**Assessing Risks and Benefits**

- **Review**
  - Attributable risk = rate difference (cohort)
    - Rate of disease above background
  - Relative risk = rate ratio (cohort)
    - Multiplicative rate relative to background
  - Odds ratio = estimate of relative risk (case control)
- **Other measures not essential for this course, but of interest for policy**

**Interpreting Epidemiologic Studies**

- Major goal of epidemiology is understanding etiology
- Want to know if observed association is:
  - due to confounding
  - due to bias
  - due chance (random fluctuations)
  - causative
- Given idiosyncrasies of individual studies, consider many studies together

**Approach for Summarizing Results from a Collection of Studies**

- Assess causation
- Estimate
  - magnitude of risk
  - population attributable risk
- Consider and explain heterogeneity

**Assessing Causation: Definition**

- According to Rothman and Greenland (1998):
  - a cause of a specific disease event is an antecedent event, condition, or characteristic that was necessary for the occurrence of the disease at the moment it occurred, given that other conditions are fixed.

**Assessing Causation—Implications**

- Implications: event, condition or characteristic
  - precedes event
  - in its absence, event:
    - would not have occurred
    - or would have occurred later
  - may not be sufficient on its own
  - may not be the only cause

**Assessing Causation: Guidelines—1**

- Various guidelines have been proposed
  - Henle (1840)
    - prior to isolation and culture of first bacteria from an infectious disease
  - Koch (1882)
    - from work related to tuberculosis
      - parasite occurs in every case
      - parasite does not occur in non-cases
      - culture of parasite also leads to disease
Assessing Causation: Guidelines--2
- Limitations of the Henle-Koch Postulates
  - Disease can be multi-factorial
  - Single agents can cause many diseases
  - I.e., a single agent is rarely both a necessary and sufficient cause for all cases of a disease

Assessing Causation: Guidelines--3
- Hill (1965)
  - First, assess role of chance (e.g., meta-analysis)
  - Then, 9 aspects to consider, **NOT** criteria
  - In light of the observations, what are the equally or most likely explanations other than causation
  - Paraphrasing, statistical significance **IS NOT** scientific significance
  - (Confidence intervals do not define importance)

Assessing Causation: Hill’s Aspects—1
- Strength
- Consistency
- Specificity
- Temporality
- Biological gradient
- Plausibility
- Coherence
- Experiment
- Analogy

Assessing Causation: Hill’s Aspects—2
- Strength
  - Size of effect
  - Do not dismiss “merely on the grounds that the observed association appears to be slight”
  - If smaller effect, harder to detect
  - If larger effect, confounding is less likely to explain
- Consistency
  - Repeated in studies of different populations, at different locations, at different times
  - Lack of consistency does not rule out causation
  - May occur only under certain circumstances

Assessing Causation: Hill’s Aspects—3
- Specificity
  - Agent gives rise to specific disease
  - “We must not, however, over-emphasize the importance of this characteristic”
  - “If specificity exists we may be able to draw conclusions without hesitation; if it is not apparent, we are not thereby left sitting irresolutely on the fence.”

Assessing Causation: Hill’s Aspects—4
- Temporality
  - Exposure precedes disease
  - Only aspect that is necessary
- Biological Gradient
  - Exposure-response effect
  - Is more worse?
- Plausibility
  - Is there a known biological mechanism
  - Lack of known mechanism often interpreted as refuting causation (e.g., EMFs)
Assessing Causation: Hill's Aspects—5

- **Coherence**
  - are results consistent with known natural history and biology of disease
- **Experiment**
  - if exposure is removed, does disease rate decline? (e.g., Woburn)
- **Analogy**
  - are the similar effects with exposure to a similar agent?

