Effect measure modification & Interaction

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Interaction + Effect Modification =  **Frustration**

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EDITORIAL

Interaction: A word with two meanings creates confusion

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Perhaps more than any other word in epidemiology, 'interaction' presents a challenge to clinical and epidemiological researchers. The problem stems from its applicability to describe two different phenomena. On the one hand, interaction refers to the biologic interaction of two or more causes of disease that together assert their influence on disease risk. On the other, interaction refers to statistical interaction which is the necessity for a product term in a linear model. In this editorial, we have two related goals: (1) dependent variables is no longer additive. A logistic regression model on the other hand is implicitly exponential and thus multiplicative. It becomes additive only after a logarithmic transformation. As a consequence, the inclusion of an interaction term in the logistic regression model implies that the investigated relation is no longer multiplicative.

The confusion around the dual meaning of the term interaction has arisen in parallel with the widespread use of statistical modeling and software

"Introduction to effect modification leaves some students of epidemiology struggling with the distinction between this and the other 'third variable' phenomenon, namely, confounding. Confusion regarding effect modification is further exacerbated by a lack of consensus on both semantic and conceptual issues" Joseph KS. *Paediatr Perinat Epidemiol*. 2009

"The term "interaction" is a minefield of potential misunderstanding…the presentation and discussion of interaction in the medical and epidemiologic literature is woefully inadequate." JS Kaufman, *Epidemiol* 2009

Terminology

- Biological interaction

- Effect modification
  - Or, more precisely, “effect-measure modification”
- Heterogeneity of effects
- Subgroup effects (i.e. effect varies across subgroups)
- Statistical Interaction
  - Deviation from a specified model form (additive or multiplicative)

Synonymous

Often used interchangeably

On the Distinction Between Interaction and Effect Modification

Tyler J. VanderWeele

Abstract: This paper contrasts the concepts of interaction and effect modification using a series of examples. Interaction and effect modification are formally defined within the counterfactual framework. Interaction is defined in terms of the effects of 2 interventions whereas effect modification is defined in terms of the effect of one intervention varying across strata of a second variable. Effect modification can be present with no interaction; interaction can be present with no effect modification. There are settings in which it is possible to assess effect modification but not interaction, or to assess interaction but not effect modification. The analytic procedures for obtaining estimates of effect modification parameters and interaction parameters using marginal structural models are compared and contrasted. A characterization is given of the settings in which interaction and effect modification coincide.

(*Epidemiology* 2009;20: 863–871)

of what will be formally defined below as an interaction of effects. Sometimes the coefficient for the product term can be interpreted both as a measure of effect modification and as a measure of interaction; sometimes only one of the 2 interpretations (or neither) is warranted.

The paper is structured as follows. First, I provide and contrast formal counterfactual definitions for interaction and effect modification. Second, examples are given showing that it is possible to have effect modification without interaction or interaction without effect modification. Third, further examples are given showing that in some cases it is possible to identify effect modification but not interaction and that in other cases it is possible to identify interaction but not effect modification. Fourth, analytic procedures to estimate interaction and effect modification parameters in marginal structural

Biological interaction

"the interdependent operation of two or more biological causes to produce, prevent or control an effect"

[Porta, Dictionary, 2008]

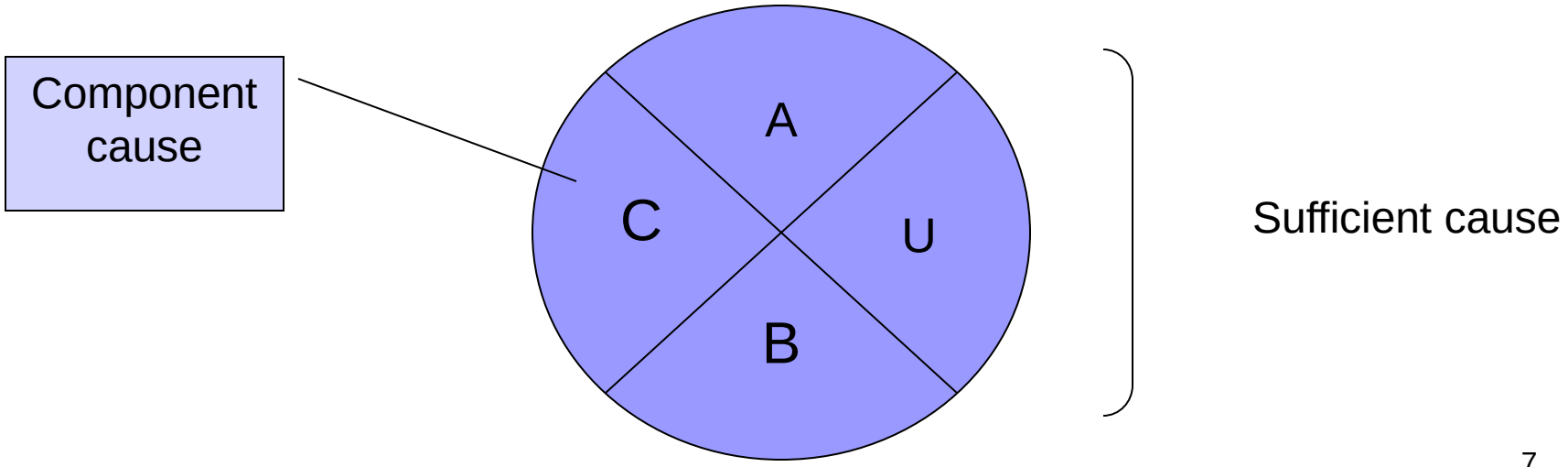
Multicausality and interdependent effects

- Disease processes tend to be multifactorial: “multicausality”
  - Very few exposures cause disease entirely by themselves
    - Exposure to measles can cause measles only if somebody is susceptible (e.g. not vaccinated)
    - Development of melanoma among those with high UV light exposure who also have fair skin
- The “one-variable-at-a-time” perspective has several limitations
- Both confounding and effect modification are manifestations of multicausality (reality is multivariate!)

Schoenbach, 2000

Biological interaction

- Refers to “co-participation in a causal mechanism of two or more component causes” (Rothman 2002)
- Illustrated by the “causal pie” model (Rothman)



Rothman, 2002

Biological interaction

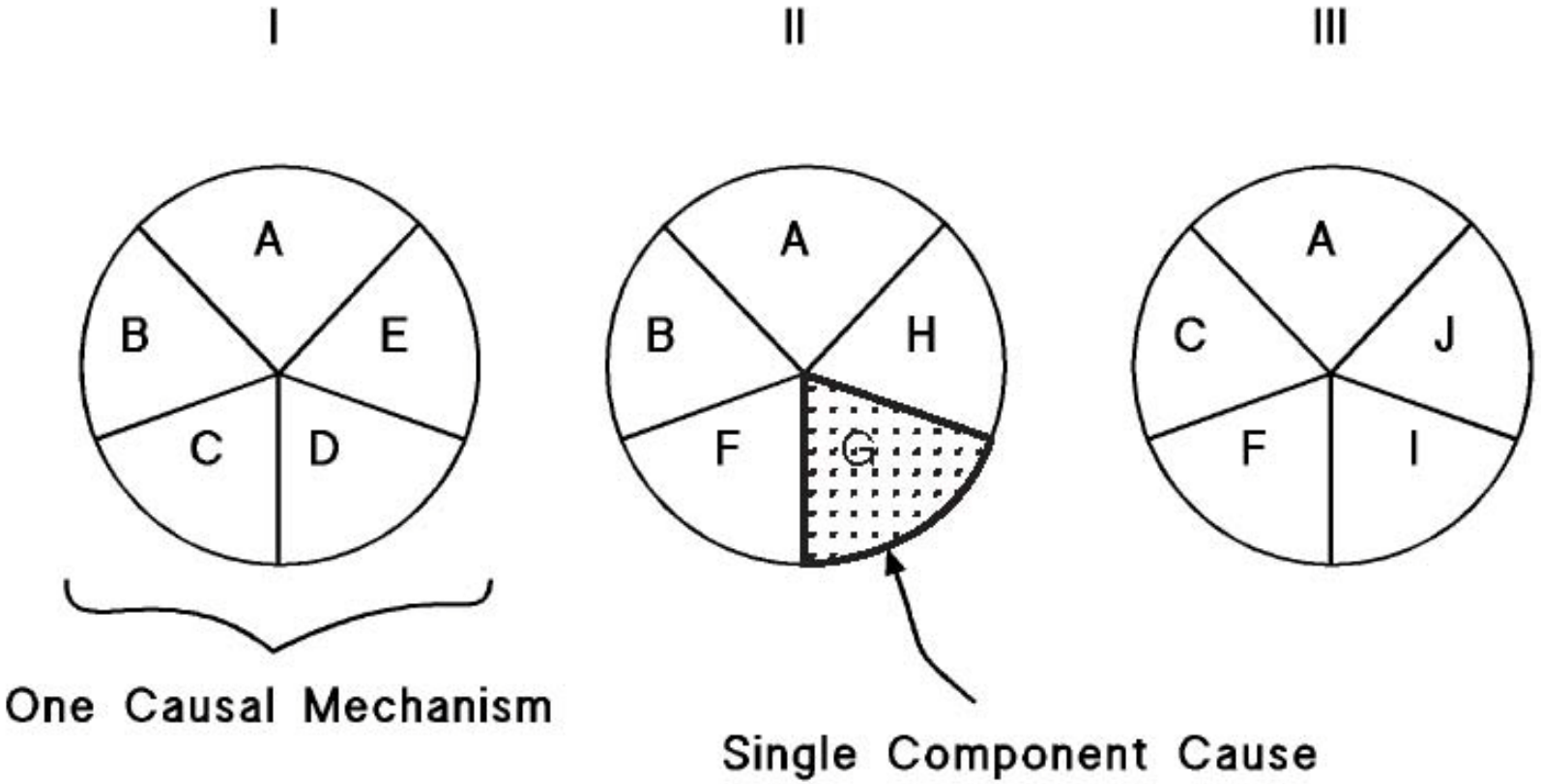
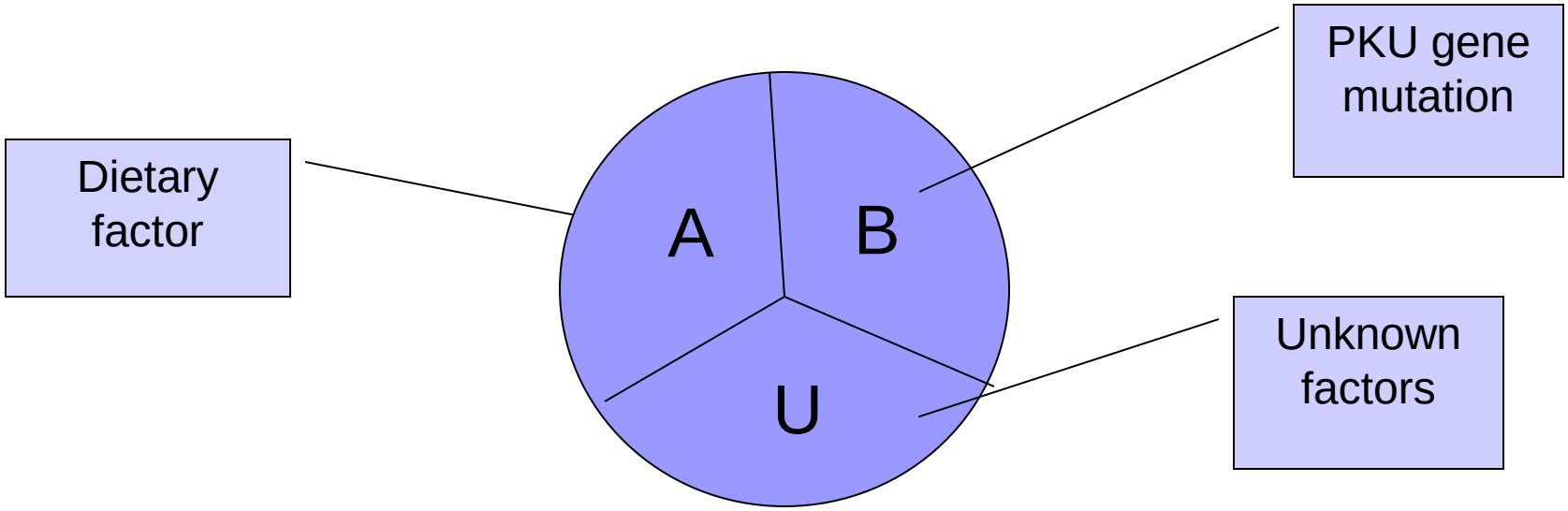


Figure 2–1. Three sufficient causes of a disease.

Rothman, 2002

Example: Phenylketonuria

- PLU is a condition linked to a dietary factor (phenylalanine) and a genetic defect (mutations in the structural gene for phenylalanine hydroxylase)



Rothman, 2002

Drinking & Driving = Lethal Interaction!

