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Overview:

Meta-analysis
   Risk associated with diabetes drug
   Genome wide association studies
Secondary data analysis
Participant selection
Ads
Meta-analysis:

**Objective:** Understand what a meta-analysis is, how to interpret, and where to go for further guidance.

Evidence-based medicine: Clinical practice should follow the best supported information on outcomes.

Why do we do meta-analysis?

Presumption—no one definitive study as any study is unlikely to address all known and unknown sources of bias.
Meta-analysis is a systematic review and statistical analysis of data from studies relevant to the question.

Two major types:

1. Studies themselves are “units” of an analysis
2. Subjects within studies are pooled

Should be as carefully planned as any other research project with a detailed, written protocol in advance and a priori definitions of eligibility for studies
Chart showing “What is a Systematic Review?”
For more information:

Simple issues:
1. Inclusion criteria
   a. Independent of results
   b. Publication bias

2. Statistical issues
   a. Big vs. small studies
   b. How present data

3. Precision does not = truth if there is a systematic bias.
Recent past:

Cox-2 inhibitors and risk of myocardial infarction

Next up:

Rosiglitazone and cardiovascular events

Type 2 diabetes mellitus-insulin resistance and beta-cell dysfunction
Many metabolic abnormalities
What are thiazolidinediones and how do they work?

Rosiglitazone and pioglitazone are potent inhibitors of peroxisome-proliferator activator-receptor γ – improve whole body insulin sensitivity with actions on adipose tissue and liver.

Graph showing “The Cardiovascular Role of the TZDs in Type 2 Diabetes

J Diabetes Complications. 2007 Sep Oct;21(5):326-34
Article: Glycemic Durability of Rosiglitazone, Metformin, or Gluburide Monotherapy
Table 4: showing Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes
Table 5: showing Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes
Press release: GlaxoSmithKline Responds to NEJM Article on Avandia
Rosiglitazone Evaluated for Cardiovascular Outcomes – An Interim Analysis

Table 2: Hospitalization or Death from Cardiovascular Causes
Summary: Rosiglitazone for type 2 diabetes mellitus (Review)
Summary: Rosiglitazone for type 2 diabetes mellitus (Review) contd.
Press Release: GSK Responds to Outline Review of Rosliglizzone by the Cochrane Collaboration
Flow Chart of Congestive Heart Failure and cardiovascular death in patients with pre-diabetes and type 2 diabetes given thiazolidinediones” a meta-analysis of randomized clinical trials.
Interpretation of clinical trials from previous table

Overall risk for congestive heart failure: status, weight, risk ratio at 95% ci numbers and figures

Overall risk for cardiovascular death: status, weight, risk ratio at 95% ci numbers and figures
Glycemic Durability of Rosiglitazone, Metformin, or Glyburide Monotherapy.

Results of study with note added: While this article was in production, further examination of data on adverse events identified a higher rate of fractures in the group receiving rosiglitazone. This was an unexpected event that was not part of the pre-specified analysis plan.
Graph showing risk of fractures in women in ADOPT at 5 years.
Rosiglitazone and Cardiovascular Risk

Rosiglitazone – Continued Uncertainty about Safety

Rosiglizasone and Cardiotoxicity – Weighing the Evidence

Cardiovascular Risk and the Thiazolidinedoines
Déjà Vu All Over Again?

Thiazolidinediones, deadly sins, surrogates, and elephants
LISTEN ONLY!!
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New horizon for meta-analysis:

GENOME-WIDE ASSOCIATION STUDIES

How to Interpret a Genome-wide Association Study
Thomas A. Pearson; Teri A. Manolio
JAMA. 2008;299(11);1335-1344(doi:10.1001/jama.299.11.1225)
Data Chart: Association of three genetic loci with uric acid concentration and risk of gout: a genome-wide association study

Table 1: Characteristics of participants to the studies
Data: Association of three genetic loci with uric acid concentration and risk of gout: a genome-wide association study
Graph: Association of three genetic loci with Eric acid concentration and risk of gout: a genome-wide association study
Overview:

Meta-analysis
Secondary data analysis
C-reactive protein
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Ads
Secondary data analysis:

Objectives:

Open up possibilities for obtaining preliminary data

Consider the range of secondary data analysis in addition to meta-analysis
Benefits:

Data often available, therefore study should be cheap to perform.

Good way to work through the problems of the study design including case definition, controls, potential biases and develop statistical techniques.

Preliminary data for applications

Networking and collaborations
Asking for data:

Sharing and collaborating, not appropriating.

Most large studies have data resources available or have standard procedures for collaborations.

Creative add-ons to existing studies—nested studies—use the original sample to answer a different but related questions. May involve using laboratory specimens.

Don’t be shy!
Sources of data:

Published statistics
Federal or local survey data (geocoding)
National Center for Health Statistics
Computerized medical records
Industrial records
dbGAP

Published studies
Observation studies – case/control
Trials – pre and post
Chart: Collected data – new hypothesis- CRP and obesity in children
National Center for Health Statistics - CDC
Chart: Novel marker – measure changes before and after intervention
Table: Ridker et al. Nested case-control WHI C-reactive protein and HRT-Synergistic effect?

