Lecture 11: Additional study designs

Lecture prepared by Dr. Hailey Banack, PhD

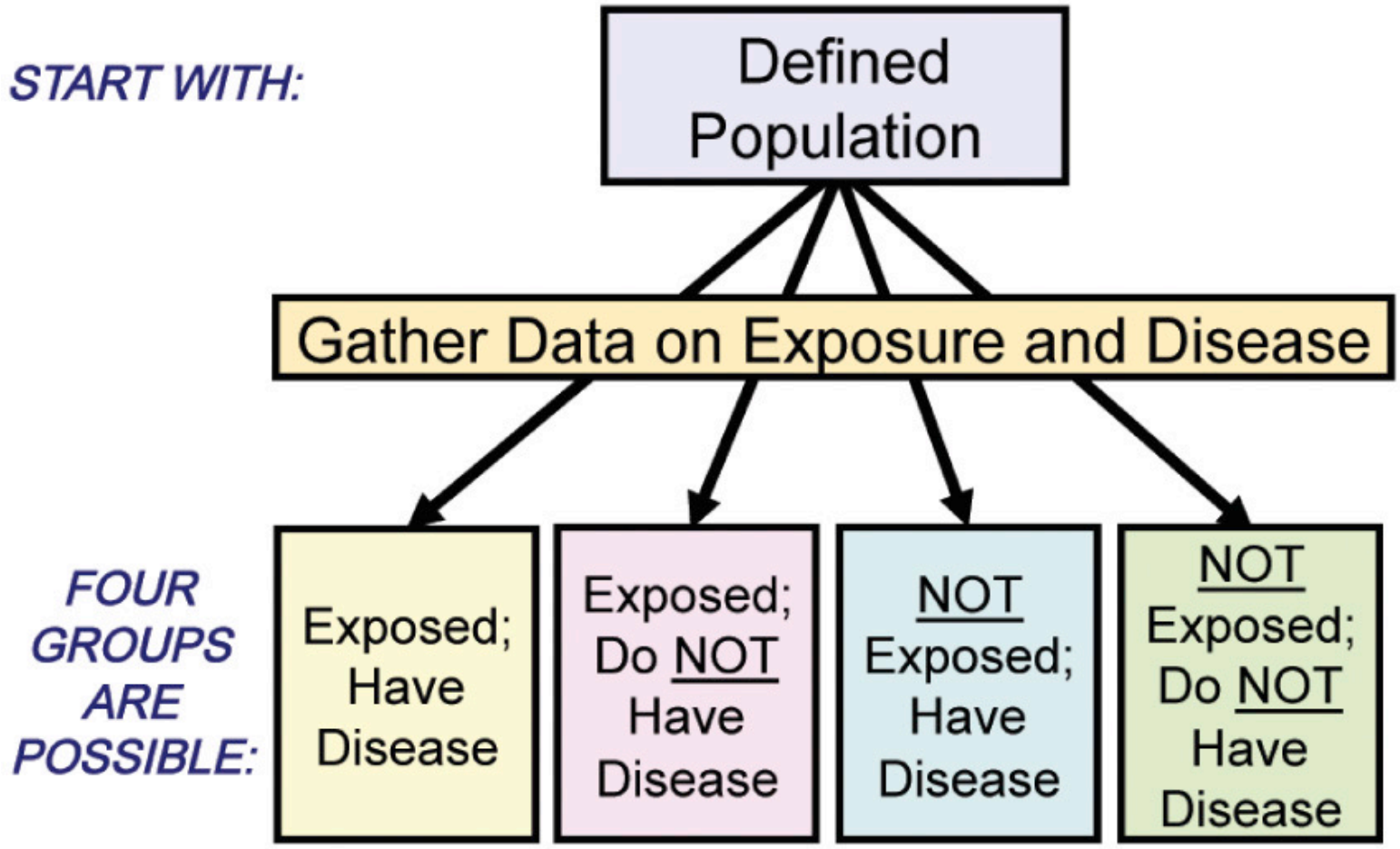
Outline

- Cross-sectional studies
- Surveillance studies
- Ecological studies

- Meta-analyses and systematic reviews

Cross Sectional Studies

- A study that examines the relationship exposure and disease simultaneously
- Both exposure and disease outcome are determined at the same point in time for each participant
  - Viewing a snapshot of the population at a certain point in time
- Identifying prevalent cases


START WITH:
Defined Population
Gather Data on Exposure and Disease
FOUR GROUPS ARE POSSIBLE:
Exposed; Have Disease
Exposed; Do NOT Have Disease
NOT Exposed; Have Disease
NOT Exposed; Do NOT Have Disease

Advantages and Disadvantages

Advantages	Disadvantages
-Inexpensive, quick -Useful for generating hypotheses -No losses to follow-up -Useful for diseases of slow onset and long duration (e.g. CHD)	-No information about temporality -Might 'miss' cases of disease (e.g., remission or treatment) -Poor choice for diseases of short duration

NHANES

National Health and Nutrition Examination Survey

https://www.cdc.gov/nchs/nhanes/index.htm

- Nationally representative survey of non-institutionalized U.S. population
- Publicly available data*(!!!)
  - GREAT for MPH projects, Master's theses and doctoral dissertations
- Continuous NHANES every 2 years 1999-present
- Prior to 1999: NHANES I (1971-1974), NHANES II (1976-1980), and NHANES III (1988-1994)