Effect modification, statistical interaction, heterogeneity of effects

Effect modification & statistical interaction

- Two definitions (but related):
  - Definition based on homogeneity or heterogeneity of effects
    - Interaction occurs when the effect of a risk factor (X) on an outcome (Y) is not homogeneous in strata formed by a third variable (Z, effect modifier)
    - “Differences in the effect measure for one factor at different levels of another factor” [Porta, 2008]
    - This is often called “effect modification”
  - Definition based on the comparison between observed and expected joint effects of a risk factor and a third variable [deviation from some specified model]
    - Interaction occurs when the observed joint effects of the risk factor (X) and third variable (Z) differs from that expected on the basis of their independent effects
    - This is often called “statistical interaction”

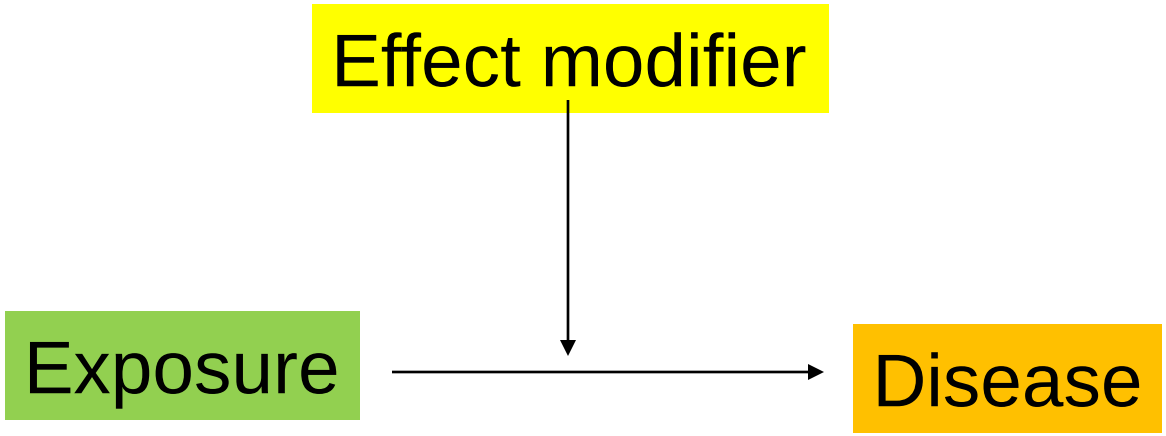
Szklo & Nieto, Epidemiology: Beyond the basics. 2007

Definition based on homogeneity or heterogeneity of effects

This is most commonly called “effect modification”

Definition based on homogeneity or heterogeneity of effects

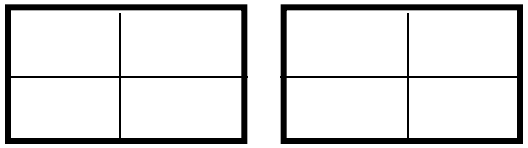
- Effect of exposure on the disease is modified (altered) depending on the value of a third variable called “effect modifier”



Crude

OR_{Crude}

Level 1 Level 2



OR_1 OR_2

Crude 2 x 2 table
Calculate Crude RR, OR

Stratify by 3rd variable

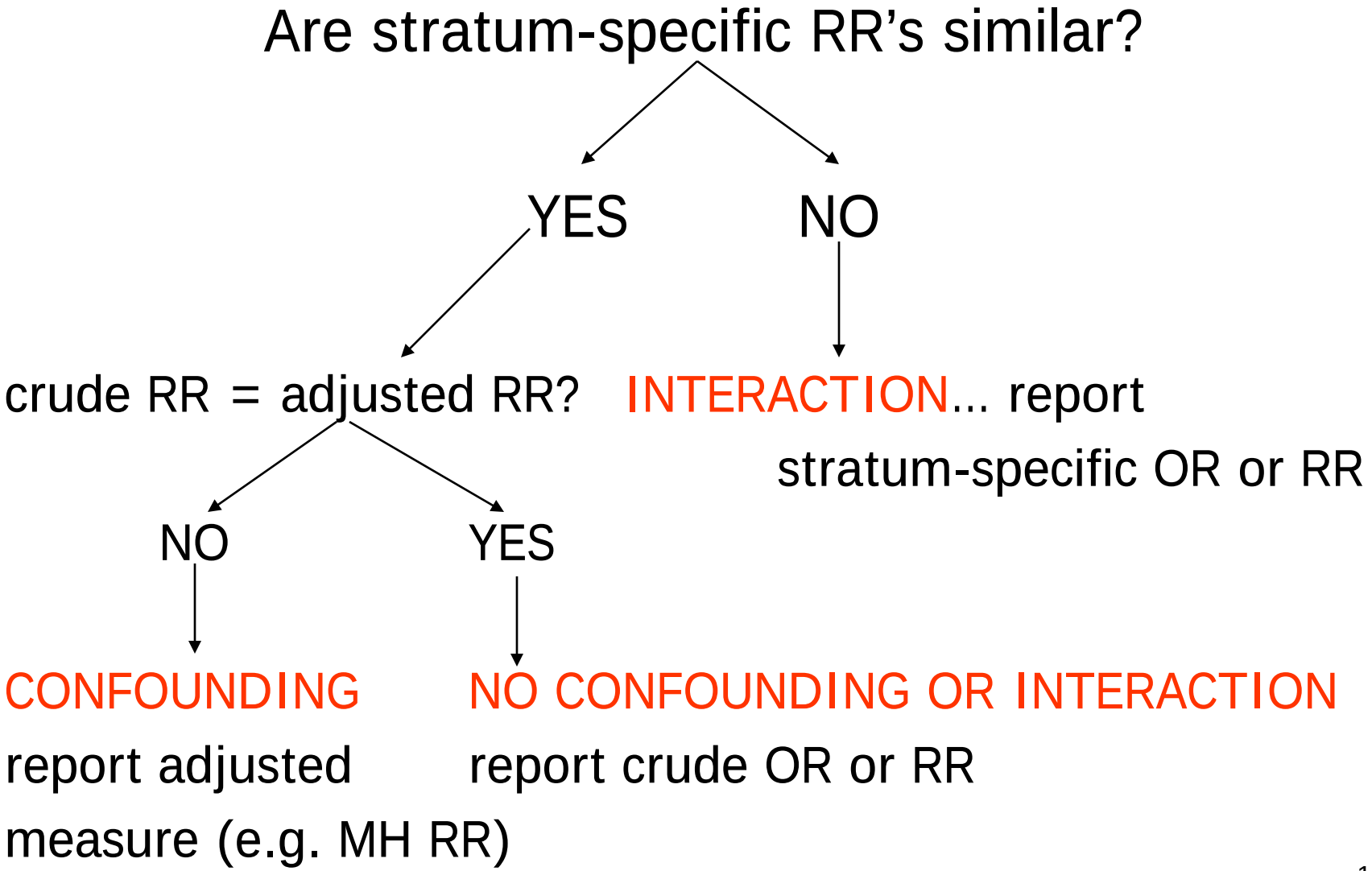
Calculate RR's, OR's
for each stratum

Test whether stratum-specific RR's, OR's are similar (test for homogeneity)

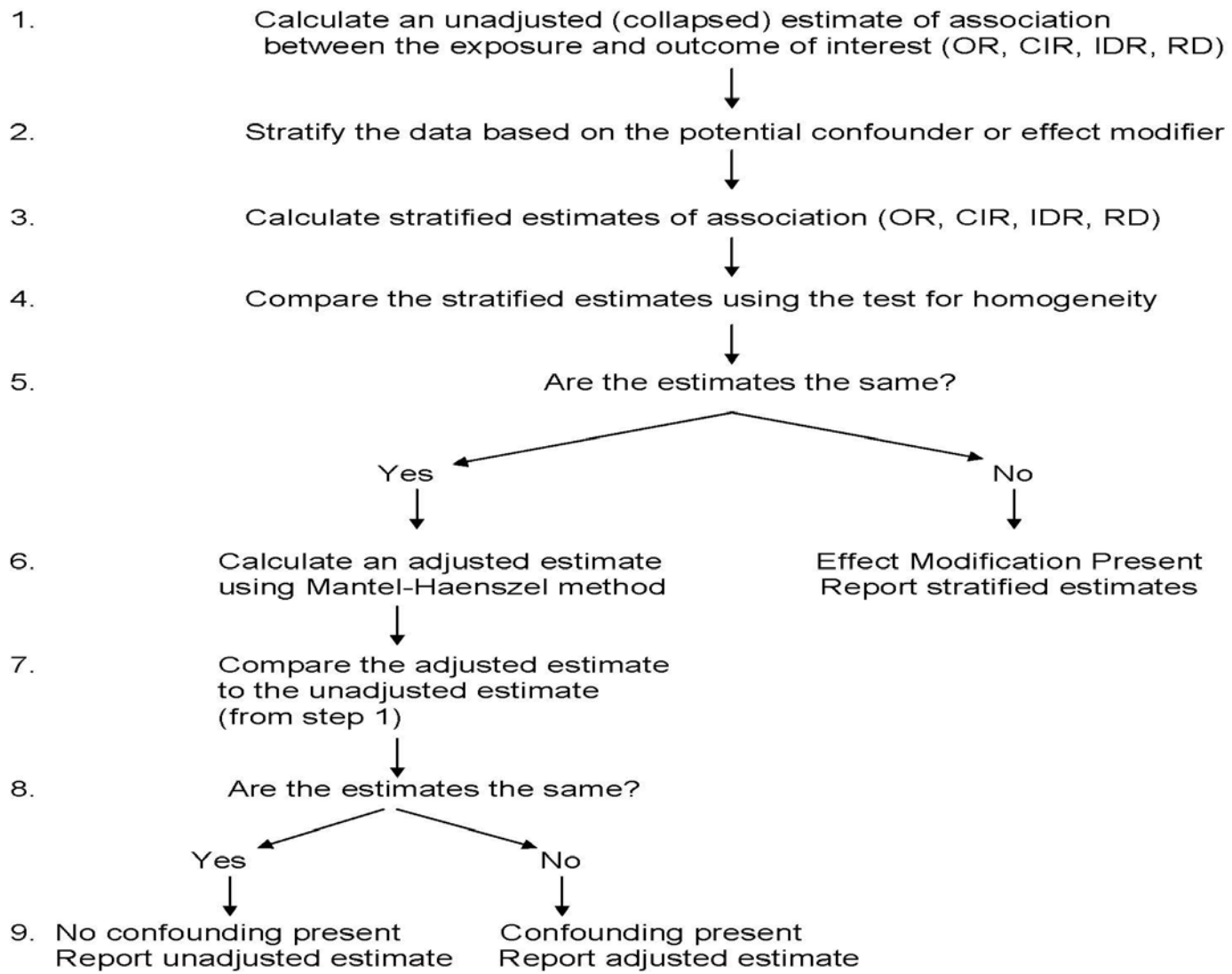
If they are similar, investigate the possibility the 3rd variable is a confounder.

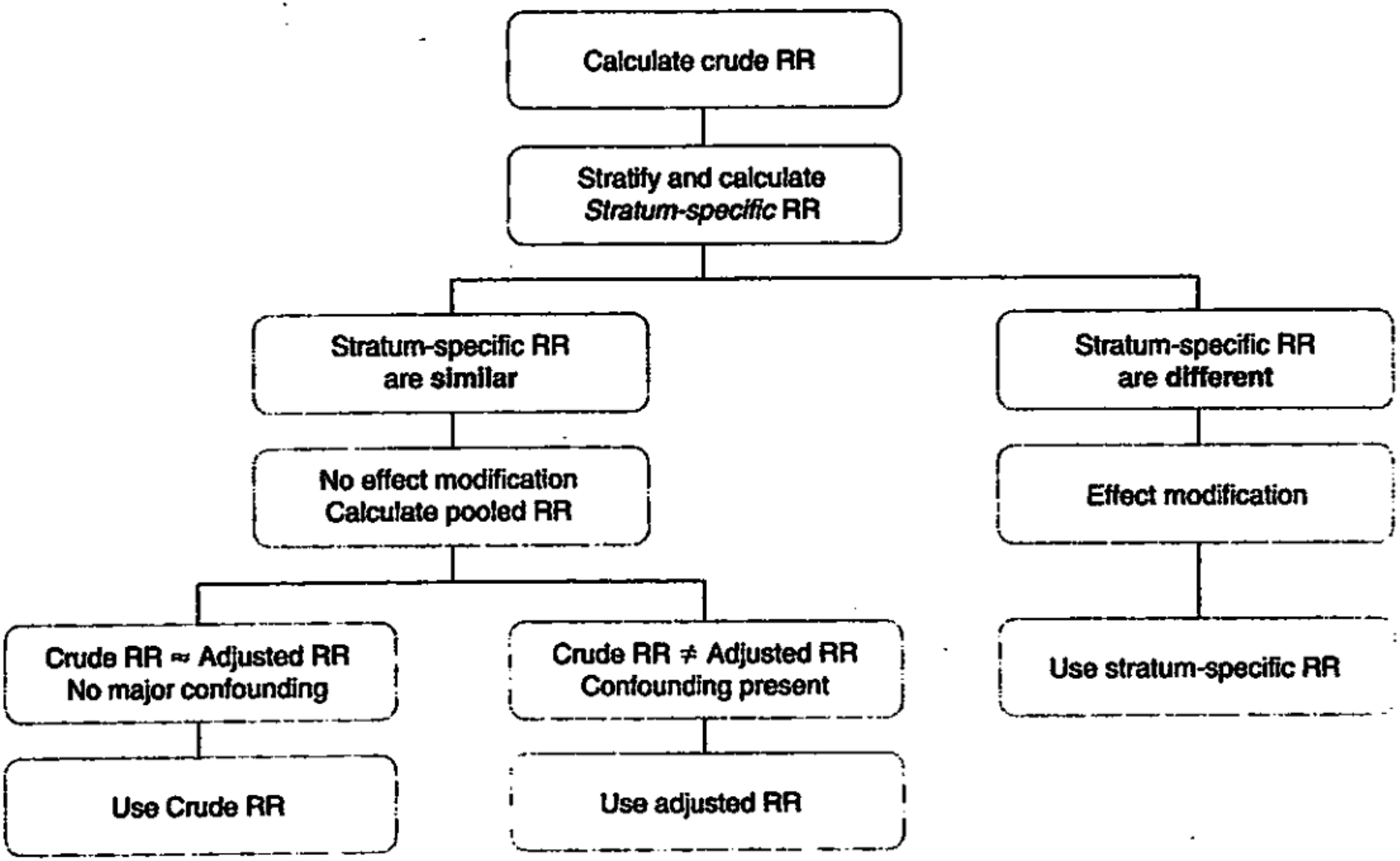
If they are different, there is evidence of effect modification

Evaluation of confounding and interaction



Decision tree for evaluating confounding and effect modification





Webb. Essential Epidemiology, Cambridge Univ Press.

Two 'average' men having an 'average' meal.

Confounding versus interaction

- Confounding is a problem we want to eliminate (control or adjust for) in our study
  - Evaluated by comparing crude vs. adjusted effect estimates: is the adjusted estimate different from the crude one?
- Interaction is a natural occurrence that we want to describe and study further
  - Evaluated by comparing stratum-specific estimates: are they different from one another?

Example: Smoking and myocardial infarction (MI)

1) Calculate crude measure of association...

	MI	no MI	Total
Smokers	42	158	200
Nonsmokers	21	175	196
Total	63	333	396

$$OR = \frac{ad}{bc}$$

OR = 2.22 (95% CI 1.26, 3.91)

Investigators decided to look at dietary fat as a confounder/effect modifier

2) Calculate stratum-specific measures of association...

