EBM Workshop: ANSWERS
Risk: The Bullwinkle Family in Brazil- Café con Azúcar

Learning Objectives:

To consider a question of prognosis / risk
Specific objectives:

- Clinical question formation
- Translation of the question to an effective search
- Critical appraisal of a cohort study
- Application of the evidence to the case

Vocabulary

- **Incidence:** Number of new cases of disease occurring during a specified period of time; expressed as a percentage of number of people at risk

- **Prevalence:** Proportion of persons affected with a particular disease at a specified time. Prevalence can be used to assess pre-test probability if it is assessed from a study of strong methodology

- **Relative Risk:**
  Also known as Risk Ratio

	Outcome		
	Outcome Present	Outcome Absent	
Treated/ Exposed (Y)	**a** Outcome present in treated patient	**b** Outcome absent in treated patient	**Y= Risk of Outcome in Treated Group** = a/(a+b)
Control / Not exposed (X)	**c** Outcome present in control patient	**d** Outcome absent in control patient	**X= Risk of Outcome in Control Group** = c/(c+d)

Risk Ratio: The ratio of risk of outcome in treated/exposed group (Y) as compared with control/ not exposed group (X)

RR=Y/X = a/(a+b) / c (c+ d)

This always tells us whether the observed outcome (effect) occurs more or less often in the exposed group than in the unexposed group. Calculations for RR are identical whether you are asking a question about therapy or a question about Harm.

- **Confounding variables**: A factor (besides the one you are studying) that distorts the true relationship of the study variable of interest to the outcome. Confounders are likely to be unequally distributed in non-random methodologies, therefore may introduce bias (see below).

- **Bias**: Systematic differences between groups which may skew the results leading to a deviation from the true result.

- **Stratified analysis**: " arranged in layers or strata" -- regarding analysis, it refers to pre-sorting of data by characteristics prior to running the analysis. When discussed in terms of randomization, it means pre-sorting data prior to randomization.

- **Causality**: To interpret whether the association is likely to be *causal*, consider the following factors: 1) strength / magnitude of the relationship; 2) dose-response relationship; 3) temporal relationship; 4) consistency to other studies; 5) reversibility; 6) biological plausibility.

Specific Questions and Tasks

Validity Section

- Table I: Baseline characteristics—are the groups equal at baseline? Why or why not?
- Table I: For each characteristic that is NOT similar between groups, how would you expect it to impact the outcome (i.e. direction of bias)

Results Section

- Table II: What's a person-year
- Table II: adjusted analyses- what's that?
- What two different ways can you discuss precision or our confidence in the results?

PICO

Patient Population: Patients without known diabetes. This patient is a 59-year-old male with GERD and hyperlipidemia

Intervention / Exposure / Prognostic Factor: Coffee Consumption

Comparison: no coffee consumption

Outcomes: incidence of diabetes

Type of Question / Type of Study desired: Risk / Prognosis: Prospective Cohort

Searching:

Coffee/	2605
Exp Diabetes Mellitus/	165,952
1 and 2	56
exp cohort studies/ or prospective studies/	482,497
3 and 4	9

CRITICAL REVIEW FORM FOR PROGNOSIS

Citation: Coffee Consumption and Risk for Type 2 Diabetes Mellitus. Ann Int Med 2004;140:1-8.
Clinical Question: Is coffee drinking associated with decrease in risk for Type 2 Diabetes Mellitus

Guide	Comments
Are the Results Valid?	
Was the sample of patients representative?	The patients were taken from 2 prospective cohort studies: Both studies included health professionals participating in a mailed survey questionnaire providing detailed information about their medical history, lifestyle and risk factors. Both studies used a methodology that included collection of data at 2 yearly intervals through a mailed survey to reassess risk factors and also to update information on newly diagnosed diseases. For this analysis: exclusion criteria for use of patient information in this study was known baseline history of DM2, CAD or cancer, non-completion of a portion of the survey items, extremes of caloric intake (<800 kcal/day or >4200 kcal/day for men; <500 kcal or >3500 kcal for women). The Health Professionals Follow up-Study **(HPFS):** Established 1886: 51,529 male health professionals (dentists, optometrists, veterinarians, osteopathic physicians, podiatrists and pharmacists) 40-75 years of age. Failure to complete >70 of 131 items on food questionnaire→ exclusion. After exclusions, analysis included 41,934 men. The Nurses Health Study **(NHS)** Established 1976: 121,700 female nurses 30-55 yrs of age from 11 states. Semi-quantitative food frequency questionnaire added in 1980. Failure to complete >10 items on food questionnaire→ exclusion. After exclusions, analysis included 84,276 women.
Were patients sufficiently homogeneous with respect to prognostic risk?	These were population based prospective cohorts. The exclusion of pre-existing disease was intended to take out prevalent disease at time of entry to the study.
Was follow-up complete?	It is not clear what proportion of individuals were lost to follow up in either cohort.