Hill's Aspects—Summary

- **Strength**
  - size of RR
- **Consistency**
  - Study replication
- **Specificity**
  - Exposure -> Single Disease
- **Temporality**
  - exposure precedes disease
- **Biological Gradient**
  - Monotonic dose-response
- **Plausibility**
  - Consistent with biology
- **Coherence**
  - Natural history of disease
- **Experiment**
  - animal or human
- **Analogy**
  - Similar to other situations

Methods for Estimating Risk from a Collection of Studies

- Weight of Evidence Review (causation only)
  - qualitative, narrative review
- Meta-Analysis (causation, risk)
  - quantitative summary of published results
- Pooled-Analysis (causation, risk)
  - re-analysis of individual data from primary studies
- Prospective Pooled Analysis (causation, risk)
  - multi-center study
- Quantitative Risk Assessment (risk only)
  - forecasts population risk using estimated potency

Weight of Evidence

- **Systematic review of the literature**
- **Strengths**
  - relatively quick
  - inexpensive
- **Limitations**
  - study selection bias
  - publication bias
  - subjective weighting of results

Weight of Evidence—2

- Several criteria for evaluation
  - US Environmental Protection Agency’s *Risk Assessment Guidelines*
  - International Agency for Research on Cancer’s *Evaluation of Carcinogenic Risks to Humans*
- Results in classifications schemes
  - adequacy of data
  - likelihood of carcinogenesis (or other effects)
Meta-Analysis

- **Primary Analysis**
  - original analysis of data in a research study

- **Secondary Analysis**
  - reanalysis of data to:
    » answer the same questions with better methods
    » answer new questions with the old data

- **Meta-Analysis (Glass, 1976)**
  - the analysis of analyses, the integration of analytic results from individual studies

What is Meta-Analysis?

- Literature review and statistical summary
  » Systematic review of studies on specified topic
  » Characterization of each study (design, subjects, results, confounding, etc.)
  » Possible quality evaluation of each study
  » Quantitative summarization (weighted average) of results of each study into a single measure
  » Assess heterogeneity and its source
  » Possibly sensitivity or influence analysis

Why Do Meta-Analysis?

- Meta-Analysis was designed for combining of clinical trials, pooling analytic results (not original data) to increase power
- Meta-Analysis is a rigorous and statistically-based review of the existing literature

Questions Meta-Analysis Should Answer (L’Abbe et al. 1987)

- Are the measures of outcome and exposure consistent from one study to the next, and can they reasonably be combined?
- Do variations in study results correlate with variations in study design?
- What is the best estimate of the value and confidence interval for the combined measure of outcome?

Statistical Methods for Meta-Analysis--1

- Vote counting (low statistical power)
- Sign test
- Combined tests (p-values)
- Heterogeneity tests (Q-tests)
- Measures of effect size
  » Linear regression approach (meta-regression)
  » fixed or random effects model
  » can model confounders (e.g., design, date)
  » Non-parametric methods (Mann-Whitney U)

Statistical Methods for Meta-Analysis--2

- Graphs
  » Funnel plots (publication bias)–effect vs. study size
  » Heterogeneity plots (P-P Plot; Radial Plot)
  » Odd Man Out Analysis
  » Date vs. effect size plot
- Assessment of Publication Bias
  » Fail Safe N
  » Needed Study Size
- Influence Analysis
**Fixed Effects Models**
- Assume underlying true effect is the same in all studies (i.e., no heterogeneity)
- Estimate is an average, with only within study precision is considered (random error)
- Examples
  - Mantel-Haenszel method
  - Peto method
  - Generalized variance method
  - Confidence interval methods

**Heterogeneity Assessment--1**
- Separate by Major Differences (Exposure Metric)
- Conduct stratified analyses
  - Stratified by assessment method—calc vs measure
  - Study characteristics considered
    - Study design
    - Exposure metric
    - Country of study
    - Maximum age of subject
    - Year of publication
  - Method to select controls
- Regress results on study characteristics
- Works only if sufficient number of studies

**Assessing Publication Bias--1**
- File Drawer Problem ("Fail-Safe N")
  - Number of null studies needed to reduce combined result to non-significance
  \[
  N^s = \left( \frac{\sum Z_i^2}{1.645} \right)^2 - N
  \]
  - Where \( Z_i = \frac{\ln(OR)}{\text{SE}(\ln(OR))} \)

**Other Issues**
- Weighting
  - Samples
  - Variability (Variance)
  - Quality
- Coding Variation
- Influence Analysis
  - Sensitivity of result to deletions of studies
  - Sensitivity to other factors (e.g., design, time)

**Meta-Analysis**
- The analysis of analyses
- Systematic Review of the literature
  - Specific criteria for study selection
- Assessment of heterogeneity (consistency)
- Statistical summarization (averaging)
  - Effect size (Dose-response)
  - Stratified analyses or meta-regression (source of heterogeneity)
  - Influence analysis
  - Publication bias