STRATUM 1: Dietary fat consumption <30% of calories

	MI	noMI	Totals
Smokers	12	133	145
Nonsmokers	11	123	134
Total	23	256	279

OR = 1.01
(0.429, 2.37)

STRATUM 2: Dietary fat consumption > 30% of calories

	MI	noMI	Totals
Smokers	30	25	55
Nonsmokers	10	52	62
Total	40	77	117

OR = 6.29
(2.64, 14.75)

Inference

- CRUDE OR for smoking and MI =2.22
- STRATUM-SPECIFIC OR for smoking and MI with dietary fat consumption as a potential interacting variable…

  DFC<30% OR = 1.01 (0.425, 2.37)

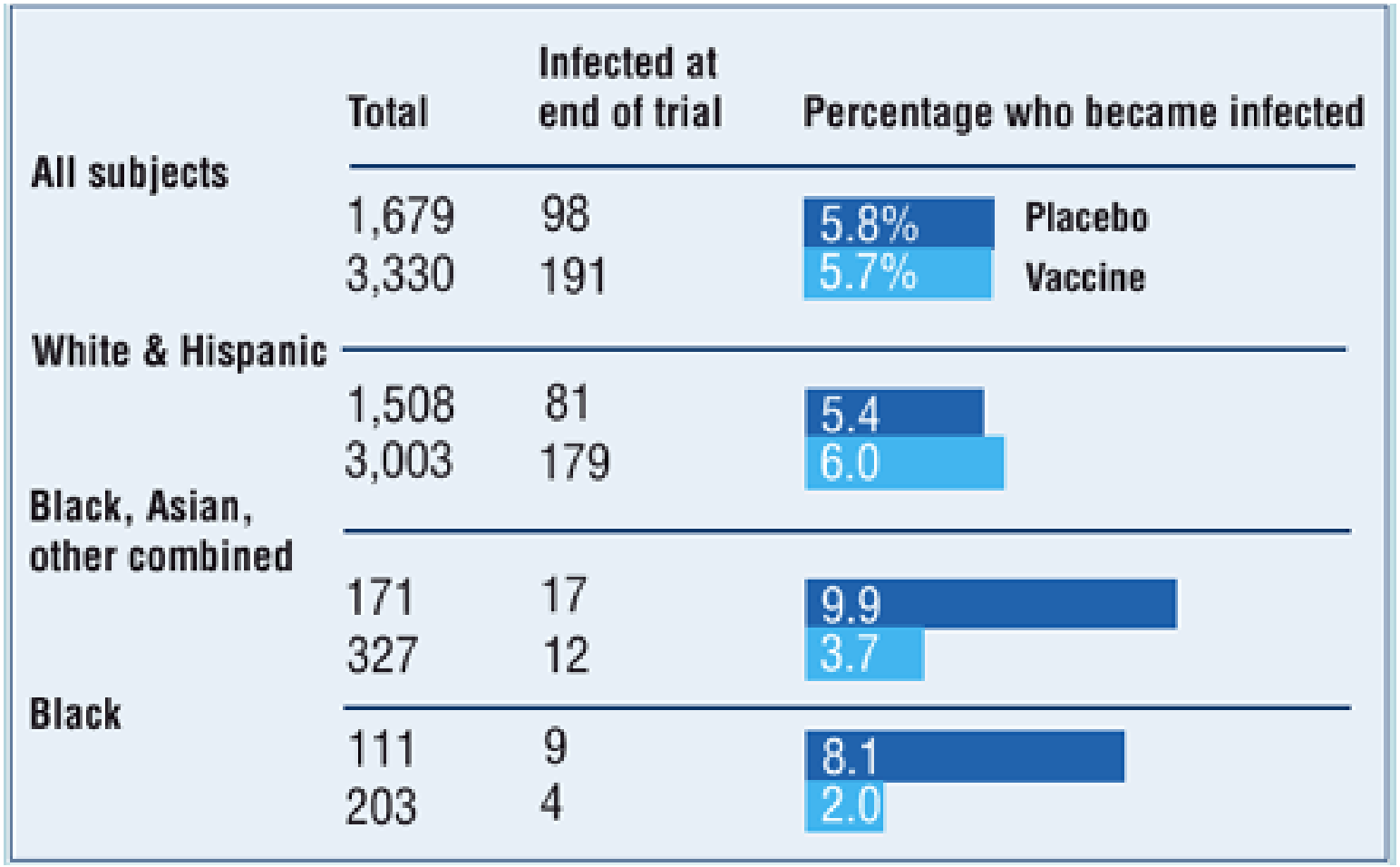
  DFC>30% OR = 6.29 (2.64, 14.75)

– Is there effect modification?
– Is there confounding?
– Which measure should we report?

More numeric examples

Study	Crude RR	Stratum1 RR	Stratum2 RR	Interaction?	Confounding?
1	6.00	1.02	3.50		
2	2.00	1.02	3.50		
3	1.70	0.03	3.50		
4	4.10	1.00	1.00		
5	4.20	4.00	4.10		

Real example: VaxGen HIV Vaccine Trial



Source: VaxGen, Inc.

Example: VaxGen HIV Vaccine Trial

Risk Ratio for all participants: 5.7% / 5.8% = 0.98

No protection

Risk Ratio for African Americans: 2.0% / 8.1% = 0.25

75% protection!

Effect modification: race modifies the effect of HIV vaccine

“race” is the “effect measure modifier” (using RR as effect measure)

Other examples

- Age and measles vaccination
- Smoking during pregnancy, birth weight, and maternal age
- Smoking, oral contraceptives, and myocardial infarction
- Cardiovascular risks of HRT: years since menopause
- Race and antihypertensive medications
- Circumcision and HIV: heterosexual vs MSM

Comparison of Vaccination with Measles-Mumps-Rubella Vaccine at 9, 12, and 15 Months of Age

Stephen C. Redd,[1] Gail E. King,[1,a] Janet L. Heath,[2] Baghar Forghani,[3] William J. Bellini,[2] and Lauri E. Markowitz[1]

[1]National Immunization Program and [2]National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia; [3]California State Department of Health Services, Viral and Rickettsial Disease Laboratory, Richmond, California

To determine seroconversion rates with measles-mumps-rubella vaccine administered to children at 9, 12, or 15 months of age, we undertook a prospective randomized trial. Among children vaccinated at 15 months of age, 98% seroconverted to measles, compared with 95% of those vaccinated at 12 months of age and 87% of those vaccinated at 9 months of age. In each age group, children of mothers born in or before 1963 had lower rates of seroconversion against measles, with the lowest rate in children vaccinated at 9 months. The seroconversion rate of rubella paralleled that of measles, with the lowest seroconversion rates in children vaccinated at 9 months of age whose mothers were born in or before 1963. The response to mumps varied little by age of the child or birth year of the child's mother. These results support the recommended age for first vaccination with measles-mumps-rubella at 12–15 months.

Age modifies the efficacy of MMR vaccination

Table 2. Seroconversion by vaccine antigen, age group vaccinated, and birth year of mother among children vaccinated with measles-mumps-rubella vaccine at 9, 12, or 15 months of age.

Vaccine antigen, birth year of mother	Randomization age group		
	9 months	12 months	15 months
Measles, overall	249/285 (87.4)	341/358 (95.3)	341/347 (98.3)
1963 or earlier	147/176 (83.5)	209/221 (94.6)	219/224 (97.8)
After 1963	102/109 (93.6)	132/137 (96.4)	122/123 (99.2)
Rubella, overall	249/273 (91.2)	335/353 (94.9)	319/331 (96.4)
1963 or earlier	148/167 (88.6)	208/218 (95.4)	206/213 (96.7)
After 1963	101/106 (95.3)	127/135 (94.1)	113/118 (95.8)
Mumps, overall	251/272 (92.3)	318/354 (89.8)	307/330 (93.0)
1963 or earlier	154/167 (92.2)	196/219 (89.5)	197/213 (92.5)
After 1963	97/105 (92.4)	122/135 (90.4)	110/117 (94.0)

NOTE. Data are no/total (%).

Journal of Infect Dis 2004

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Birth Weight and Smoking During Pregnancy—Effect Modification by Maternal Age

Steven H. Fox,[1,2] Thomas D. Koepsell,[1] and Janet R. Daling[1]

Cigarette smoking during pregnancy is an important, avoidable factor associated with low birth weight. Maternal age is also associated with variations in birth weight. Using birth certificate data from all 347,650 singleton births for which maternal age and birth weight were recorded during 1984–1988 in Washington State, this study investigated birth weight and smoking during pregnancy (yes/no) for mothers of different ages. In multiple linear regressions adjusted for race, marital status, parity, adequacy of prenatal care, and urban/rural residence, the decrement in mean birth weight associated with smoking grew steadily from 117 g for the youngest mothers (age less than 16 years) to 376 g for the oldest (age 40 years or more). Similarly, the adjusted relative risk of having a low weight birth (less than 2,500 g) for smokers compared with nonsmokers was lowest for mothers aged 16–17 years, at 1.43 (95% confidence interval 1.22–1.68), and increased steadily to 2.63 (95% confidence interval 1.77–3.90) for mothers aged 40 or more. This result suggests that the effect of exposure to cigarette smoking during pregnancy is modified by advancing maternal age. Further research using data that more precisely measure the exposure (cigarettes per day, years smoked) could help further clarify this issue and better address the public health question of whether smoking cessation programs ought to focus limited resources more selectively toward pregnant smokers in particular age groups. *Am J Epidemiol* 1994;139:1008–15.

Age 16 – 17 years:

RR = 1.43

Age: 40+ years:

RR = 2.63

Smoking has a bigger effect on risk of low birth weight in older than younger moms

ORIGINAL INVESTIGATION

Low-Dose Oral Contraceptive Use and the Risk of Myocardial Infarction

Lynn Rosenberg, ScD; Julie R. Palmer, ScD; R. Sowmya Rao, MS; Samuel Shapiro, MB, FRCP(Edin)

Background: Studies of oral contraceptives (OCs) containing 50 µg or more of estrogen suggest an increased risk of myocardial infarction (MI) among current users, particularly if they smoke heavily.

Objective: To assess whether use of the newer lower-dose OCs increases the risk of MI.

Methods: A case-control study was conducted from January 1985 through March 1999 in 75 hospitals in the greater-Boston and greater-Philadelphia areas. Data on OC use and MI risk factors were obtained by interview from 627 women with a nonfatal first MI (cases) and 2947 female hospital controls younger than 45 years.

Results: The overall odds ratio (OR) for current OC use relative to never used was 1.3 (95% confidence interval [CI], 0.8-2. 2). The OR was elevated, 2.5 (95% CI, 0.9-7.5), among heavy smokers (≥25 cigarettes per day) but close to 1.0 among lighter smokers (OR=0.8) and nonsmokers (OR=1.3). For current OC use together with heavy smoking relative to nonuse and nonsmoking, the OR was 32 (95 % CI, 12-81), considerably greater than that for heavy smoking alone, 12 (95% CI, 8.6-16). The ORs did not vary according to the type of formulation or the dose of estrogen; there were too few users to assess the new 20-µg preparations. Past OC use was unrelated to risk.

Conclusion: Current use of low-dose OCs in the United States is unrelated to an increased risk of MI among nonsmokers and light smokers, but users who smoke heavily may be at greatly increased risk.

Arch Intern Med. 2001;161:1065-1070

Low-dose OC use is a risk factor for MI in heavy smokers, but not in non-smokers and light smokers

Postmenopausal Hormone Therapy and Risk of Cardiovascular Disease by Age and Years Since Menopause

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JoAnn E. Manson, MD, DrPH
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Vanessa M. Barnabei, MD, PhD
Marcia Ko, MD
Andrea Z. LaCroix, PhD
Karen L. Margolis, MD
Marcia L. Stefanick, PhD

Context The timing of initiation of hormone therapy may influence its effect on cardiovascular disease.

Objective To explore whether the effects of hormone therapy on risk of cardiovascular disease vary by age or years since menopause began.

Design, Setting, and Participants Secondary analysis of the Women's Health Initiative (WHI) randomized controlled trials of hormone therapy in which 10 739 postmenopausal women who had undergone a hysterectomy were randomized to conjugated equine estrogens (CEE) or placebo and 16 608 postmenopausal women who had not had a hysterectomy were randomized to CEE plus medroxyprogesterone acetate (CEE + MPA) or placebo. Women aged 50 to 79 years were recruited to the study from 40 US clinical centers between September 1993 and October 1998.

Main Outcome Measures Statistical test for trend of the effect of hormone therapy on coronary heart disease (CHD) and stroke across categories of age and years since menopause in the combined trials.

Results In the combined trials, there were 396 cases of CHD and 327 cases of stroke in the hormone therapy group vs 379 cases of CHD and 239 cases of stroke in the placebo group. For women with less than 10 years since menopause began, the hazard ratio (HR) for CHD was 0.76 (95% confidence interval [CI], 0.50-1.16); 10 to 19 years, 1.10 (95% CI, 0.84-1.45); and 20 or more years, 1.28 (95% CI, 1.03-1.58) (*P* for trend = .02). The estimated absolute excess risk for CHD for women within 10 years of menopause was –6 per 10 000 person-years; for women 10 to 19 years since menopause began, 4 per 10 000 person-years; and for women 20 or more years from menopause onset, 17 per 10 000 person-years. For the age group of 50 to 59 years, the HR for CHD was 0.93 (95% CI, 0.65-1.33) and the absolute excess risk was –2 per 10 000 person-years; 60 to 69 years, 0.98 (95% CI, 0.79-1.21) and –1 per 10 000 person-years; and 70 to 79 years, 1.26 (95% CI, 1.00-1.59) and 19 per 10 000 person-years (*P* for trend = .16). Hormone therapy increased the risk of stroke (HR, 1.32; 95% CI, 1.12-1.56). Risk did not vary significantly by age or time since menopause. There was a nonsignificant tendency for the effects of hormone therapy on total mortality to be more favorable in younger than older women (HR of 0.70 for 50-59 years; 1.05 for 60-69 years, and 1.14 for 70-79 years; *P* for trend = .06).

Conclusions Women who initiated hormone therapy closer to menopause tended to have reduced CHD risk compared with the increase in CHD risk among women more distant from menopause, but this trend test did not meet our criterion for statistical significance. A similar nonsignificant trend was observed for total mortality but the risk of stroke was elevated regardless of years since menopause. These data should be considered in regard to the short-term treatment of menopausal symptoms.

IN OBSERVATIONAL STUDIES OF women with and without existing coronary heart disease (CHD), the use of postmenopausal hormone therapy is associated with a reduced risk of CHD events.[1] In contrast, clinical trials have shown no benefit and some trials have suggested an increased risk of CHD during the first year after randomization.[2,3] The Women's Health Initiative (WHI) reported a hazard ratio (HR) for CHD of 0.95 (95% confidence interval [CI], 0.70-1.16) in the trial of conjugated equine estrogens (CEE) and an HR of 1.24 (95% CI, 1.00-1.54) in the trial of CEE plus medroxyprogesterone acetate (CEE + MPA).[3,4] While observational studies have evidently overestimated benefit due to confounding, selection biases, and other limita-

If HRT is used soon after menopause, it appears protective for CHD.

If HRT is used years after menopause,
It appears to be a risk factor for CHD

LESSER RESPONSE TO ANGIOTENSIN-CONVERTING–ENZYME INHIBITOR THERAPY IN BLACK AS COMPARED WITH WHITE PATIENTS WITH LEFT VENTRICULAR DYSFUNCTION

DEREK V. EXNER, M.D., M.P.H., DANIEL L. DRIES, M.D., M.P.H., MICHAEL J. DOMANSKI, M.D., AND JAY N. COHN, M.D.

ABSTRACT

Background Black patients with heart failure have a poorer prognosis than white patients, a difference that has not been adequately explained. Whether racial differences in the response to drug treatment contribute to differences in outcome is unclear. To address this issue, we pooled and analyzed data from the Studies of Left Ventricular Dysfunction (SOLVD) prevention and treatment trials, two large, randomized trials comparing enalapril with placebo in patients with left ventricular dysfunction.

Methods We used a matched-cohort design in which up to four white patients were matched with each black patient according to trial, treatment assignment, sex, left ventricular ejection fraction, and age. A total of 1196 white patients (580 from the prevention trial and 616 from the treatment trial) were matched with 800 black patients (404 from the prevention trial and 396 from the treatment trial). The average duration of follow-up was 35 months in the prevention trial and 33 months in the treatment trial.