Novel marker in cases and controls--?? Risk
Chart: Do statins reduce both lipids and CRP?
Figure 3: Mean change in CRP levels over time according to observed changes in LDL cholesterol. Data are shown for those allocated to prevastatin (solid bars) or to placebo (open bars).
Chart: Result from clinical trial- lowering LDL cholesterol and CRP is synergistic
Downside:

Hypothesis-generating, power, compromises in design and problems of data-dredging

Easy to make errors because you didn’t design study-need to learn as much as you can before starting to use data

Statistical help

Still need to assess the validity of the results
Does the literature support your observation?
Is the result biologically plausible?
Overview:

Meta-analysis
Secondary data analysis
Participant selection
Estrogen risk story
Ads
Overview:

Your research question:

What are the health effects of estrogen therapy for postmenopausal women?
Meta-analysis: Estrogen use and CHD risk, 1991

Figure 2: Summary relative risks and 95% interval estimates for studies of estrogen use and risk of coronary disease, by study design. There was significant (p<0.001) heterogeneity by study design.
Can a meta-analysis reach the wrong conclusion??

Even if biologically plausible, may be wrong
Biases may overestimate benefit, underestimate risk

Healthy use selection bias
   Better health=usage=better outcomes

Compliance bias
   Good adherers=good health=good outcomes

Surveillance bias
   See doctor more often=better outcomes

Survivor bias
   Continue to use=better health=better outcomes
Choosing subjects to address potential bias
THE HERS STUDY
Heart and Estrogen/progestin Replacement Study
guidelines
Exclusions from HERS:

CHS event within 6 months of randomization
Serum triglycerides >300 mg/dL
Use of hormones within 3 months of screening
History of DVT or pulmonary embolism
History of breast cancer or suggestive mammogram
History of endometrial cancer, abnormal uterine bleeding, endometrial thickness of greater than 5mm on screening
Abnormal PAP test
Serum aspartate aminotransferase level > 1.2 times normal
Planning to move within 4 years
Disease other than CHD deemed likely to be fatal within 4 years
NYHA Class III or IV congestive failure
Alcoholism
Uncontrolled hypertension, diabetes
Participation in another clinical study
Less than 80% compliance with placebo runin prior to randomization
History of intolerance to hormone therapy
Participant selection:

On exposure:

Say HRT....

“Are you currently using HRT?”

Criteria:
What type of HRT? [Is it really an HRT?]
Which formulation? [Response may vary by type]
How long has it been taken?
Taken continuously or intermittently? [Years taken may affect the effect]
Has she taken the same type for the whole time?
Participant selection:

On “case” status:

Defining a case also identifies your controls

You want your controls from the same reference population, but to truly differ from your cases in terms of the underlying feature you are studying

Mixing of “cases” in your “control” group pushes toward a null result!
HOW MANY WAYS TO IDENTIFY CHD?

Large, simple:  Told of MI by MD
   Report of hospitalization for MI
   Hospital records for MI
   Pathognomonic medications

Molecular epidemiology:
Cholesterol
Coagulation, inflammation markers
Adhesion molecules
Technoepidemiology:

**Low tech:**
- MI on ECG (40% MI silent)
- Ischemic pattern on ECG
- Peripheral vascular disease by ankle/arm blood pressure
- Arterial pulse-wave velocity
- Carotid thickening, distensibility, plaque

**High tech:**
- Electron-beam CT for calcium
- Angiography
- Echo-wall motion studies
- MRI studies of the heart or carotids
Table 1: Baseline Characteristics of HERS Participants (n=2763) by Treatment Group*

Hers indicates Heart and Estrogen Replace Study; CHD coronary heart disease LDL, low-density lipoprotein; and HDL high density-lipoprotein. Pvalues are for difference between treatment groups by $t$ test or $x^2$. 

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Treatment Group 1</th>
<th>Treatment Group 2</th>
<th>Pvalue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>71.5</td>
<td>71.3</td>
<td>0.12</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>30.7</td>
<td>30.9</td>
<td>0.08</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>200.4</td>
<td>201.3</td>
<td>0.78</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>53.7</td>
<td>53.9</td>
<td>0.63</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>120.2</td>
<td>119.8</td>
<td>0.65</td>
</tr>
</tbody>
</table>
Table 3 – Outcome by Treatment Group and Year Since Randomization
Cartoon of man pushing large question mark up a steep hill.
Graph: WHI Results for CHD and Breast Cancer
Graph: WHI Results for colorectal cancer and hip fracture
Updated meta-analysis of estrogen risks, 2003

Table 4: Hormone Replacement Therapy Use in 10,000 women: *Benefits and Harms* per Year

<table>
<thead>
<tr>
<th>Benefit</th>
<th>Harm</th>
<th>Yearly Incidence</th>
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*Benefits and Harms* per Year
Table 4: Results of Randomized Trials of the Effect of Hormone Replacement Therapy on Atherosclerosis Progression Measured by Coronary Angiography
Health Risks After Stopping Estrogen and Progretin

Figure 2: Risk of Death from all Causes and Global Risk by Randomized Assignment to Conjugated Equine Estrogen Plus Medroxyprogesterone Acetate or Placebo Before and After Termination of the Intervention in the Women’s Health Initiative Estrogen Plus Progestin Trial.
Table: Effects of raloxifene on cardiovascular events and breast cancer in postmenopausal women.
Conclusions: Among women 50 – 59 years old at enrollment the calcified-plaque burden in the coronary arteries after trial completion was lower in women assigned to estrogen than in those assigned to placebo. However, estrogen has complex biologic effects and may influence the risk of cardiovascular events and other outcomes through multiple pathways. (ClinicalTrials.gov number, NCT00000611.)
Data related to previously mentioned study.
HRT and the Young at Heart

The translation of basis research to the bedside and to public guidelines a collaborative and interactive process conducted with patience and persistence. Just such an interactive process has enabled our emerging appreciation for the potential cardiovascular benefits of hormone-replacement therapy in younger women who have recently undergone menopause.
Review

Prevention of cardiovascular events in early menopause: A possible role for hormone replacement therapy.
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