**Strengths of Meta-Analysis**
- Increases overall power and precision
- Examines consistency among studies
- May resolve disparity between studies
- Minimizes reviewers' subjectiveness
- Provides combined risk estimate
- Can be used to explain heterogeneity
- Can be used to answer new questions
Criticisms of Meta-Analysis

- Single index is oversimplification
- Inappropriate combination of studies
  - different designs, measurement techniques, study quality, subjects
- Publication bias against negative studies
  - unpublised or repeatedly published studies
- Heterogeneity among studies common
- Often do not adjust for
  - differences in measurement techniques
  - differences in study “quality”
  - use of multiple results from same study
- confounding and effect modification (individual study adjustments vary by study)

Comparison of Meta-Analysis with Weight of Evidence Reviews—1

- Selective inclusion (exclusion) of studies
  - Meta-Analysis includes all studies
- Subjective weighting of studies
  - Meta-Analysis weights by variance
  - Meta-Analysis also may use quality score
- No quantitative summary
  - Meta-Analysis provides overall relative risk

Comparison of Meta-Analysis with Weight of Evidence Reviews—2

- Misinterpretation of study findings
  - Meta-Analysis uses quantitative result
  - Interpretation of meta-analysis can be questioned
- Failure to adequately incorporate study design differences or adjust for confounding and effect modification
  - Meta-Regression can model these effects, but only to the degree addressed in the original studies

What are EMFs?

- EMFs is an abbreviation for electric and magnetic fields
- Poor use of technical term
- These are types of non-ionizing (low energy) radiation
- They are produced by electric potential (electric) or electric current (magnetic)

Why are EMFs of Interest?

- Some evidence of adverse health effects; interpretation controversial
- Exposure is ubiquitous and from many sources
- Public is concerned
  - invisible
  - “radiation”
  - may cause “cancer”

Magnetic Field Exposure and Childhood leukemia—1

- Problem:
  - Does exposure to magnetic fields cause cancer?
- State of the Science:
  - Most recent reviews
    - NAS 1997
      - childhood leukemia linked to “wire codes”
        - magnetic field data less clear
        - appliances insufficient data
    - NIEHS Working Group (1998) classifies as possible human carcinogen (Group 2B)
    - IARC (2001)—possible carcinogen (RR=2 for >0.4uT)
Epidemiologic Studies: Residential

• Childhood Cancer
  – Leukemia
    » 26 studies
    » 8 meta-analyses
    » 2 pooled analyses
    » Results positive
  – Brain Cancer
    » 7 studies
    » 1 meta-analysis
    » Results mixed
  – Lymphoma
    » Few studies
    » Results weak

• Adult Studies
  – Cancer
    » 10 studies
  – Leukemia
  – Brain Cancer
  – Breast Cancer
  – Results mixed
  – Non-Cancer Endpoints
    » Depression
    » Suicide
    » Adverse Repro Outcome
    » Results mixed to negative

Childhood Leukemia Studies

• 26 studies
  – Conducted in over 10 countries
  – Cohort, case control and nested c-c
  – Variety of exposure metrics
  – Mostly positive, small risk (<2)
    » Higher risks in specific exposure subgroups

Inferring Risk: Childhood Residential studies

• Does the agent cause disease?
  – Hill’s Aspects of Causation

• If so, how potent is the agent?
  – Three approaches for COMBINED ASSESSMENT
    » weight of evidence
    » meta-analysis
    » quantitative risk assessment

EMFs: Hill’s Causation Aspects

• strength
• consistency
• specificity
• temporality
• biological gradient
• plausibility
• coherence
• experiment
• analogy

• RR 1.1-1.5
• heterogeneity varies
• other causes exist
• yes
• some evidence
• model at high dose
• possible
• not applicable
• no obvious case

Childhood Leukemia and Residential Exposure

Examples of weight of evidence

• NAS
  – all relevant published papers through 1994
  – conducted own meta-analysis

• NIEHS
  – all relevant published papers through mid-1998
  – subgroups selected papers of “acceptable” quality
  – used NIEHS commissioned meta-analysis

• Foster et al. (1997)
  – All relevant published papers
Criteria for Conclusions