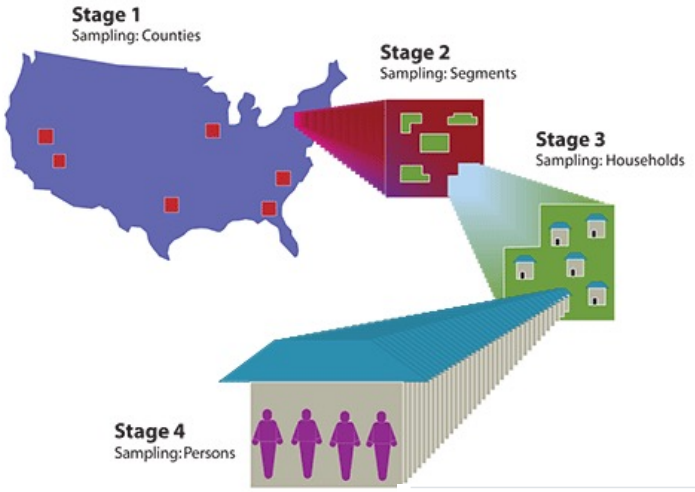
NHANES data

- Questionnaires, examinations, laboratory components

https://wwwn.cdc.gov/nchs/data/nhanes/survey_contents.pdf

- Data collected on the prevalence of chronic conditions in the population

NHANES Sampling



"complex, multi-stage, probability sampling design"

All the counties in the United States are divided into 15 groups based on their characteristics. One county is selected from each large group, and together they form the 15 counties in the NHANES surveys for each year.

Within each county, smaller groups (with a large number of households in each group) are formed, and between 20 and 24 of these small groups are selected.

All of the houses or apartments within those selected small groups are identified, and a sample of about 30 households are selected within each group.

NHANES interviewers go to each selected household and ask for information (age, race, and gender) on all persons in the household.

A computer algorithm randomly selects some, all, or none of the household members.

Oversampling

- NHANES oversamples specific subgroups :
  - Older adults (60+)
  - African Americans
  - Hispanic Americans
  - Low-income groups

Race/Ethnicity	NHANES Sample (1999-2002)	US Population (1999-2002)
Mexican American	28%	9%
Non-Hispanic White and Other	47%	78%
Non-Hispanic Black	25%	13%

Oversampling allows us to obtain reliable and precise estimates in groups that would be otherwise too small to report on

NHANES Survey Weights

- Used to account for oversampling and survey non-response
- NHANES creates these weights for each survey year
- Sample weights are assigned to each person based on the number of people they represent in the U.S. population
- Once the weights are applied, the NHANES sample will better reflect the US population

Constructing Survey Weights

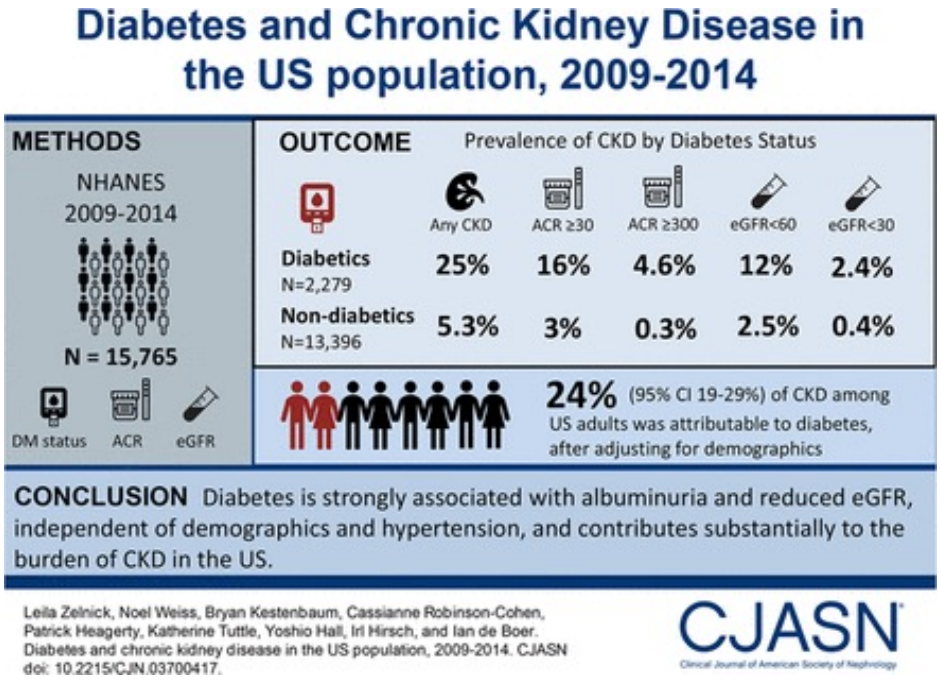
- NHANES accounts for three components in their weights: probability of selection, non-response, and adjustment to match US population.
- For a simple random sample, a sampling weight is just the inverse of the probability of being selected to the sample:

  Sample Weight=1/P(selection in sample)

- With multi-stage sampling, the probability of selection is the product of the probability at each stage.
  - NHANES has multiple stages in their sampling process, so there is a probability of selection at each stage.

NHANES research

- Majority of research from NHANES is <u>cross-sectional</u>
  - Only mortality follow-up data available is on mortality through the National Death Index (NDI)
  - Most research is descriptive (i.e., prevalence studies, descriptive epidemiology)
  - Example:



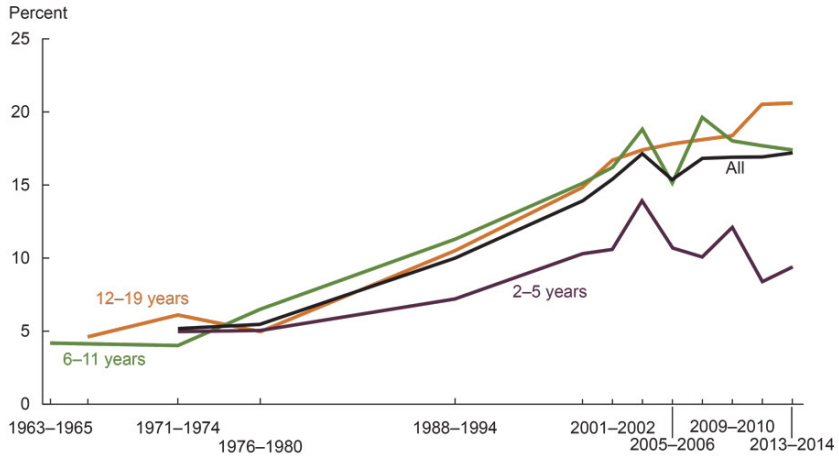
NHANES for population health surveillance

- As a series of cross-sectional surveys, NHANES can be used to monitor long-term trends in population health
- Examine characteristics across years:
  - Track trends
  - Compare health among groups of people
  - Determine whether something is improving or worsening for a specific group of people

NHANES as a surveillance tool

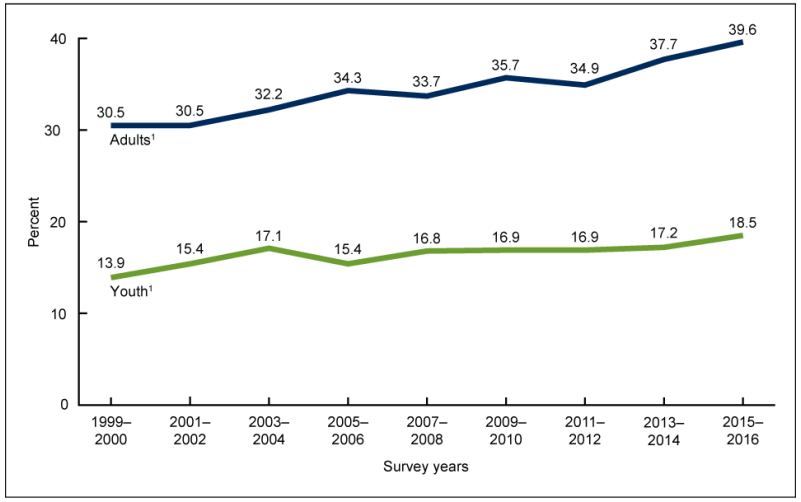
- Can help us understand patterns of disease and population characteristics over time
- Population health surveillance

Trends in obesity among children and adolescents aged 2–19 years, by age: United States, 1963–1965 through 2013–2014



NOTES: Obesity is defined as body mass index (BMI) greater than or equal to the 95th percentile from the sex-specific BMI-for-age 2000 CDC Growth Charts.
SOURCES: NCHS, National Health Examination Surveys II (ages 6–11) and III (ages 12–17); and National Health and Nutrition Examination Surveys (NHANES) I–III, and NHANES 1999–2000, 2001–2002, 2003–2004, 2005–2006, 2007–2008, 2009–2010, 2011–2012, and 2013–2014.

Figure 5. Trends in obesity prevalence among adults aged 20 and over (age adjusted) and youth aged 2–19 years: United States, 1999–2000 through 2015–2016



[1]Significant increasing linear trend from 1999–2000 through 2015–2016.
NOTES: All estimates for adults are age adjusted by the direct method to the 2000 U.S. census population using the age groups 20–39, 40–59, and 60 and over.
Access data table for Figure 5 at: https://www.cdc.gov/nchs/data/databriefs/db288_table.pdf#5.
SOURCE: NCHS, National Health and Nutrition Examination Survey, 1999–2016.

Public Health Surveillance

Public health surveillance is “the ongoing, systematic collection, analysis, and interpretation of health-related data essential to planning, implementation, and evaluation of public health practice.”

— CDC *Field Epidemiology guide*

Goal: Provide information that can be used for health action by public health personnel, government leaders, and the public to guide public health policy and programs

Surveillance Studies

Must decide "what is the overarching goal of the surveillance study"?
(≈ **research question)**

- What will we monitor?
-
- Who will collect the data, and how will it be collected?
-
- Who is the target population?

Nationally Notifiable Disease Surveillance System (NNDSS)

- NNDSS helps monitor, control, and prevent about 120 diseases/conditions
- Notifiable disease surveillance begins at the level of local, state, and territorial public health departments
- Jurisdictional laws and regulations mandate reporting of cases of specified infectious and non-infectious conditions to health departments.
- **Examples**: West Nile Virus, measles, elevated blood levels, botulism, E.coli, anthrax

Internationally Reportable Diseases

- Reporting to WHO is always required for cases of

- Smallpox
- Poliomyelitis (wild type)
- Human influenza caused by any new subtype
- Severe acute respiratory syndrome (SARS)

Potentially notifiable events:

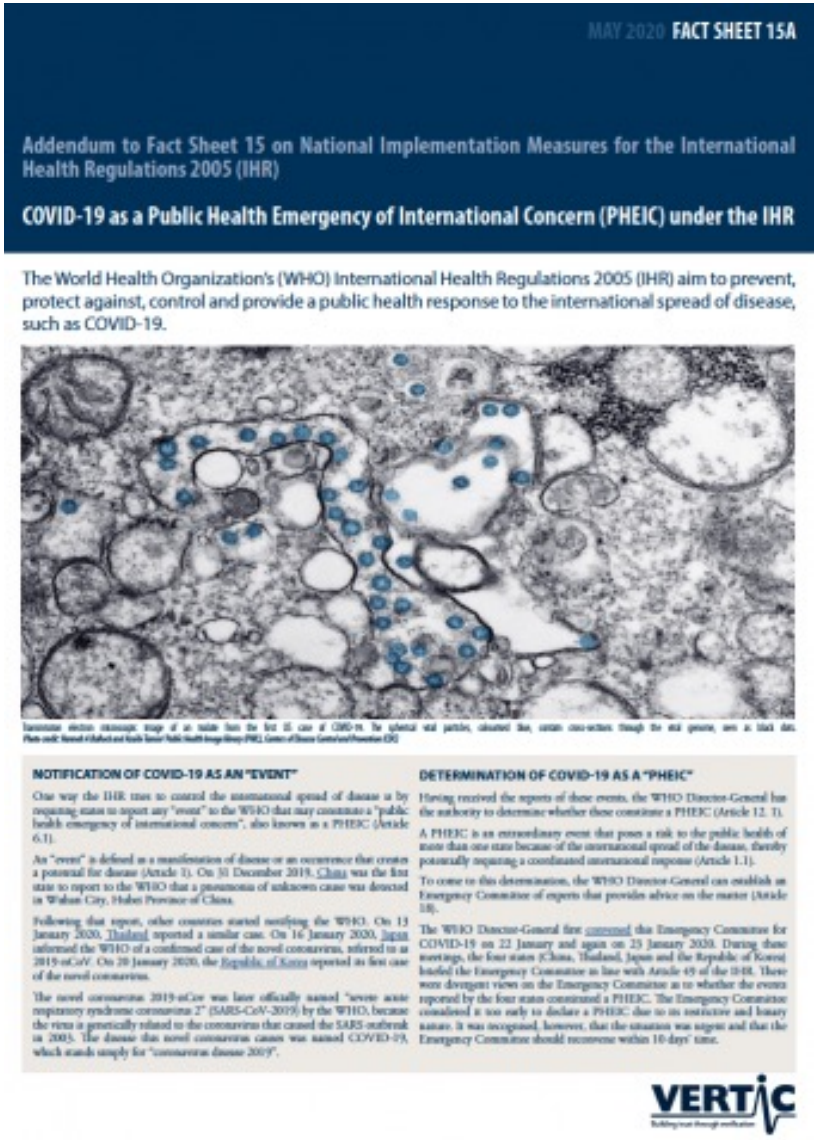
•May include cholera, pneumonic plague, yellow fever, viral hemorrhagic fever, and West Nile fever

Public health emergency of international concern (PHEIC)

Countries must detect and report events if they meet the 2 of 4 criteria to be deemed a PHEIC:

- Is the public health impact of the event serious?
- Is the event unusual or unexpected?
- Is there a significant risk of international spread?
- Is there a significant risk of international travel or trade restrictions?

Since 2005, five PHEICs: H1N1 (2009), Polio (2014), Ebola (2014), Zika (2016), and COVID (2020).



MAY 2020 **FACT SHEET 15A**

Addendum to Fact Sheet 15 on National Implementation Measures for the International Health Regulations 2005 (IHR)

COVID-19 as a Public Health Emergency of International Concern (PHEIC) under the IHR

The World Health Organization's (WHO) International Health Regulations 2005 (IHR) aim to prevent, protect against, control and provide a public health response to the international spread of disease, such as COVID-19.

NOTIFICATION OF COVID-19 AS AN "EVENT"

One way the IHR uses to control the international spread of disease is by requiring states to report any "event" to the WHO that may constitute a "public health emergency of international concern", also known as a PHEIC (Article 6.1).

An "event" is defined as a manifestation of disease or an occurrence that creates a potential for disease (Article 1). On 31 December 2019, China was the first state to report to the WHO that a pneumonia of unknown cause was detected in Wuhan City, Hubei Province of China.

Following that report, other countries started notifying the WHO. On 13 January 2020, Thailand reported a similar case. On 16 January 2020, Japan informed the WHO of a confirmed case of the novel coronavirus, referred to as 2019-nCoV. On 20 January 2020, the Republic of Korea reported its first case of the novel coronavirus.

The novel coronavirus 2019-nCov was later officially named "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2019) by the WHO, because the virus is genetically related to the coronavirus that caused the SARS outbreak in 2003. The disease that novel coronavirus causes was named COVID-19, which stands simply for "coronavirus disease 2019".

DETERMINATION OF COVID-19 AS A "PHEIC"

Having received the reports of these events, the WHO Director-General has the authority to determine whether these constitute a PHEIC (Article 12. 1).

A PHEIC is an extraordinary event that poses a risk to the public health of more than one state because of the international spread of the disease, thereby potentially requiring a coordinated international response (Article 1.1).

To come to this determination, the WHO Director-General can establish an Emergency Committee of experts that provides advice on the matter (Article 18).

The WHO Director-General first convened this Emergency Committee for COVID-19 on 22 January and again on 23 January 2020. During these meetings, the four states (China, Thailand, Japan and the Republic of Korea) briefed the Emergency Committee in line with Article 49 of the IHR. There were divergent views on the Emergency Committee as to whether the events reported by the four states constituted a PHEIC. The Emergency Committee considered it too early to declare a PHEIC due to its restrictive and binary nature. It was recognised, however, that the situation was urgent and that the Emergency Committee should reconvene within 10-days' time.

VERTIC

PHEIC OR PANDEMIC?

Besides declaring COVID-19 a PHEIC on 30 January 2020, the WHO made the assessment on 11 March 2020 that COVID-19 can be characterised as a pandemic, defined as the "worldwide spread of a new disease."

End of module 1

Ecological Studies

Ecological Studies

- "*An ecologic study focuses on the comparison of groups rather than individuals*" (Morgenstern 2008)
- Sometimes, we cannot accurately measure relevant exposures for a large number of subjects with available time and resources
- Frequently used in environmental epidemiology
- Target of inference is the <u>population</u>, useful for policy evaluation

Why do ecological studies?