Were objective and unbiased outcome criteria used?	Assessment of Coffee / Caffeine Intake: Validated dietary questionnaires sent to HPFS and NHS participants multiple times. Question asked: how often on average during the previous year did you consume coffee and tea? Both groups also added a second question about decaffeinated coffee and different types of caffeinated items (added in 1986 in HPFS and 1984 in NHS). Intake of caffeine was calculated by summing the caffeine content for a specific amount of each food during the prior year. A validation subset confirmed high correlations with1-week diet diaries. Coffee consumption was categorized in 5 groups (never, <1cup per day, 1-3 cups per day, 4-5 cups per day, 6+ cups per day Caffeine intake: categorized by quintiles. Assessment of Diabetes Cases (consistent with National Diabetes Data Group): New cases of DM defined by: 1) symptoms + elevated fasting glucose levels $\geq$ 140 or random measured glucose $\geq$ 200; 2) 2+ elevated plasma glucose concentrations ($\geq$ 200) on different occasions without symptoms 2+ hours after Glucose tolerance test; 3) use of insulin or oral hypoglycemics. A validation subset confirmed the validity of this diagnostic algorithm of determining new dx of DM. Dx of Type II DM was confirmed by medical records in 98% of participants.

II. What are the results?

How likely are the outcomes over time?

How precise are the estimates of likelihood?

Baseline characteristics: (Table I)

Higher coffee consumption was strongly associated with cigarette smoking and alcohol use. Also higher coffee consumption was associated with total and saturated fats and magnesium and inversely associated with physical activity, intake of cereal fiber, glycemic load and tea.

Coffee consumption was NOT associated with BMI.

Development of DM:

Overall, 1,333/4,1934 men (3%) and 4.085/84,276 women (4.8%) were diagnosed with DM.

Relative Risk of Diabetes: according to **coffee consumption** (Table 2 pg 4)

Multivariate Model: adjusted for age, BMI, physical activity, Family history of DM, hormonal use (women), tobacco, alcohol, total calories, quintiles of trans fat, glycemic load, cereal fiber, magnesium.

Cups/ Day	Men (CI)	Women (CI)
Never	1.00	1.00
<1	0.98 (0.84-1.15)	1.16 (1.05-1.29)
1-3	0.93 (0.80-1.08)	0.99 (0.90-1.08)
4-5	0.71 (0.53-0.94)	0.70 (0.60-0.82)
6+	0.46 (0.26-0.82)	0.71 (0.56-0.89)
P value for trend	0.007	<0.001

Relative Risk of Diabetes: according to **Tea consumption** (Table 2 pg 4)
No statistically sign relationship (P value for trend: >0.2)

Note: alternative analysis, which adjusted only for age and BMI, showed similar results.

Relative Risk of Diabetes: according to **caffeine intake** (Table 3 pg 5)
Statistically significant inverse association (P value for trends in the multivariate model: <0.001 in HPFS and NHS)

Controlling for confounders:
Multivariate analysis (as above)
A modest inverse association was noted between decaffeinated coffee and risk of DM (table 2)
Stratified analysis by BMI, Smoking status, Physical activity (table 4) suggests inverse association was independent of lifestyle risk factors.

How can I apply the results to patient care?	
Were the study patients and their management similar to my own?	If we wish to apply this to a member of the general population without comorbid disease who wishes to drink coffee, then the population is appropriate. If, however you wish to apply this to a patient in my general medicine clinic (who is very likely to have comorbid illness already, it may be less applicable. For Mr. Bullwinkle, the study population is directly relevant and he would have met inclusion criteria.
Was the follow-up sufficiently long?	Follow up was up to 12 years in the HPFS study (1986-January 98) and 18 years in the NHS (1980-98). Follow up was calculated from return of baseline information (in 1986 for men and 1980 for women) to the diagnosis of DM, death or end of follow up period in 1998.
Can I use the results in managing patients in my practice?	Caffeine intake is one of many lifestyle issues that physicians counsel patients as well as family members about. The data presented from these two studies supports an inverse association between caffeine intake and diabetes incidence. However, these observational data cannot prove a cause-effect relationship. For Mr. Bullwinkle, we can counsel him to drink coffee while in Brazil if he enjoys doing that. However, the coffee may also upset his GERD and without stronger evidence that this will decrease his risk of development of diabetes, I would encourage him to limit his coffee drinking if it worsens his symptoms. Also, there are many other lifestyle modifications that he could possibly make that may decrease his risk for the development of diabetes such as physical activity, weight reduction and dietary modification.