Results The black patients and the matched white patients had similar demographic and clinical characteristics, but the black patients had higher rates of death from any cause (12.2 vs. 9.7 per 100 person-years) and of hospitalization for heart failure (13.2 vs. 7.7 per 100 person-years). Despite similar doses of drug in the two groups, enalapril therapy, as compared with placebo, was associated with a 44 percent reduction (95 percent confidence interval, 27 to 57 percent) in the risk of hospitalization for heart failure among the white patients ($P<0.001$) but with no significant reduction among black patients ($P=0.74$). At one year, enalapril therapy was associated with significant reductions from base line in systolic blood pressure (by a mean [±SD] of 5.0±17.1 mm Hg) and diastolic blood pressure (3.6±10.6 mm Hg) among the white patients, but not among the black patients. No significant change in the risk of death was observed in association with enalapril therapy in either group.

Conclusions Enalapril therapy is associated with a significant reduction in the risk of hospitalization for heart failure among white patients with left ventricular dysfunction, but not among similar black patients. This finding underscores the need for additional research on the efficacy of therapies for heart failure in black patients. (N Engl J Med 2001;344:1351-7.)

LARGE-SCALE trials of therapy for heart failure over the past decade have shown improvements in outcome with angiotensin-converting–enzyme (ACE) inhibitors and beta-blockers.[1-7] In the Studies of Left Ventricular Dysfunction (SOLVD), two concurrent trials evaluating the efficacy of enalapril in patients with left ventricular systolic dysfunction, enalapril was associated with a 16 percent reduction in the risk of death from any cause among patients with symptoms[6] and a 20 percent reduction in the risk of death from any cause or hospitalization for heart failure among patients without symptoms.[7] These results and the results of other studies[1-5] led to the recommendation that all patients who have heart failure accompanied by a low ejection fraction and who can tolerate ACE inhibitors and beta-blockers should be treated with both agents.[8,9]

However, data from the second Vasodilator–Heart Failure Trial (V-HeFT II) indicated that although enalapril therapy, as compared with treatment with a combination of hydralazine and isosorbide dinitrate, was associated with a significant reduction in the risk of death from any cause among white patients, no such benefit was observed among black patients.[10] Furthermore, in the Beta-Blocker Evaluation of Survival Trial it was found that white, but not black, patients with heart failure appear to benefit from the beta-blocker bucindolol,[11] suggesting that there may be racial differences in therapeutic response. A critical impediment to the analysis of racial differences in therapeutic response is the underrepresentation of black patients in trials of therapy for heart failure. In V-HeFT I and II,[2,12] 27 percent of the patients were black, and in SOLVD,[6,7] 12 percent were black. In other trials, the proportion of black patients was considerably smaller,[1-5] in part because of the inclusion of patients from large numbers of European centers.

A previous analysis of data from SOLVD identified a poorer outcome in black patients than in white patients.[13] Black patients were 28 percent more likely to die from any cause and 37 percent more likely to

Certain anti-hypertensives do not work well in black patients (race is an effect modifier)

U.S. Food and Drug Administration

U.S. Department of Health and Human Services

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P05-32
June 23, 2005

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FDA Approves BiDil Heart Failure Drug for Black Patients

The Food and Drug Administration (FDA) approved BiDil (bye-DILL), a drug for the treatment of heart failure in self-identified black patients, representing a step toward the promise of personalized medicine.

Heart failure is a condition in which the heart is weakened and does not pump enough blood. It can be caused by a variety of damage to the heart, including heart attacks, high blood pressure, and infections.

The approval of BiDil was based in part on the results of the African-American Heart Failure Trial (A-HeFT). The study, which involved 1,050 self-identified black patients with severe heart failure who had already been treated with the best available therapy, was conducted because two previous trials in the general population of severe heart failure patients found no benefit, but suggested a benefit of BiDil in black patients. Patients on BiDil experienced a 43% reduction in death and a 39% decrease in hospitalization for heart failure compared to placebo, and a decrease of their symptoms of heart failure.

"Today's approval of a drug to treat severe heart failure in self-identified black population is a striking example of how a treatment can benefit some patients even if it does not help all patients," said Dr. Robert Temple, FDA Associate Director of Medical Policy. "The information presented to the FDA clearly showed that blacks suffering from heart failure will now have an additional safe and effective option for treating their condition. In the future, we hope to discover characteristics that identify people of any race who might be helped by Bidil."

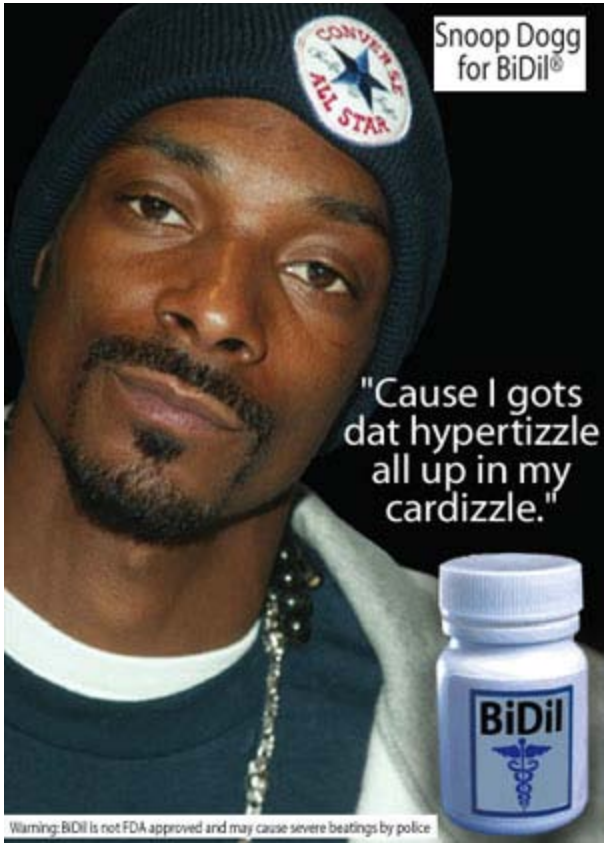
BiDil is a combination of two older drugs, neither approved for heart failure--hydralazine and isosorbide dinitrate.

As an anti-hypertensive agent, hydralazine relaxes the arteries, and decreases the work of the heart. The anti-anginal agent, isosorbide dinitrate, relaxes the veins as well as the arteries. Isosorbide seems to work by releasing nitric oxide at the blood vessel wall, but its effect usually wears off after half a day. Hydralazine may prevent this loss of effect. But how the two drugs work together is not fully known.

Some common side effects with the use of BiDil are headache and dizziness.

BiDil is marketed by NitroMed, Inc. of Lexington, MA.

Certain anti-hypertensives appear to work better in black patients (race is an effect modifier)


Snoop Dogg for BiDil®
"Cause I gots dat hypertizzle all up in my cardizzle."
BiDil
Warning: BiDil is not FDA approved and may cause severe beatings by police


THE K CHRONICLES
BY KEITH KNIGHT
I ain't gonna try it... You try it!!
No way!! I ain't gonna try it!!
Well.. Somebody's gotta try it!!
Well, that somebody ain't gonna be me!!
©1995 K. KNIGHT
BIDIL, THE FIRST GOVERNMENT APPROVED DRUG SPECIFICLY MADE FOR A PARTICULAR RACE, IS SUPPOSED TO HELP BLACK FOLKS COMBAT HEART FAILURE...
WRITE!! P.O. BOX 591794 SAN FRANCISCO CA 94159
NOW... GIVEN THE UNITED STATES GOVERNMENT'S LESS THAN STELLAR TRACK RECORD CONCERNING THE HEALTH OF ITS BLACK CITIZENS...
TUSKEGEE SYPHILIS EXPERIMENT (1932-1972)
EUGENIC STERILIZATION (1907-1970s)
RADIATION EXPERIMENTS (1932-1988)
..IT'S REALLY NO SURPRISE THAT FOLKS MAY BE A BIT RELUCTANT TO TRY THE DRUG..
DO YOU REMEMBER THE LAST DRUG THE U.S. GOVT. TARGETED TOWARDS BLACKS?
CRACK!!
TOO BAD THIS STUFF DIDN'T COME OUT BACK WHEN I WAS IN COLLEGE....
Here, Keith.. Try These...
Sure!! What are they?
BIRTH CONTROL PILLS
CUZ I TOOK ANYTHING PEOPLE HANDED ME...
I CAN'T WAIT TO HEAR THE APOLOGY THE SENATE WILL GIVE 50 YEARS FROM NOW FOR THE INFAMOUS BIDIL "MISTAKE"..
THE U.S. SENATE hereby apologizes to THE LAST surviving black person..
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Journal of Asthma, 44:639–648, 2007

ISSN: 0277-0903 print / 1532-4303 online
DOI: 10.1080/02770900701554441

informa
healthcare

ORIGINAL ARTICLE

Ethnic-Specific Differences in Bronchodilator Responsiveness Among African Americans, Puerto Ricans, and Mexicans with Asthma

MARIAM NAQVI, B.S.,[1,†] SHANNON THYNE, M.D.,[1,*,†] SHWETA CHOUDHRY, PH.D., M.SC.,[1] HUI-JU TSAI, PH.D.,[1] DANIEL NAVARRO, M.D.,[1] RICHARD A. CASTRO, M.D.,[1] SYLVETTE NAZARIO, M.D.,[2] JOSE R. RODRIGUEZ-SANTANA, M.D.,[3] JESUS CASAL, M.D.,[2] ALFONSO TORRES, M.D.,[2] ROCIO CHAPELA, M.D.,[4] H. GEOFFREY WATSON, M.D.,[5] KELLEY MEADE, M.D.,[6] MICHAEL LENOIR, M.D.,[7] PEDRO C. AVILA, M.D.,[8] WILLIAM RODRIGUEZ-CINTRON, M.D.,[3] AND ESTEBAN GONZÁLEZ, BURCHARD, M.D., M.P.H.[1]

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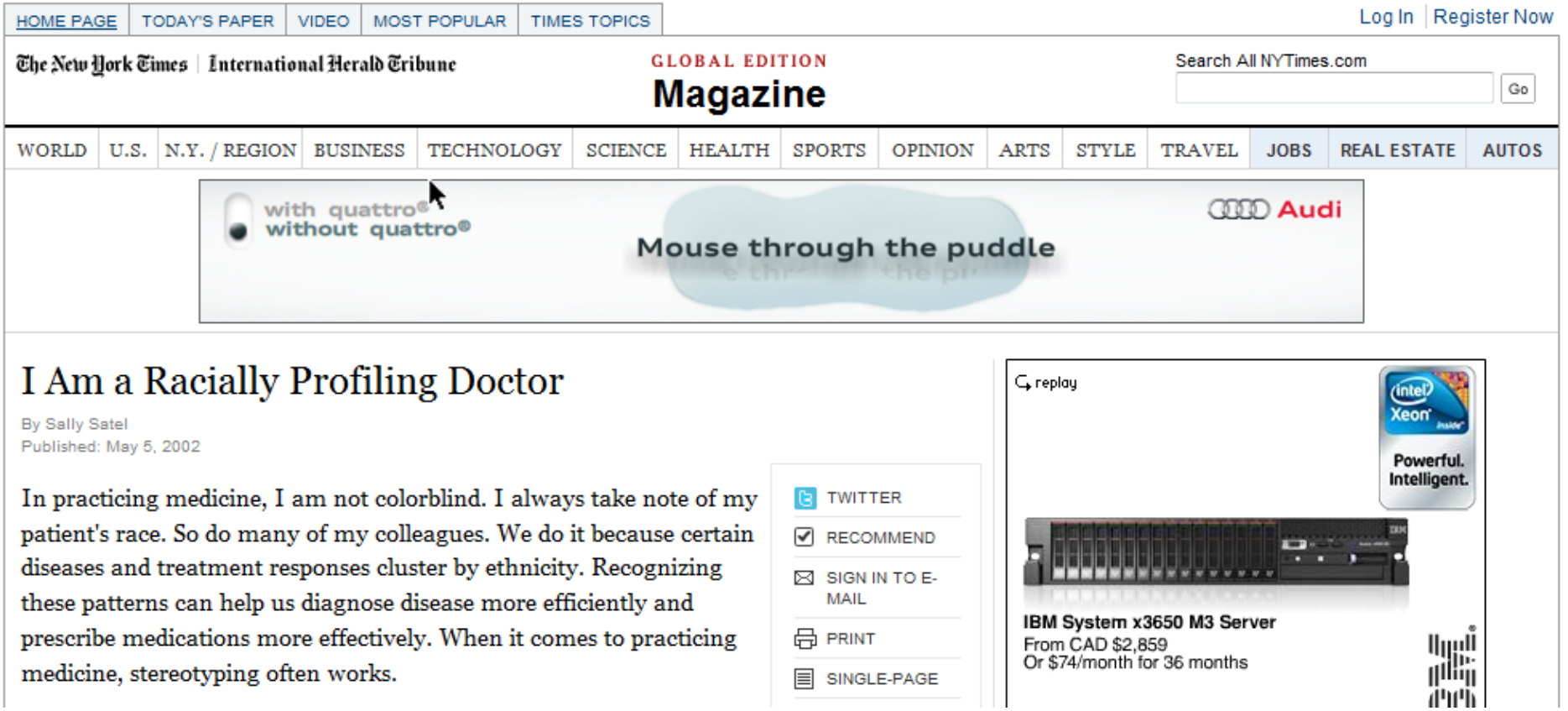
[5]*The James A. Watson Wellness Center, Oakland, California*
[6]*Children's Hospital and Research Institute, Oakland, California*
[7]*Bay Area Pediatrics, Oakland, California*
[8]*Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA*

Socioeconomic and environmental differences do not fully explain differences in asthma prevalence, morbidity, and mortality among Puerto Ricans, African Americans, and Mexican Americans. Differences in response to albuterol may be a factor. We compared bronchodilator responsiveness between these three populations. All groups demonstrated below expected responsiveness. Puerto Ricans of all ages and African American children with moderate-to-severe asthma demonstrated the lowest responsiveness overall. Among subjects with moderate-to-severe asthma, children were even less likely than adults to show the expected bronchodilator response. We conclude that ethnic-specific differences in bronchodilator drug responsiveness exist between Mexicans, Puerto Ricans, and African Americans with asthma. This may be of importance in asthma management.



http://www.nytimes.com/2002/05/05/magazine/i-am-a-racially-profiling-doctor.html

Is “personalized medicine” the ultimate example of effect modification?

