confounding factors
- Broader range of treatments and dosages
- Subject to recall bias when retrospective
- Cannot be used to evaluate treatments that physicians routinely select for the sickest patients
- Selection bias

Advantages of Randomized Clinical Trials

- Prospective, protocol-driven experimental study with predefined variables
- Confounding Variables

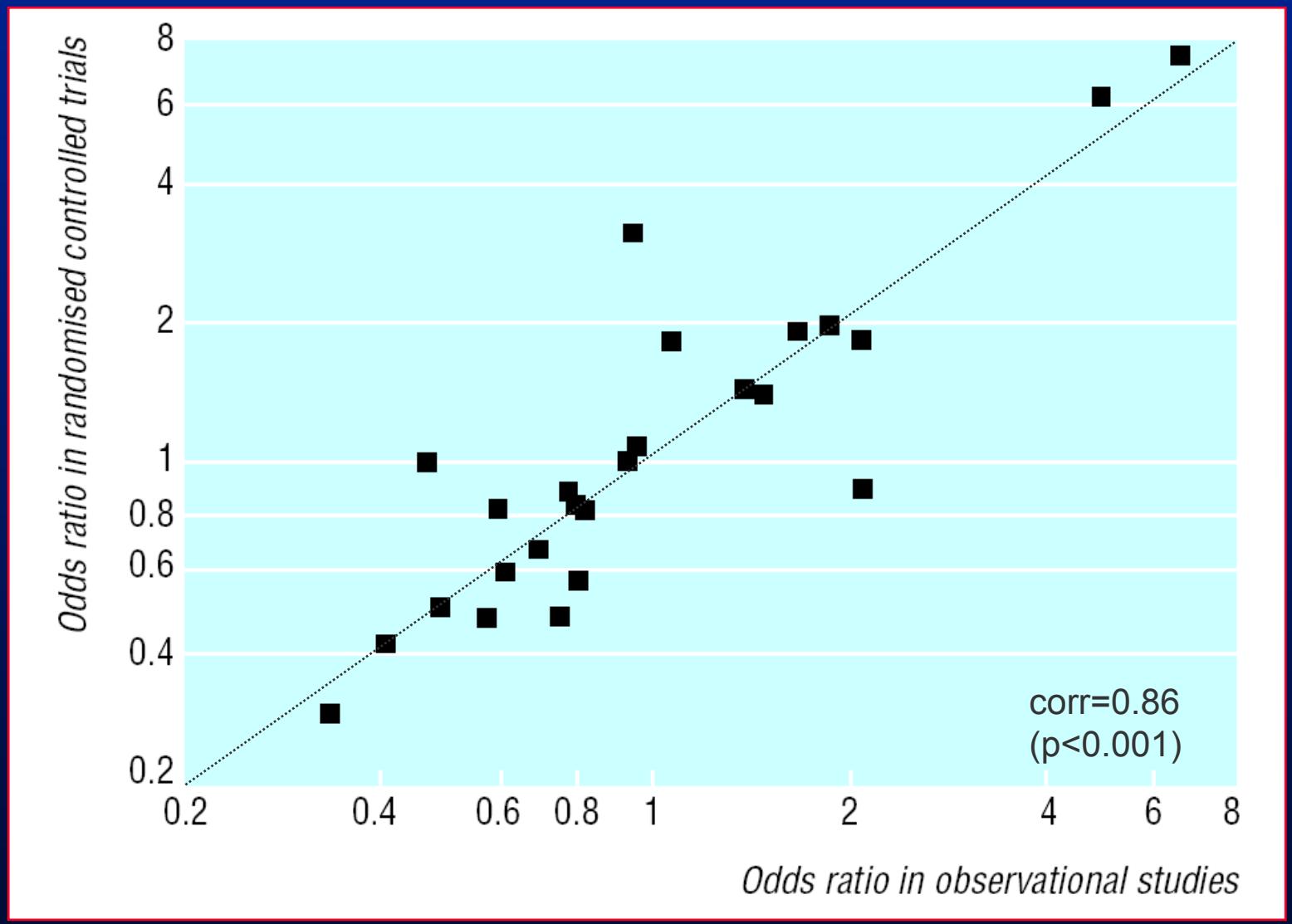
Factors known to be associated both with the exposure of interest and the disease under study

The purpose of randomization is to equally distribute known and unknown confounders between the treatment groups

Pitfalls of Randomized Clinical Trials

- Incomplete blinding
- Subjects can't be blinded (e.g., intervention requires their participation)
- Choice of dose, duration, timing of exposure
- Clinicians may not accept there is uncertainty and thus deem the trial unethical
- Selection bias

Odds Ratios from Observational Studies Versus RCT on the Same Question



Ioannidis, BMJ 2001

Examples in which randomized studies found different results from observational studies

Agent	Outcome
Estrogen & Progestin	CAD Dementia/AD
Vitamin E, B carotene	Lung/other cancers
Vitamin E	Cardiovascular events
Lowfat, high fiber diet	Recurrence of colorectal adenomas
Autologous marrow or stem cell transplantation	Breast cancer


The New York Times Magazine
MARCH 16, 2003 / SECTION 6
This War's Medic
Half of what doctors know is wrong.
Can prevention kill you?
Is it ever O.K. for a doctor to refuse to treat a patient?
Are nurses expendable?
Should the results of an insidious experiment be ignored?
Are men the stronger sex?
What's really responsible for the malpractice morass?
Can old-fashioned treatments still work?
An issue exploring medicine and its myths.

The Half We Don't Know

- Scientists do experiments, including observational studies and RCT's, to find out what they don't know. Both types of studies are valid.
- Many experiments are necessary before we understand a clinical problem.