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**

Hill's Aspects—Summary

- **These 9 aspects provide a framework**
- **None, save temporality, is necessary**
- **No single aspect, in general, is sufficient**
- **Use these 9 aspects to think about the problem, look for explanations, seek the most likely**
- **In short, review all the data and make a judgement**
  - **Assess bias, chance, confounding and causation**

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**
- **Quantative 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 by 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 charateristics
- 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

$$N^{fs} = \left(\frac{\sum_{i=1}^{N} Z^i}{1.645}\right)^2 - N$$

$$where\ Z_i = \frac{\ln(OR)}{\quad}$$

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

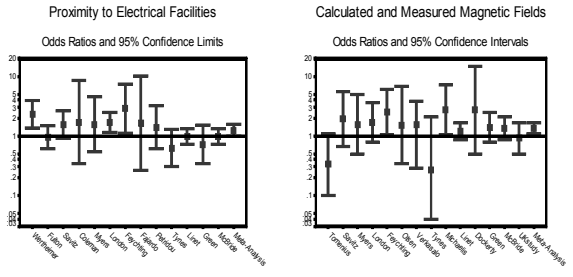
- **Does the agent cause disease?**
  - **Hill's Aspects of Causation**
- **If so, how potent is the agent?**
  - **Three approaches for *COMBINED ASSESSMENT***
    - » **weight of evidence**
    - » **meta-analysis**
    - » **quantitative risk assessment**

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**

	Exposure Metric	Pooled Analysis		Meta-Analysis
		Ahlbom et al. (2000)	Greenland et al. (2000)	Wartenberg (2001)
Continuous Analysis (per 0.2 uT)	Measured	1.2 (1.0-1.3)		1.2 (1.0-1.5)
	Calculated	1.1 (0.9-1.3)		1.4 (1.1-2.0)
Dichotomous Analysis	Measured or Calculated	2.0 (1.3-3.1) (>0.4 uT)	1.7 (1.2-2.3) (>0.3 uT)	1.3 (1.1-1.7) (>0.2 uT)

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**

Characteristic (reference/alternative)	Odds Ratio and 95% Confidence Interval	
	Measured/ Calculated	Proximity
Intercept	0.7 (0.2-2.6)	1.5 (1.0-2.3)
Design (case-control/ cohort or nested case control)	3.6 (0.9-13.9)	0.8 (0.3-2.3)
Country (US/other)	1.1 (0.5-2.4)	1.1 (0.5-2.5)
Year (<1993/>1993)	0.8 (0.4-1.7)	0.6 (0.3-1.0)
Metric (measured or calculated/ wire codes or distance)	0.6 (0.2-1.6)	1.2 (0.5-3.0)
Controls (other/ random digit dialing)	0.7 (0.3-2.3)	1.1 (0.5-2.5)
Age limit (<15/>15)	0.3 (0.2-0.6)	1.0 (0.4-2.5)