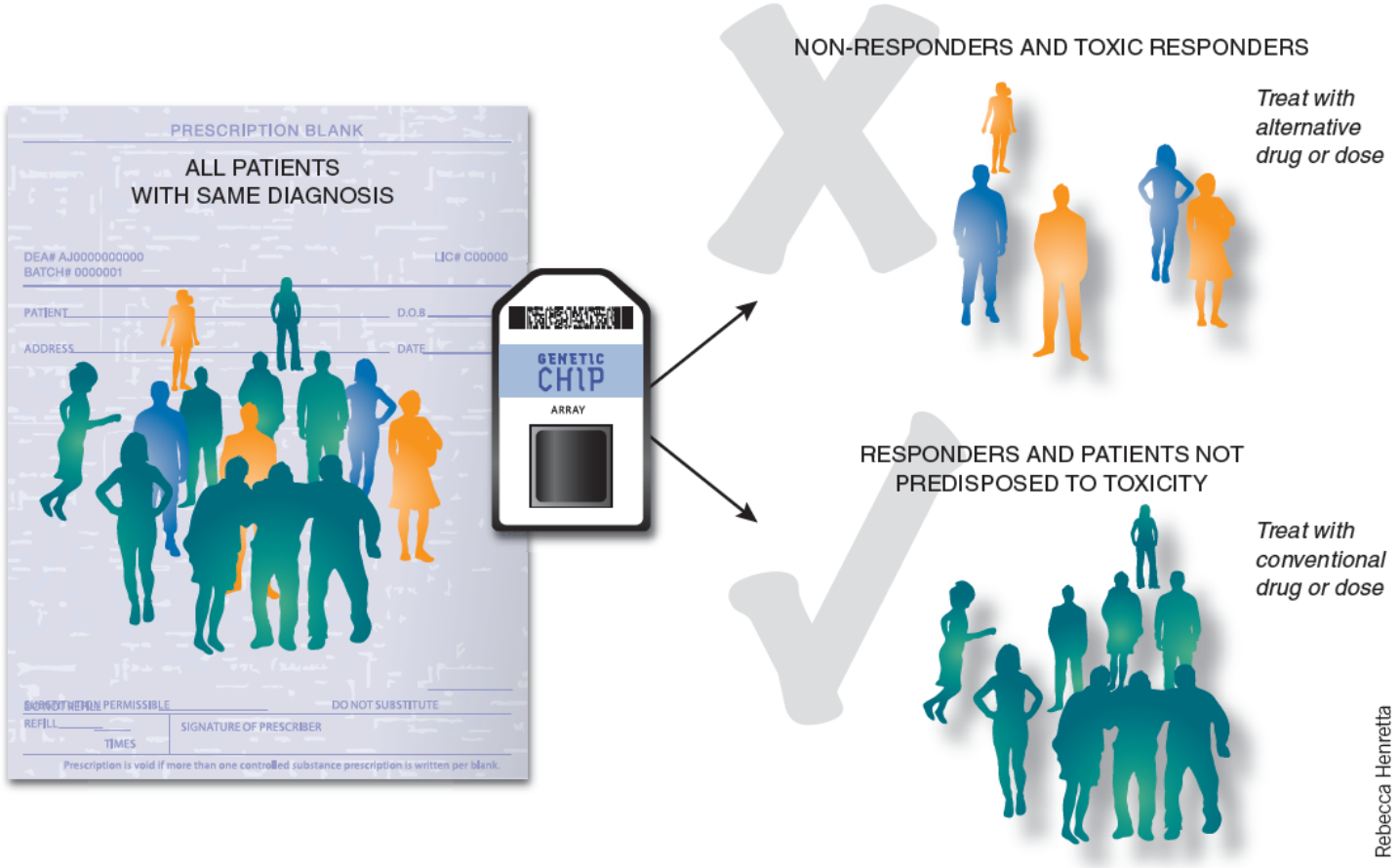


Figure 1 Pharmacogenomic approach to personalized medicine. Drug therapy is chosen for each patient based on their particular genetic profile.

Clinical Pharmacology & Therapeutics (2007) **81,** 311–315.

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- Restless Legs Syndrome
- Age-related Macular Degeneration
- Parkinson's Disease
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June 24, 2010

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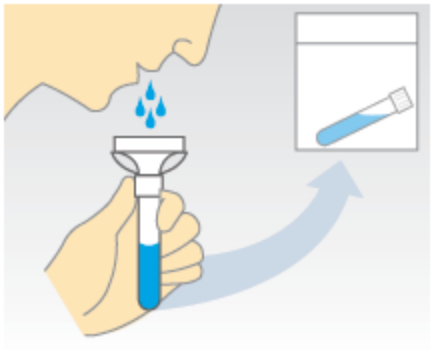
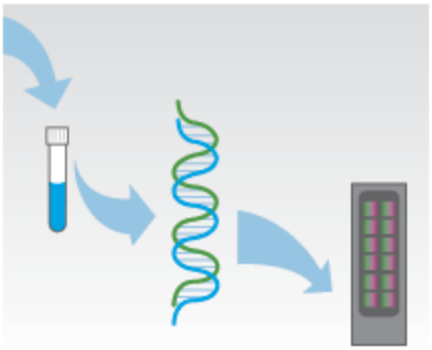


2. Claim your kit, spit into the tube, and send it to the lab.



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There are several reasons why we cannot provide diagnoses or otherwise assess your health. First, because we don't sequence your entire genome, we may miss variation that has an impact on your health. Genetic testing services, which restrict themselves to a relatively small set of diseases, provide more exhaustive analysis of the relevant genes. More importantly, in order to make a diagnosis, your doctor considers not only your genetic information, but also your particular personal and family history and your physical condition, as well as any symptoms you are experiencing. Other confirmatory tests are usually required, since your genotype is only part of the equation. If you learn that your personal genetic information suggests that you have a higher than average chance of developing a particular disease, you may wish to discuss your genetic information with your physician or another medical expert.

New Debate Over Circumcision, HIV Reduction

By CATHERINE GUTHRIE Tuesday, Oct. 07, 2008

Lenora Gim / Photonica / Getty

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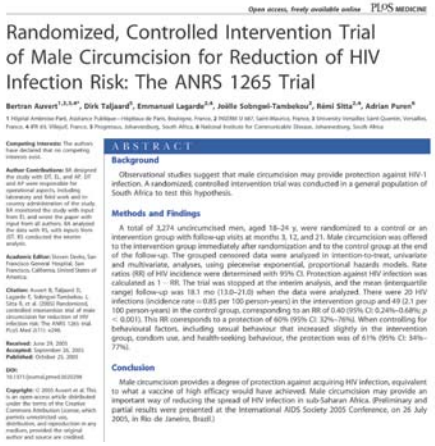
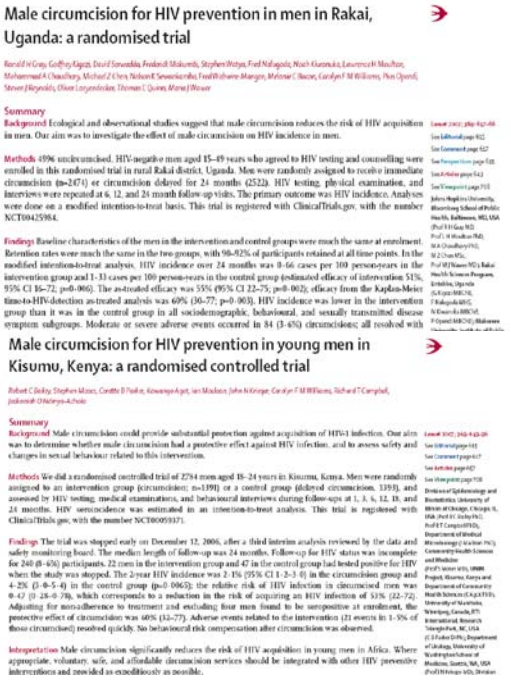
Male circumcision has been shown to protect men from acquiring H.I.V. infection during sex with women — it has reduced female-to-male transmission rates by 48% to 60% in sub-Saharan Africa — but that protective effect appears less reliable among men who have sex with men, according to a new meta-analysis published Oct. 7 in the *Journal of the American Medical Association (J.A.M.A.)*.

Heterosexual



Randomized, Controlled Intervention Trial of Male Circumcision for Reduction of HIV Infection Risk: The ANRS 1265 Trial



Male circumcision for HIV prevention in men in Rakai, Uganda: a randomised trial

Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomised controlled trial

Men who have sex with men

Circumcision Status and Risk of HIV and Sexually Transmitted Infections Among Men Who Have Sex With Men

A Meta-analysis

Gregorio A. Millett, MPH
Stephen A. Flores, PhD
Gary Marks, PhD
J. Bailey Reed, MD, MPH
Jeffrey H. Herbst, PhD

Circumcision appears to have a protective effect in heterosexual men, but not homosexual men

Heterogeneity of effects

- Can occur at the level of:
  - Individual study: within subgroups of a single study or trial
    - Seen in subgroup or stratified analyses within a study
  - Across studies: if several studies are done on the same topic, the effect measures may vary across studies
    - Seen in meta-analyses (across trials)

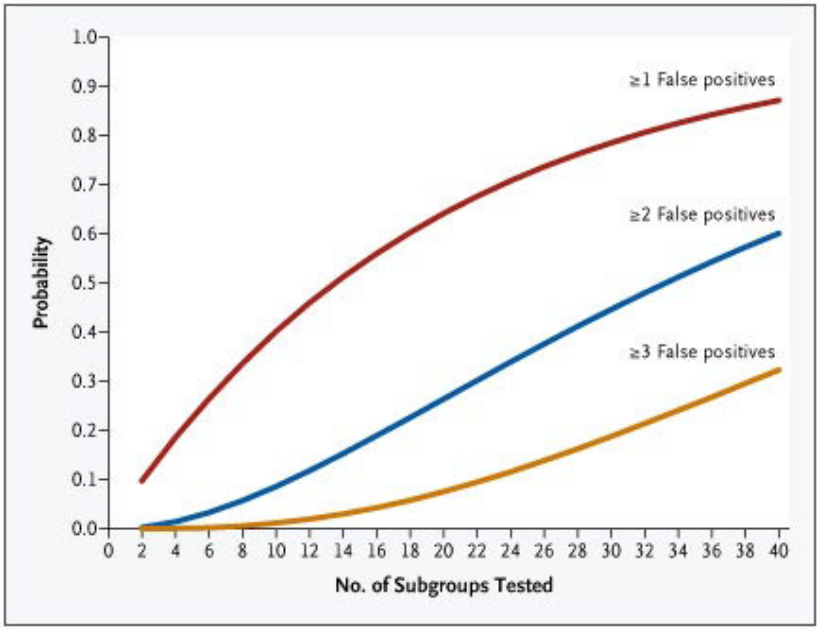
Heterogeneity of effects within a trial or study

- The GISSI trial showed that streptokinase reduced overall mortality roughly 20%. Subgroup analyses suggested that benefit was confined to patients with anterior myocardial infarction, to those under the age of 65 years, and to those treated within 6 hours of the onset of symptoms. But power in each subgroup was low.
  - Subsequent studies demonstrated benefit irrespective of site of infarction, age of patient, and time from onset of symptoms to treatment.
- ISIS-2 trial on streptokinase and aspirin: investigators presented results by the astrological sign under which patients were born. Aspirin was clearly beneficial overall and for persons born under all signs except Libra and Gemini, for which apparent harmful effects were observed.

Yusuf S et al. JAMA 1991

Hazards of subgroup analyses

- When multiple interaction tests are conducted, each using a nominal criterion (say, P=0.05) to assess statistical significance, the probability of a false positive result — that is, of appearing to find an interaction when none exists — can be greatly inflated.
- For example, when treatments have identical efficacy, the probability of finding at least one "statistically significant" interaction test when 10 independent interaction tests are undertaken is 40 percent



Lagakos, NEJM 2006

3: Probability of at least one significant result at the 5% significance level given no true differences

Number of tests	Probability
1	0.05
2	0.10
3	0.14
5	0.23
10	0.40
20	0.64

Cook, MJA, 2004

A consumer's guide to subgroup analyses

Guidelines for deciding whether apparent differences in subgroup response are real

1. Is the magnitude of the difference clinically important?
2. Was the difference statistically significant?
3. Did the hypothesis precede rather than follow the analysis?
4. Was the subgroup analysis one of a small number of hypotheses tested?
5. Was the difference suggested by comparisons within rather than between studies?
6. Was the difference consistent across studies?
7. Is there indirect evidence that supports the hypothesised difference?

AD Oxman, GH Guyatt. Annals of Internal Medicine 1992 116:78-84.

Heterogeneity in effects across studies (meta-analyses)

Association between smoking and TB mortality

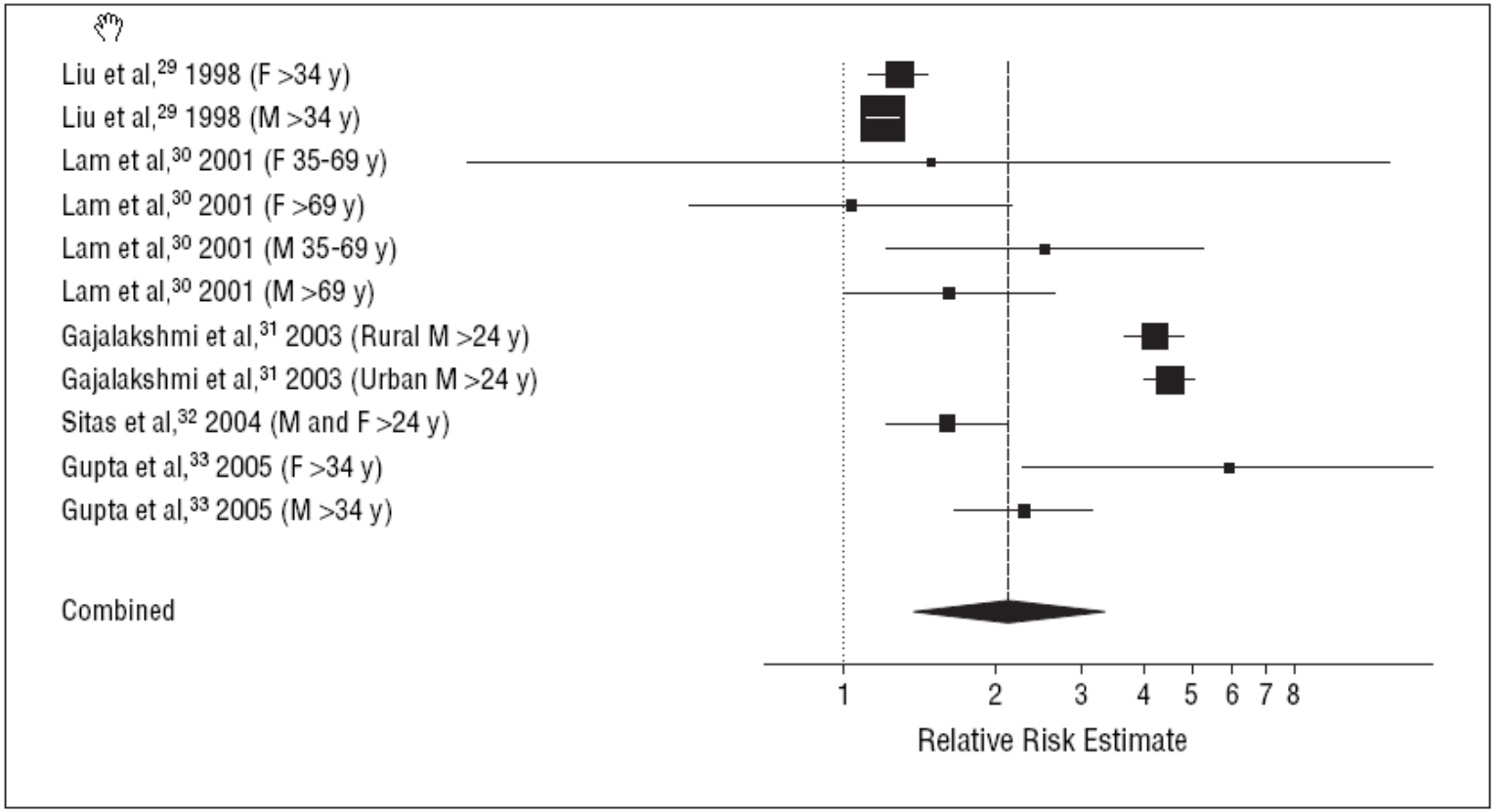


Figure 5. Forest plot of studies[29-33] that examined smoking and tuberculosis mortality. The sex and age of the study population are shown on the y-axis.