- Inexpensive and take little time when various secondary data sources can be used and linked at the aggregate level (e.g., census data, vital statistics registries)

- When ecological effects are the main interest, rather than individual level effects

Variability in ecologic studies

- Ecologic studies are useful when variability within a population is low, especially when compared to between population variability

Shanghai, China

Auckland, NZ

Concepts related to ecological studies

- Levels of measurement

1. Aggregate measures: Means or proportions in groups, derived from individuals measures within groups (e.g. % smokers in a city)

2. Environmental measures: e.g., Yearly air pollution levels

3. Global measures: Attributes for groups for which there is no individual analog (e.g. population density, type of health care system)

Levels of Inference

Individual (aka “Biologic”) inferences about effects on individual risks

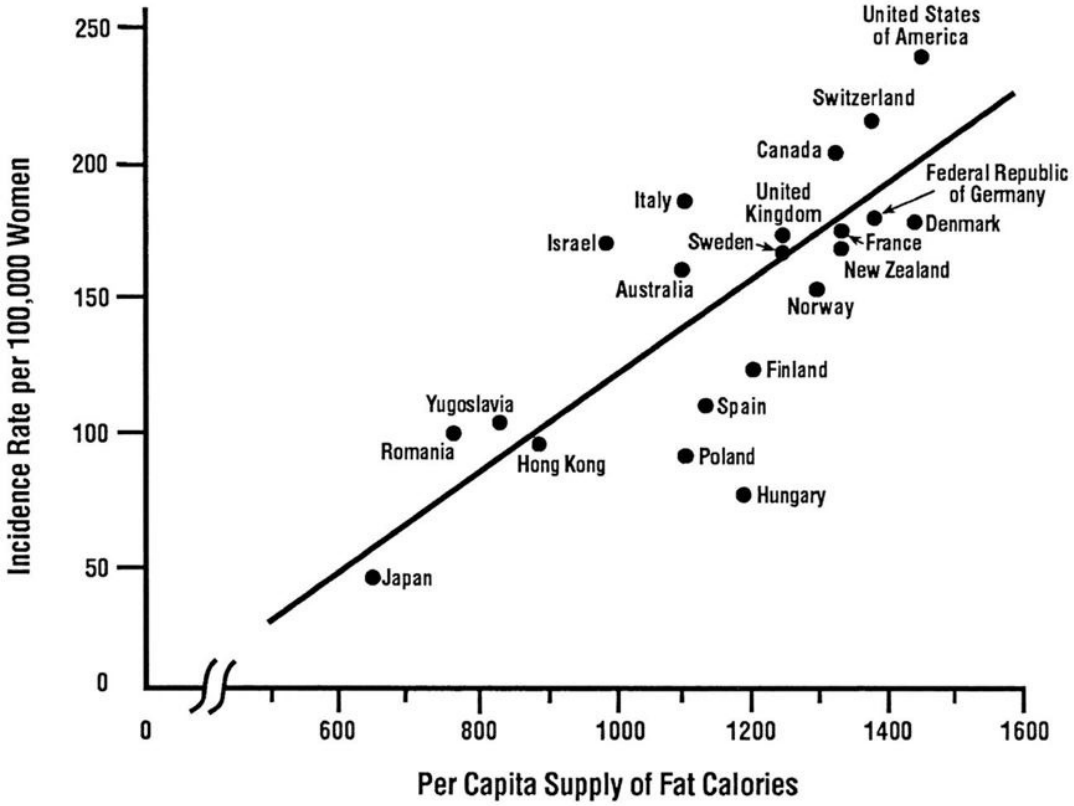
- E.g. if individual motorcyclists wear helmets, will it lower their risk of mortality?

Ecologic inferences about effects on group rates

- E.g. Do rates of motorcycle-related mortality of riders vary across different states that have different helmet laws in place?

Cross-level inferences

- “Cross-level” inferences are often made using results from ecological studies:
  - When ecological effects are interpreted as individual effects
  - This can produce ”ecological fallacy”
    - When drawing inferences at the individual level (that is, regarding relations between individual level variables) based on group level data (Diez Roux, 2002)

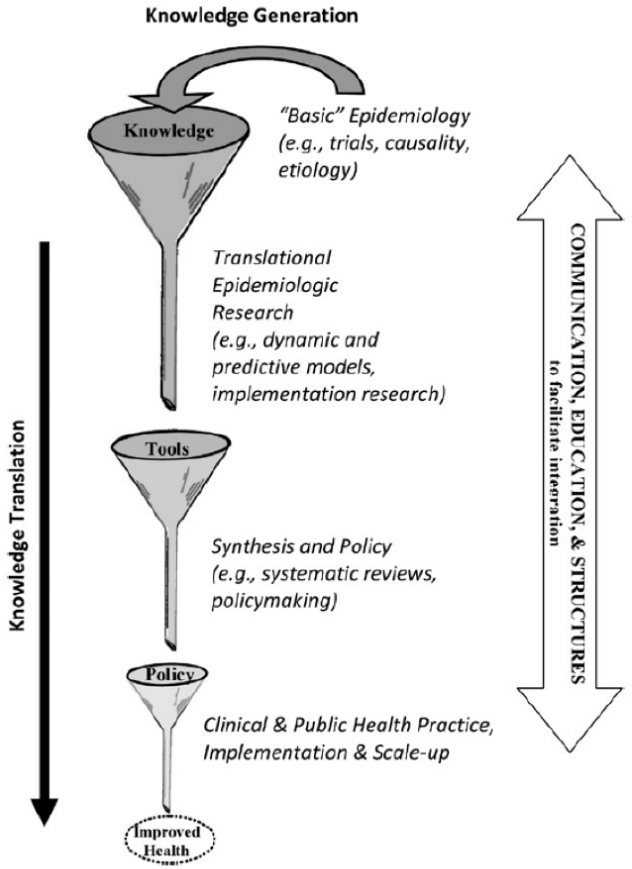


- Higher average fat consumption= higher BC incidence in the country
- We do not know whether the individuals in whom breast cancer developed in that country actually had high dietary fat intake. Only average values of fat consumption in the population.
- Example of cross-level inferences leading to **ecological fallacy**