• **NAS**
  - set by committee members
  - determine if “human health hazard”
  - consistent and conclusive evidence
    > extremely high standard

• **NIEHS**
  - set up by NIEHS to follow IARC guidelines
  - determine "carcinogenic risk to humans"
  - Classes 1, 2A, 2B, 3, 4 (often misinterpreted)

EMFs: Weight of Evidence--1

• **NAS**
  - “no conclusive and consistent evidence...that exposures to residential electric and magnetic fields produce cancer”
  - “[there is] an association between residential wiring configuration...and childhood leukemia”
  - average measured magnetic fields not associated with childhood leukemia
  - since not conclusively carcinogenic, chose not to conduct risk assessment

EMFs: Weight of Evidence--2

• **NIEHS**
  - ELF EMF possibly carcinogenic (Group 2B)
  - childhood residential exposure and leukemia
    > support for calculated fields
    > some support for 24-hour measured fields
  - adult occupational exposure and CLL
  - *in vitro* and mechanistic data weakly supportive
    (studies at high exposures (>100 uT)
  - since possible carcinogen, NIEHS (not Working Group) will conduct risk assessment

EMFs: Weight of Evidence--3

• Foster et al. (1997)
  - greater emphasis on *in vitro* and *in vivo*
  - lack of evidence of genotoxicity
  - lack of plausible biological mechanism
  - apparent inconsistencies in epidemiology
  - "evidence in support of links between [electromagnetic] fields and cancer is weak and inconsistent”
  - issue is how probable, not if possible

EMFs: Meta-Analysis Summary

• Dichotomous exposure: RR 1.2-1.4
• Continuous exposure: RR 1.1-2.7 (per 0.1 uT)
  > results imprecise—wide confidence intervals
• Wire codes heterogeneous
• Measures, calculations homogeneous
• Publication bias unlikely
• Individual study influence is small

Magnetic Field Exposure and Childhood leukemia—2

• Combined Analyses of Studies Show
  - Small but consistent elevations of risk
  - A moderate exposure-response gradient
  - Few subjects and “high” exposures

<table>
<thead>
<tr>
<th>Exposure Metric</th>
<th>Pooled Analysis</th>
<th>Meta-Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dichotomous</td>
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<td>Continuous</td>
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<tr>
<td>Calculated</td>
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</table>

Heterogeneity Assessment--1

- Stratified by exposure metric
  - magnetic field (calculated and measured)
  - proximity to electrical facility
- Study characteristics considered
  - study design -- exposure metric
  - country of study -- maximum age of subject
  - year of publication -- method to select controls

Heterogeneity Assessment--2

- Measured/Calculated Magnetic Fields
  - overall: $p>0.3$; larger effects for:
    - cohort studies
    - studies before 1994
    - studies using subjects under 15
- Proximity to Electrical Facilities
  - overall: $p<0.1$; larger effects for:
    - studies in US
    - studies before 1994
    - studies using distance rather than wire codes
    - studies using subjects over 14

Meta-Regression

- No effects are statistically significant

<table>
<thead>
<tr>
<th>Characteristic (reference/alternative)</th>
<th>Measured/Calculated</th>
<th>Proximity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>0.7 (0.2-2.6)</td>
<td>1.5 (1.0-2.5)</td>
</tr>
<tr>
<td>Design (case-control/case-control study)</td>
<td>3.4 (0.9-13.9)</td>
<td>0.8 (0.3-2.3)</td>
</tr>
<tr>
<td>Country (US/other)</td>
<td>1.1 (0.5-2.4)</td>
<td>1.1 (0.5-2.2)</td>
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<tr>
<td>Year (&lt;1993/1993)</td>
<td>0.8 (0.4-1.7)</td>
<td>0.6 (0.3-1.9)</td>
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<td>Metric (measured or calculated/wire codes or distance)</td>
<td>0.6 (0.2-1.6)</td>
<td>1.2 (0.5-3.0)</td>
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<td>Controls (other/random digit dialing)</td>
<td>0.7 (0.3-2.3)</td>
<td>1.1 (0.5-2.5)</td>
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<tr>
<td>Age limit (&lt;15/&gt;15)</td>
<td>0.3 (0.2-0.6)</td>
<td>1.0 (0.4-2.5)</td>
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