Bates et al. Arch Intern Med 2007

Heterogeneity in effects across studies (meta-analyses)

Meta-analysis on efficacy of BCG vaccination for TB

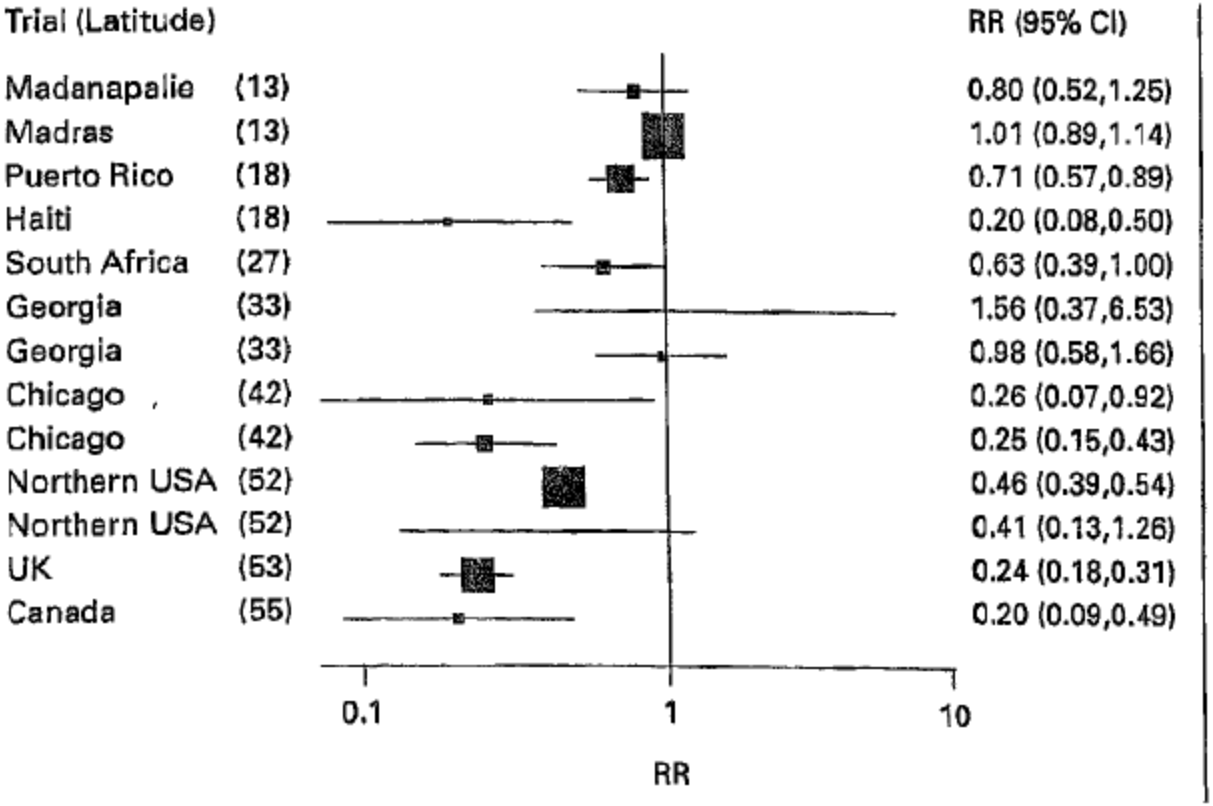
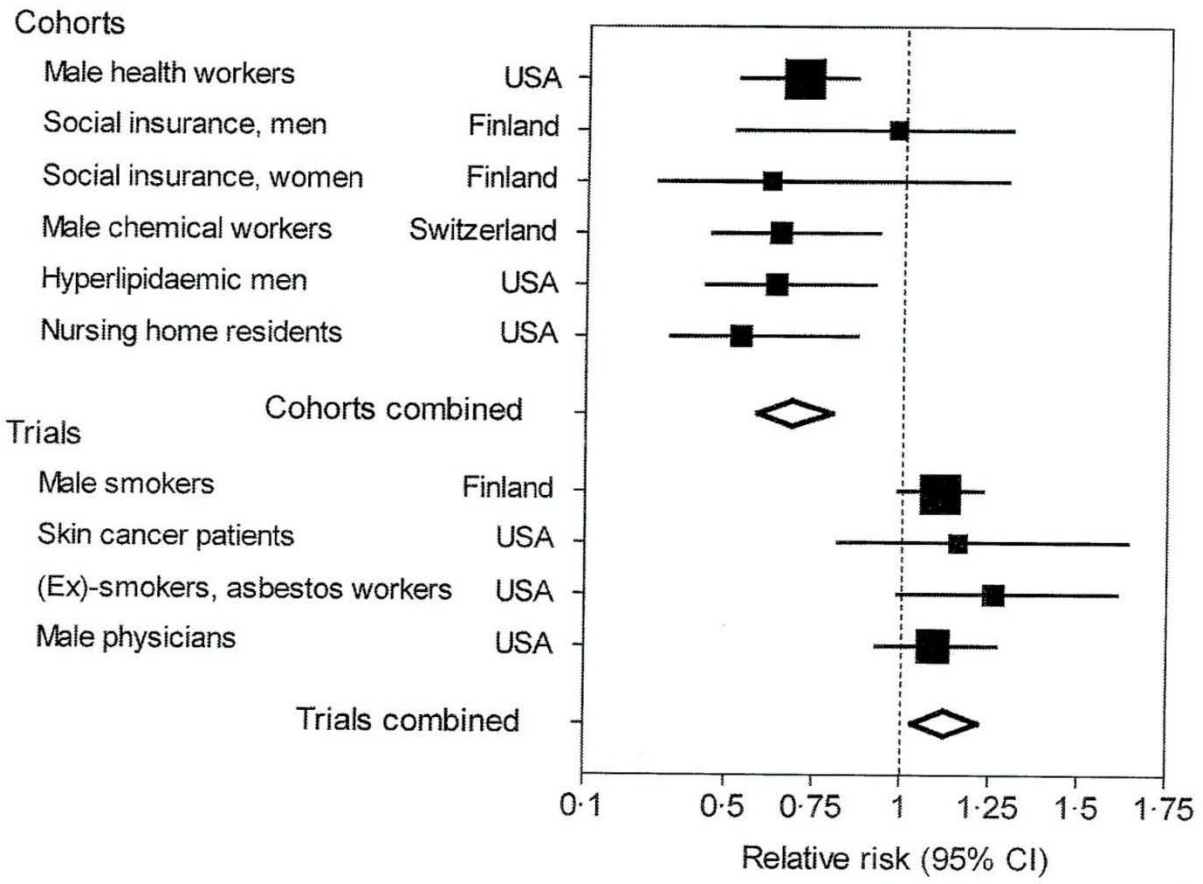


Fig 4. Forest plot of trials of BCG vaccine to prevent tuberculosis. Trials are ordered according to the latitude of the study location, expressed as degrees from the equator. No meta-analysis is shown (CI = confidence intervals, RR = relative risk) (adapted from Colditz *et al.*[47]).

Subgroup analysis within meta-analysis

Beta-carotene intake and cardiovascular mortality



Egger et al. Systematic reviews in health care. London: BMJ books, 2001.

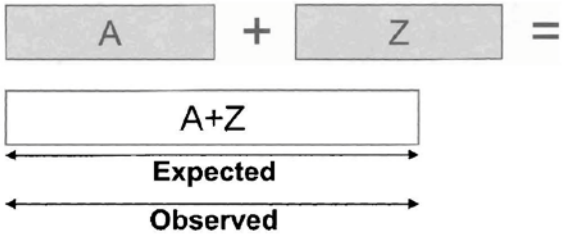
Definition based on the comparison between observed and expected joint effects of a risk factor and a third variable
[deviation from additive or multiplicative joint effects]

Is the whole more (or less) than the sum (or product) of its parts?

This is often called “statistical interaction”

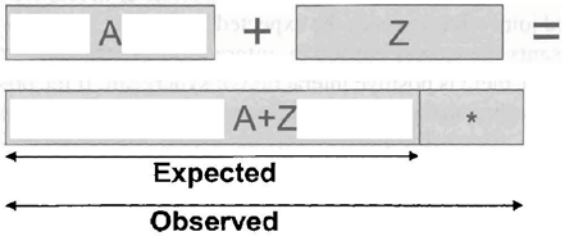
Observed vs expected joint effects of a risk factor and a third variable

A. When there is *no* interaction, the *observed* joint effect of risk factors A and Z equals the sum of their independent effects:



No interaction

B. When there is *positive* interaction (*synergism*), the *observed* joint effect of risk factors A and Z is *greater* than the *expected* on the basis of summing their independent effects:



* Excess due to positive interaction

Positive interaction

C. When there is *negative* interaction (*antagonism*), the *observed* joint effect of risk factors A and Z is *smaller* than the *expected* on the basis of summing their independent effects:

† "Deficit" due to negative interaction

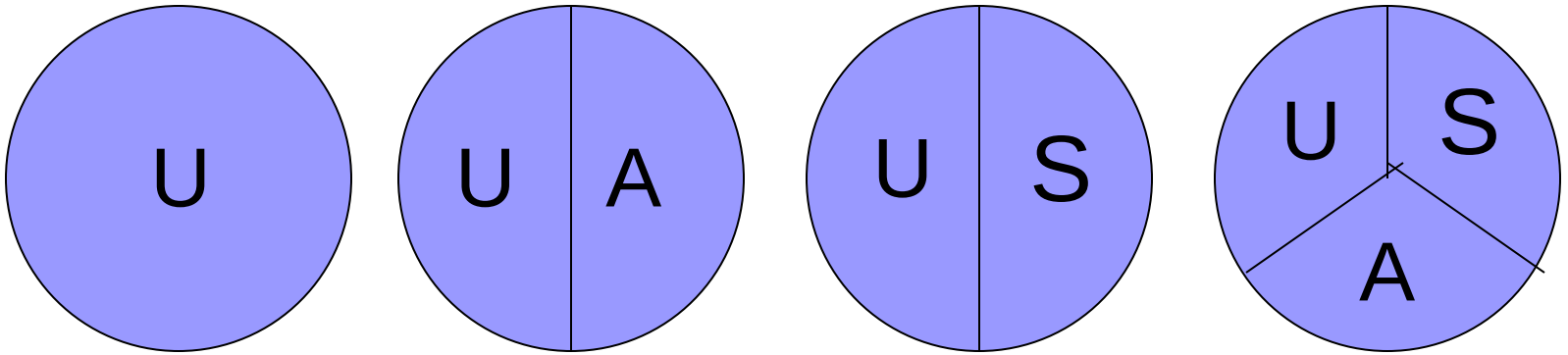
Negative interaction

Szklo & Nieto, Epidemiology: Beyond the basics. 2007

Definition based on the comparison between observed and expected joint effects of a risk factor and a third variable

- Interaction on an "additive" scale (additive interaction)
  - Effect measure modification when risk difference is used as measure of effect
  - Additive statistical model:
    - Linear regression: $y = a + b_1x_1 + b_2x_2$
- Interaction on a "multiplicative" scale (multiplicative interaction)
  - Effect measure modification when risk ratio is used as measure of effect
  - Multiplicative statistical model:
    - Logistic regression: $odds = \frac{p}{1-p} = e^{b0} \times e^{b1X1} \times e^{b2X2} \times e^{b3X3} \times \ldots \times e^{bkXk}$

Example: Smoking, asbestos, lung cancer



Example: Smoking, asbestos & lung cancer

Death rates from lung cancer (per 100,000)

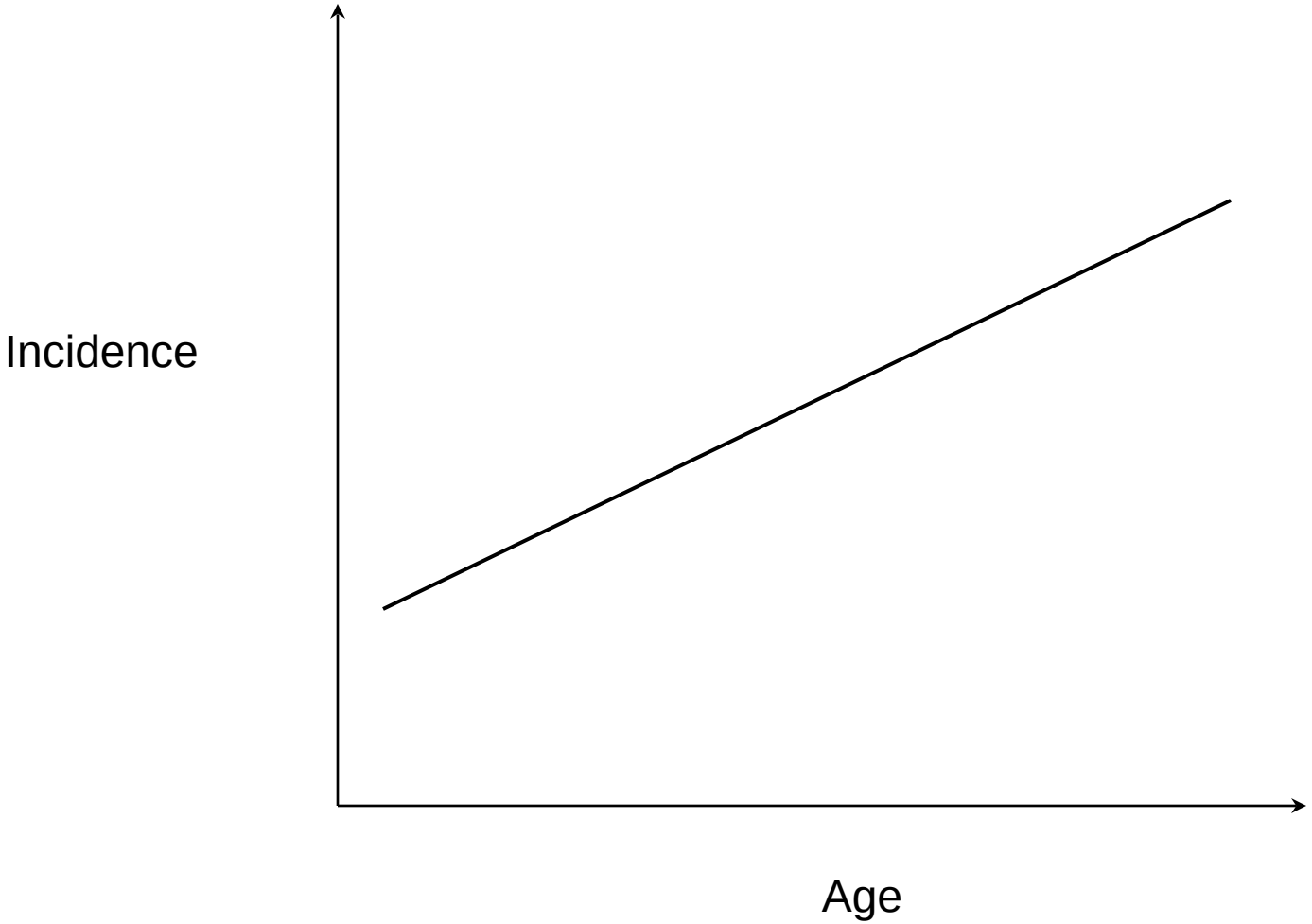
Cigarette smoking	Asbestos exposure	
	No	Yes
No	11	58
Yes	123	602

Does smoking modify the effect of asbestos on cancer?