Systematic Reviews & Meta-Analysis

The importance of research synthesis

- Systematic reviews and meta-analysis are both a form of research synthesis
- Approaches to help convert knowledge into practice

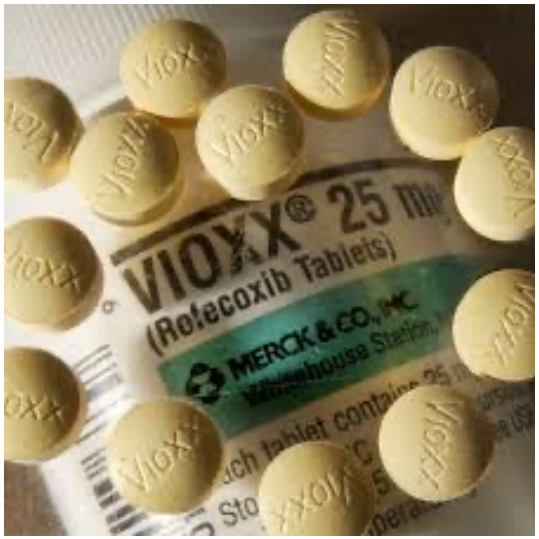


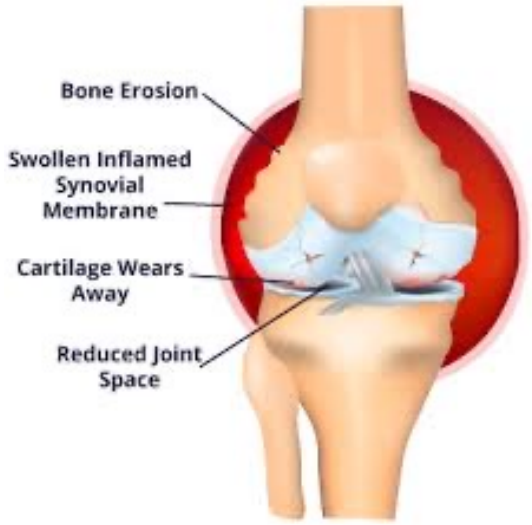
Research Synthesis

- We need evidence for both clinical practice and public health decision making

- Where does good evidence come from?
  - Synthesis of current evidence on a specific research question
    - Review articles play a huge role in clinical medicine
    - Very difficult to keep up with the number of articles published daily

Why do we need systematic reviews?





Case study: Vioxx

- Drug approved for pain management (mainly arthritis), low risk of GI side effects, such as heartburn, nausea, diarrhea, and bleeding in the digestive tract, compared to traditional NSAIDs used to treat joint pain
- Vioxx RCT showed an RR of 0.2 (95% CI: 0.1, 0.7) meaning individuals who took the drug were more likely to have a CVD even than those who took the comparator (naproxen)

COMPARISON OF UPPER GASTROINTESTINAL TOXICITY OF ROFECOXIB AND NAPROXEN IN PATIENTS WITH RHEUMATOID ARTHRITIS

CLAIRE BOMBARDIER, M.D., LOREN LAINE, M.D., ALISE REICIN, M.D., DEBORAH SHAPIRO, DR.P.H., RUBEN BURGOS-VARGAS, M.D., BARRY DAVIS, M.D., PH.D., RICHARD DAY, M.D., MARCOS BOSI FERRAZ, M.D., PH.D., CHRISTOPHER J. HAWKEY, M.D., MARC C. HOCHBERG, M.D., TORE K. KVIEN, M.D., AND THOMAS J. SCHNITZER, M.D., PH.D., FOR THE VIGOR STUDY GROUP

Results Rofecoxib and naproxen had similar efficacy against rheumatoid arthritis. During a median follow-up of 9.0 months, 2.1 confirmed gastrointestinal events per 100 patient-years occurred with rofecoxib, as compared with 4.5 per 100 patient-years with naproxen (relative risk, 0.5; 95 percent confidence interval, 0.3 to 0.6; $P<0.001$). The respective rates of complicated confirmed events (perforation, obstruction, and severe upper gastrointestinal bleeding) were 0.6 per 100 patient-years and 1.4 per 100 patient-years (relative risk, 0.4; 95 percent confidence interval, 0.2 to 0.8; $P=0.005$). The incidence of myocardial infarction was lower among patients in the naproxen group than among those in the rofecoxib group (0.1 percent vs. 0.4 percent; relative risk, 0.2; 95 percent confidence interval, 0.1 to 0.7); the overall mortality rate and the rate of death from cardiovascular causes were similar in the two groups.

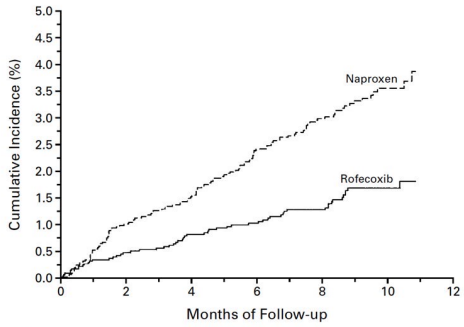


Figure 1. Cumulative Incidence of the Primary End Point of a Confirmed Upper Gastrointestinal Ev among All Randomized Patients.

We were told nothing wrong with Vioxx, just that Naproxen is protective vs heart attack

The overall mortality rate was similar in the two groups, as were the rates of death from gastrointestinal events and from cardiovascular causes. The rate of myocardial infarction was significantly lower in the naproxen group than in the rofecoxib group (0.1 percent vs. 0.4 percent). This difference was primarily accounted for by the high rate of myocardial infarction among the 4 percent of the study population with the highest risk of a myocardial infarction, for whom low-dose aspirin is indicated.[22] The difference in the rates of myocardial infarction between the rofecoxib and naproxen groups was not significant among the patients without indications for aspirin therapy as secondary prophylaxis.

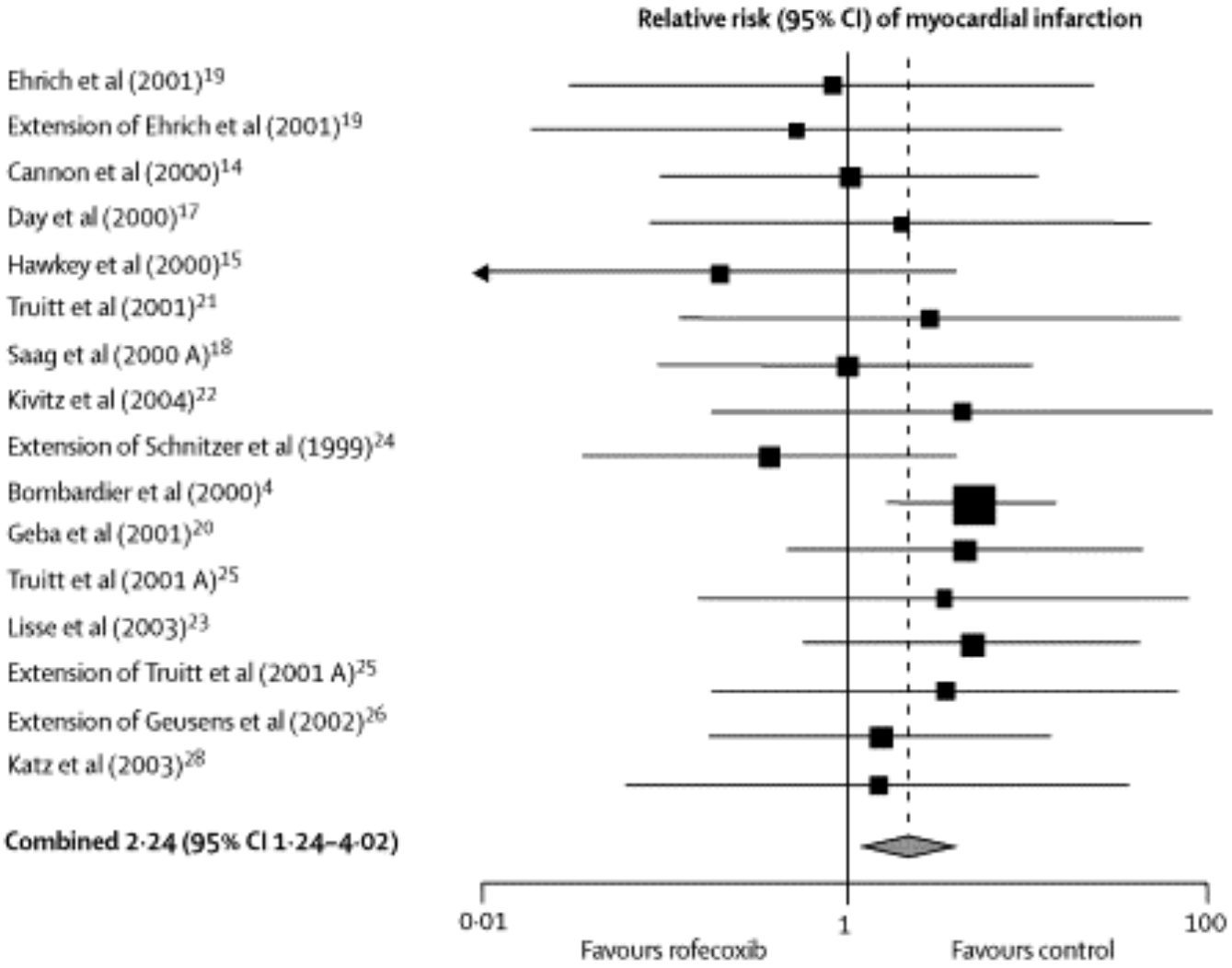
Vioxx and CVD Complications

- Pulled from the market ("voluntarily" by manufacturer in 2004
  - Merck announced the withdrawal of Vioxx because of an increased cardiovascular risk in patients taking the drug for >18 months