Risk difference in non-smokers = 47 (58 – 11)
Risk difference in smokers = 479 (602 – 123)
Risk ratio in non-smokers = 5.2 (58/11)
Risk ratio in smokers = 4.9 (602/123)

Data: Hammond, 1979

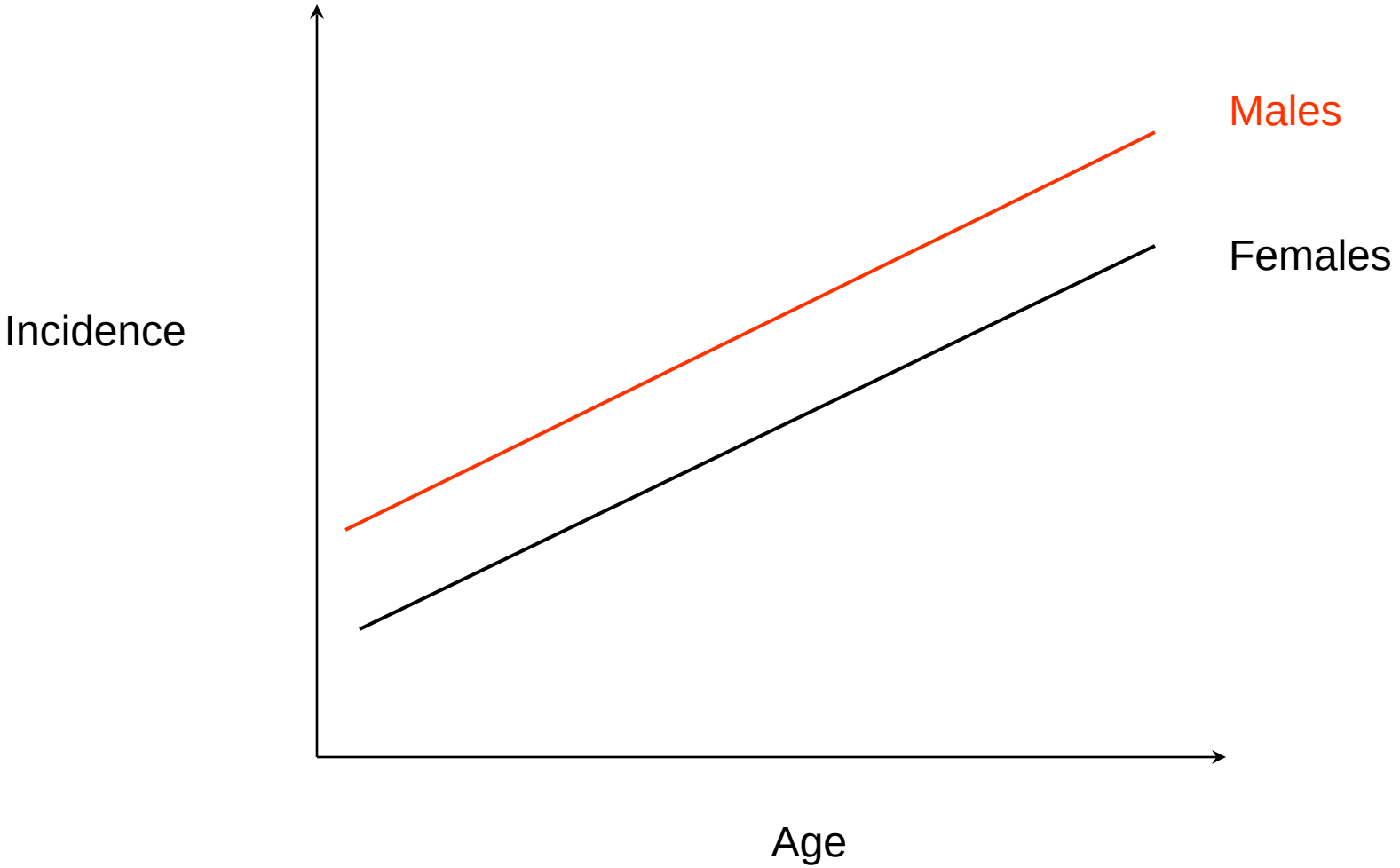
Consider a study to explore the association between age and incidence of a disease



Question: is the association between age and disease modified by sex?

Rothman, 2002

When data are stratified (by sex):



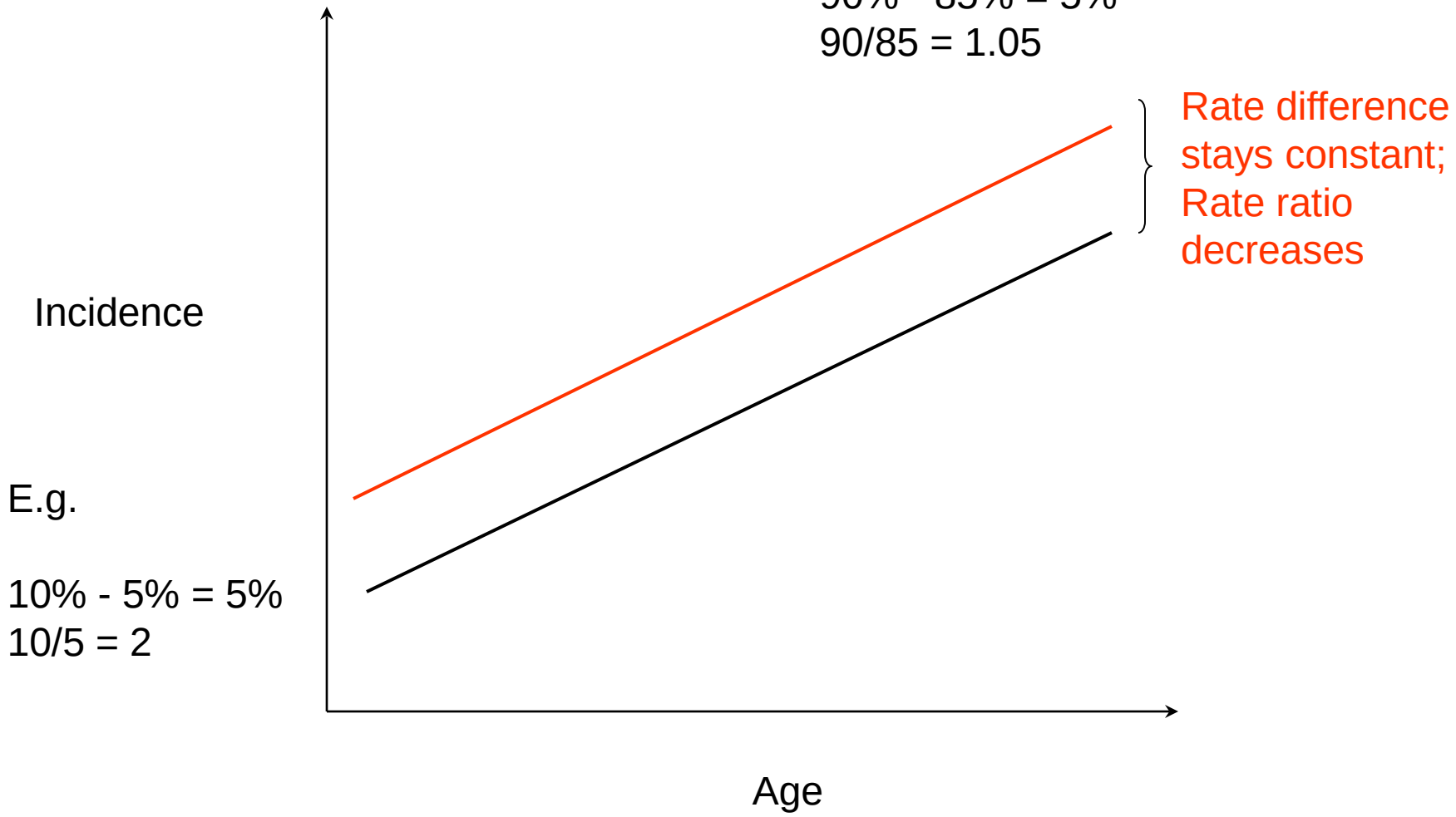
Question: is the association between age and disease modified by sex?

Rothman, 2002

Answer: depends on the scale used!

E.g.

90% - 85% = 5%
90/85 = 1.05

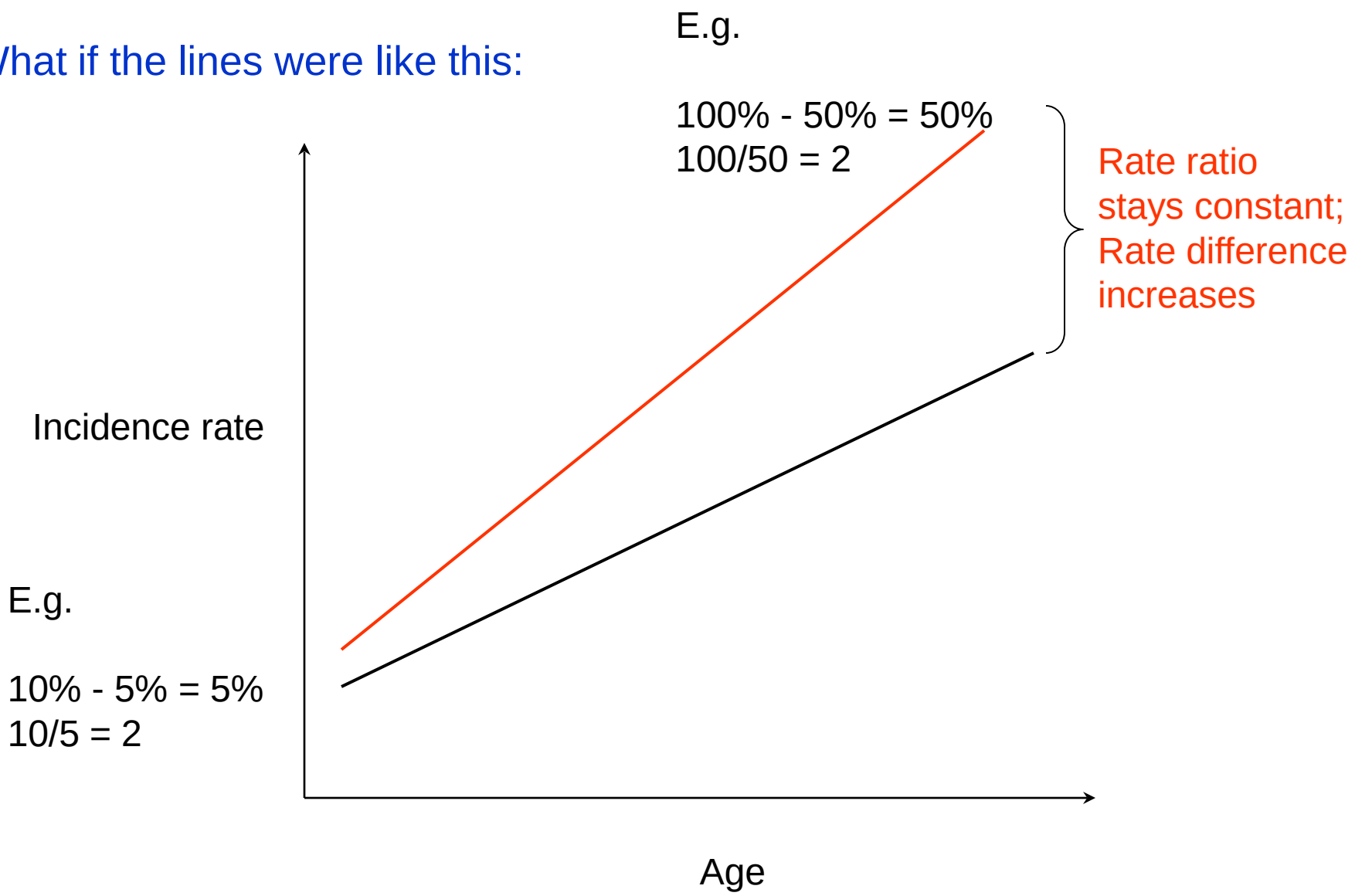


E.g.

10% - 5% = 5%
10/5 = 2

Rothman, 2002

What if the lines were like this:



Different Slopes for *Different Folks!*

Rothman, 2002

Statistical interaction is scale-dependent!

- When interaction is absent using ratio measures, it will necessarily be present when risk difference measures are used, and *vice versa*
- Because interaction is "scale-dependent" the term "effect measure modification" is more specific than "effect modification"
  - Its important to specify which scale (risk difference vs. risk ratio) was used in the analysis

Additive Interaction: departure from an additive statistical model

Death rates from Lung cancer (per 100,000)

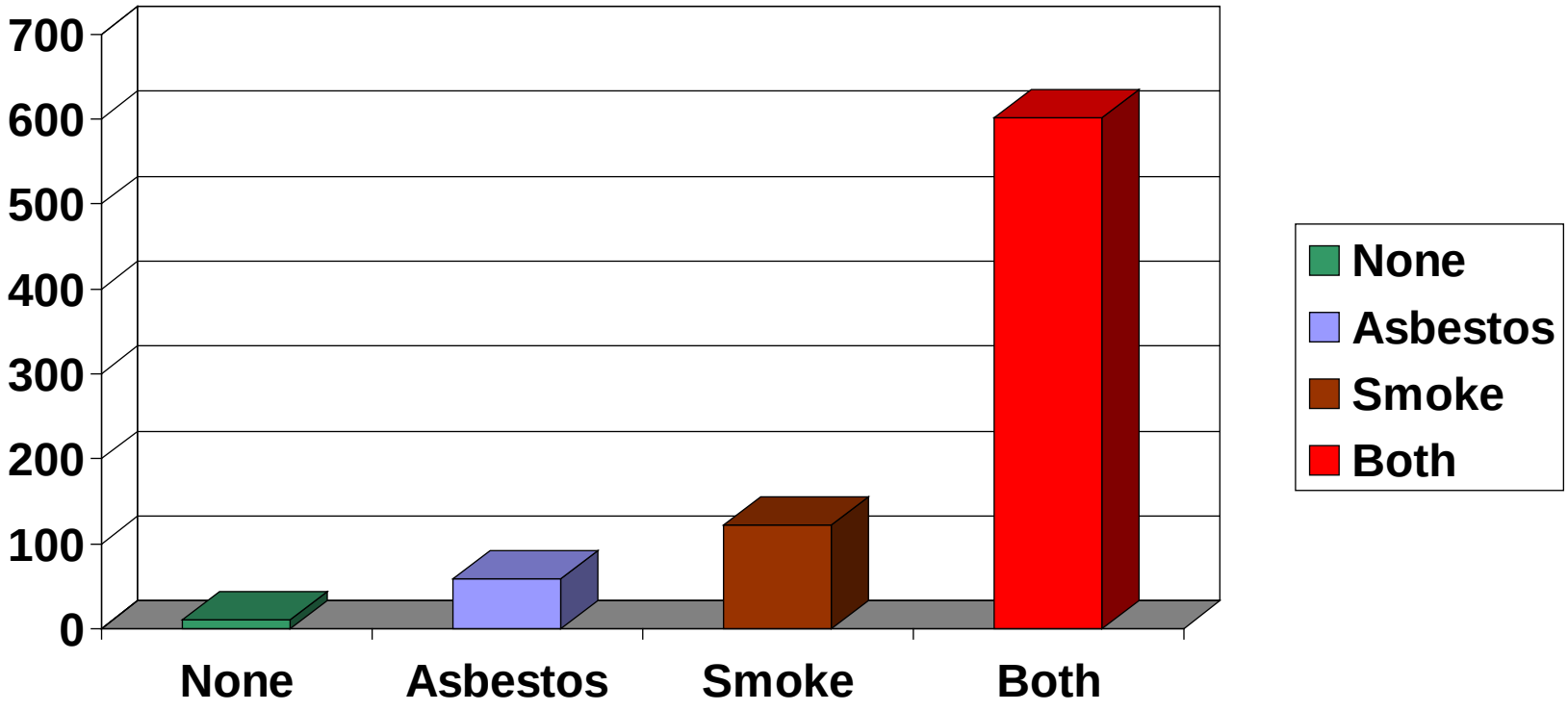
Cigarette smoking	Asbestos exposure	
	No	Yes
No	11 (baseline risk)	58
Yes	123	602

- Excess risk due to smoking: 123 – 11 = 112
- Excess risk due to asbestos: 58 – 11 = 47
- Excess risk expected due to both (under + model): 112 + 47 = 159
- Total observed excess risk: 602 – 11 = 591 !!

Observed excess risk is much higher than what we expect from our additive model: there is interaction (on additive scale)!

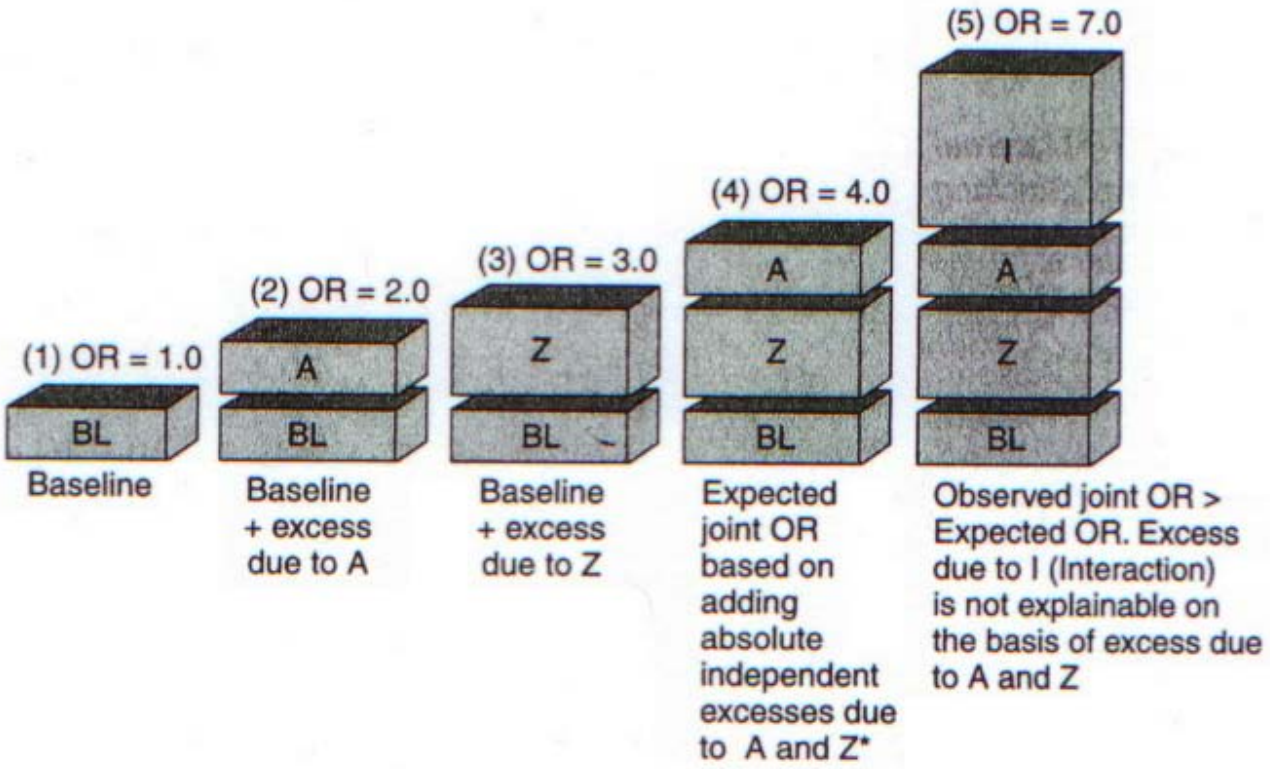
Data: Hammond, 1979

Example: Smoking & Asbestos



Death rates from Lung cancer (per 100,000)

Data: Hammond, 1979



*Note that when the independent relative odds for A and Z are added, the baseline is added twice; thus, it is necessary to subtract 1.0 from the expected joint OR: that is, Expected OR_{A+Z+} = (Excess due to A + baseline) + (Excess due to Z + baseline) − baseline = $OR_{A+Z-} + OR_{A-Z+} - 1.0$.

Figure 6–3 Schematic representation of the meaning of the formula, Expected OR_{A+Z+} = Observed OR_{A+Z-} + Observed OR_{A-Z+} − 1.0.

Szklo & Nieto, Epidemiology: Beyond the basics. 2007

Multiplicative Interaction: departure from a multiplicative statistical model

Death rates from Lung cancer (per 100,000)

Cigarette smoking	Asbestos exposure	
	No	Yes
No	11	58
Yes	123	602

- RR due to smoking: 123 / 11 = 11.2
- RR due to asbestos: 58 / 11 = 5.3
- RR expected due to both (under x model): 11.2 x 5.3 = 59.4
- Total observed RR: 602 / 11 = 54.7

Observed RR is close to what we expect from our multiplicative model: this is NO interaction on a multiplicative scale

Data: Hammond, 1979

Mortality of tuberculosis patients in Chennai, India

C Kolappan,[a] R Subramani,[a] K Karunakaran,[b] & PR Narayanan[a]

Objective We aimed to measure the mortality rate and excess general mortality as well as identify groups at high risk for mortality among a cohort of tuberculosis patients treated in Chennai Corporation clinics in south India.
Methods In this retrospective cohort study we followed up 2674 patients (1800 males and 874 females) who were registered and treated under the DOTS strategy in Chennai Corporation clinics in 2000. The follow-up period from the date of start of treatment to either the date of interview, or death was 600 days.
Findings The mortality rate among this cohort of tuberculosis patients was 60/1000 person-years. The excess general mortality expressed as standardized mortality ratio (SMR) was 6.1 (95% confidence interval (CI) = 5.4–6.9). Younger patients, men, patients with Category II disease, patients who defaulted on, or failed courses of treatment, and male smokers who were alcoholics, all had higher mortality ratios when compared to the rest of the cohort.
Conclusion The excess mortality in this cohort was six times more than that in the general population. Young age, male sex, smear-positivity, treatment default, treatment failure and the combination of smoking and alcoholism were identified as risk factors for tuberculosis mortality. We suggest that mortality rate and excess mortality be routinely used as a monitoring tool for evaluating the efficiency of the national control programme.

Bulletin of the World Health Organization 2006;84:555-560.

Male TB patients who were both smokers and alcoholics had a higher RR than those who were either only smokers or only alcoholics.

Is there interaction on a multiplicative scale?

	No. registered	No. of deaths	% of deaths	Hazard ratio	
				Crude	Adjusted[b] (95% confidence interval)
Non-smokers and non-alcoholics	1127	36	3	1.0	1.0
Smokers	182	8	4	1.4	1.1 (0.5–2.3)
Alcoholics	86	5	6	1.8	1.3 (0.5–3.4)
Smokers and alcoholics	329	40	12	3.8	2.9 (1.8–4.7)

Additive or multiplicative model?

- The additive model underpins the methods for assessing biological interaction (causal pie model by Rothman)
  - Interaction here means a departure from additivity of disease rates (risk difference is the key measure)
  - Some believe that risk difference scale is of greatest public health importance (because its based on AR and PAR)

- In contrast, many of the models used in epi analyses are inherently multiplicative (e.g. logistic regression)
  - vast majority of epi analyses are based on a multiplicative model and hence most epi studies implicitly use the multiplicative scale (risk ratio is the key measure)
  - this is because most epi studies report RR and OR estimates and use regression models such as logistic and survival analyses – these models inherently use ratio measures and are therefore multiplicative

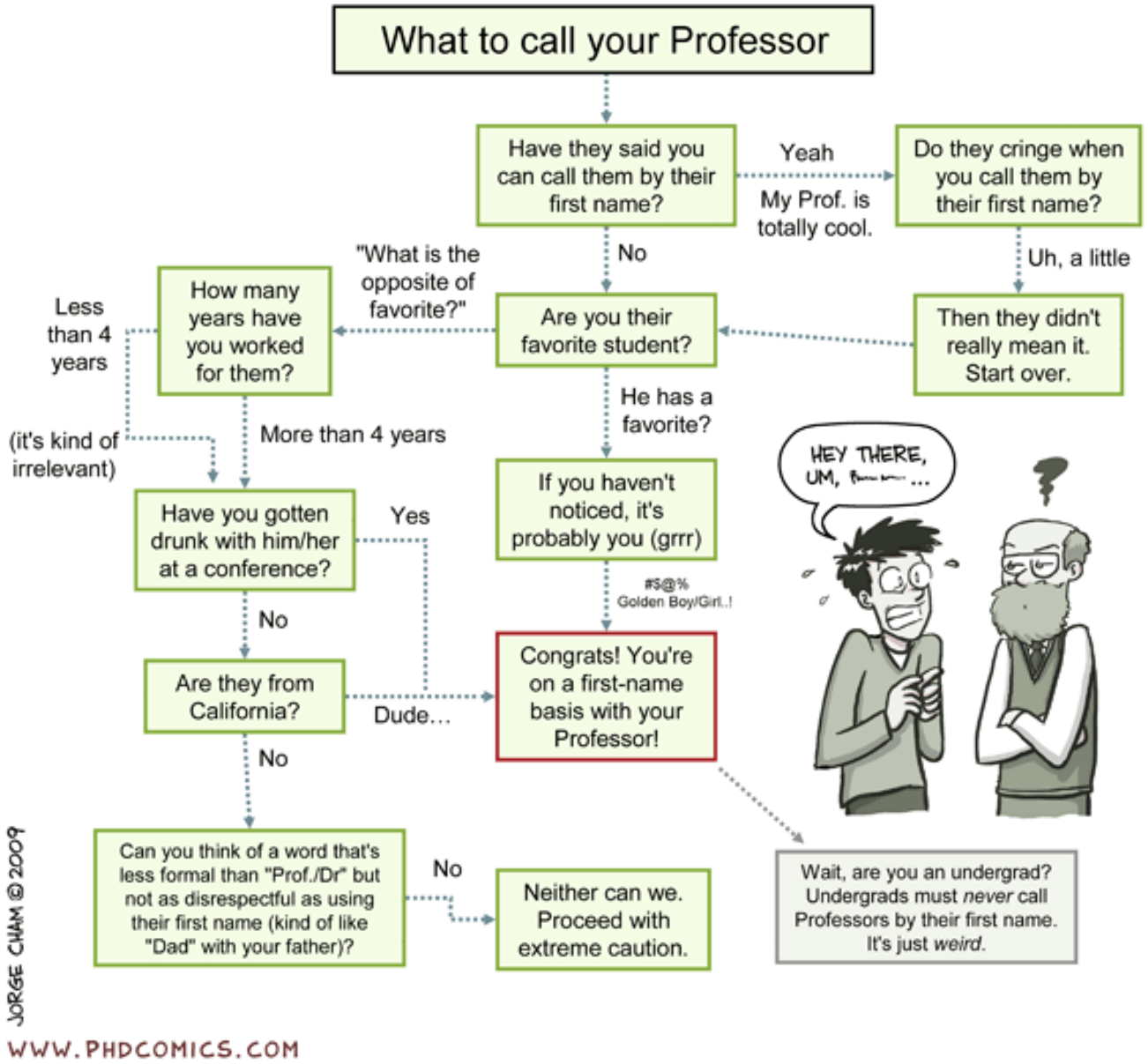
Ahlbom A et al. Eur J Epi 2005

Regardless of the scale, why is interaction/effect modification important?

- Better understanding of causation
  - e.g. smoking and asbestos; diet and PKU
- Identification of “high-risk” groups
  - e.g. influenza can lead to serious complications in specific groups: young, elderly, and those with chronic diseases
  - e.g. women who smoke heavily and use OC are at high risk for myocardial infarction
  - e.g. TB patients who smoke and drink are at high risk for mortality
- Target interventions at specific subgroups
  - e.g. flu vaccines are usually given to only specific groups – aged 65 or older
  - e.g. best time to give measles vaccine is 12 – 15 months
  - e.g. circumcision for heterosexual men

Readings

- Rothman text:
  - Chapter 9: Measuring Interactions
- Gordis text:
  - Chapter 15


What to call your Professor
Have they said you can call them by their first name?
Yeah
My Prof. is totally cool.
Do they cringe when you call them by their first name?
Uh, a little
No
"What is the opposite of favorite?"
How many years have you worked for them?
Less than 4 years
(it's kind of irrelevant)
More than 4 years
Are you their favorite student?
Then they didn't really mean it. Start over.
He has a favorite?
If you haven't noticed, it's probably you (grrr)
#$@% Golden Boy/Girl..!
HEY THERE, UM, ...
Have you gotten drunk with him/her at a conference?
Yes
No
Are they from California?
Dude…
No
Congrats! You're on a first-name basis with your Professor!
Can you think of a word that's less formal than "Prof./Dr" but not as disrespectful as using their first name (kind of like "Dad" with your father)?
No
Neither can we. Proceed with extreme caution.
Wait, are you an undergrad? Undergrads must *never* call Professors by their first name. It's just *weird*.
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