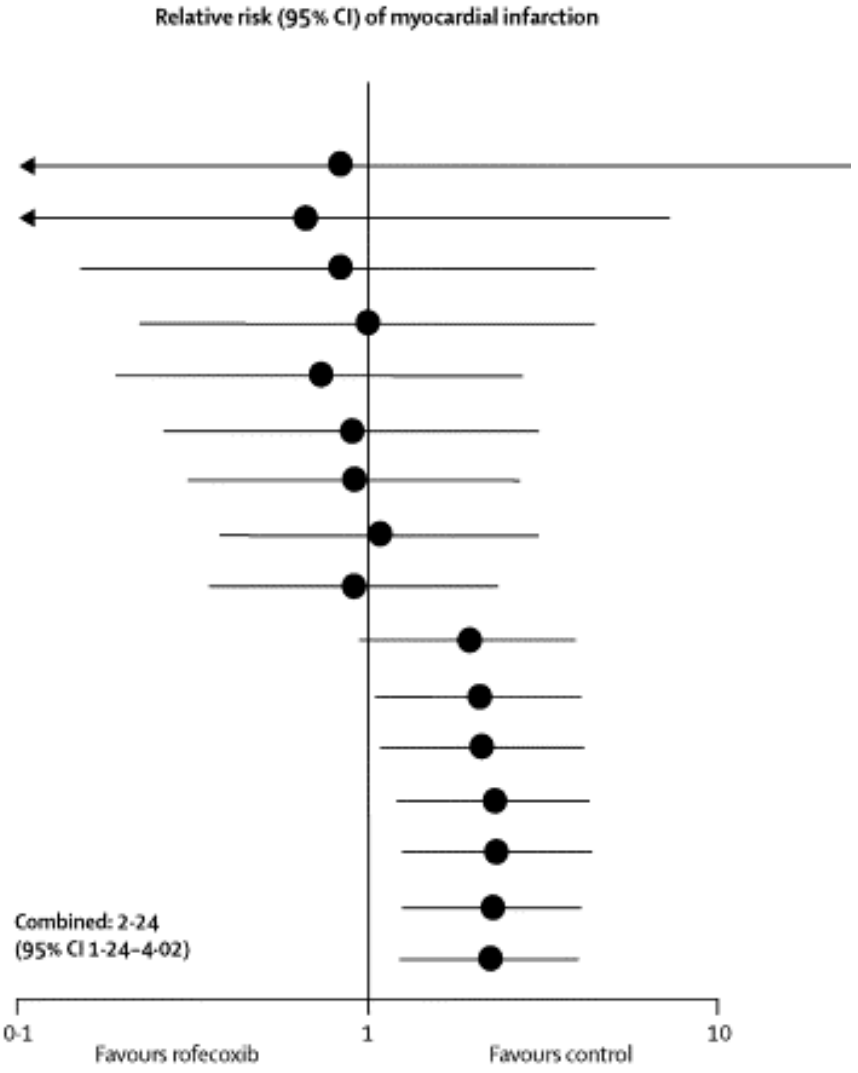
- Decision was based on the 3-year result of the unpublished APPPROVe study of Vioxx for the prevention of colorectal polyps in patients with a history of colorectal adenomas
  - Does Vioxx prevent the recurrent of colorectal polyps?
  - Among patients taking the medication for >18 mo, nearly twice the risk of serious cardiovascular events (i.e., MI, Stroke; RR=1.8)
  - 25 MI in placebo group, 45 MI in Vioxx group

Role of meta-analysis

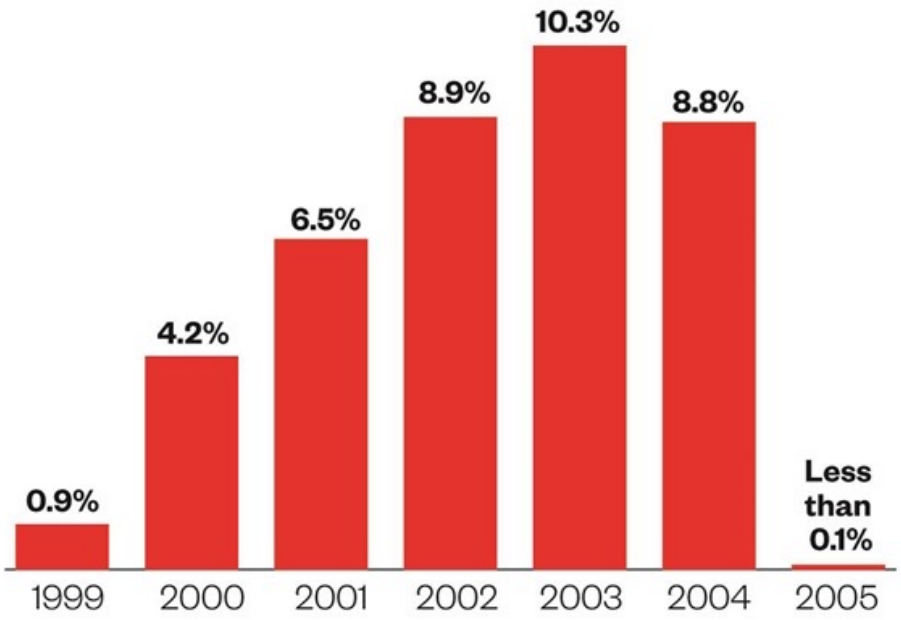
- Juni et al., did a meta-analysis of 18 RCTs and 11 observational studies
- By the end of 2000 (52 events, 20742 patients) the relative risk from RCTs was 2.30 (95% CI 1.22-4.33)
- Juni et al., concluded that “rofecoxib should have been withdrawn several years earlier; the reasons why manufacturing and drug licensing authorities did not continuously monitor and summarize the accumulating evidence needs to be clarified”


Relative risk (95% CI) of myocardial infarction
Ehrich et al (2001)[19]
Extension of Ehrich et al (2001)[19]
Cannon et al (2000)[14]
Day et al (2000)[17]
Hawkey et al (2000)[15]
Truitt et al (2001)[21]
Saag et al (2000 A)[18]
Kivitz et al (2004)[22]
Extension of Schnitzer et al (1999)[24]
Bombardier et al (2000)[4]
Geba et al (2001)[20]
Truitt et al (2001 A)[25]
Lisse et al (2003)[23]
Extension of Truitt et al (2001 A)[25]
Extension of Geusens et al (2002)[26]
Katz et al (2003)[28]
Combined 2·24 (95% CI 1·24–4·02)
0·01
1
100
Favours rofecoxib
Favours control

Year	Patients	Events	p
1997	523	1	0·916
1998	615	2	0·736
	1399	5	0·828
	2208	6	0·996
	2983	8	0·649
	3324	9	0·866
1999	4017	12	0·879
	5059	13	0·881
2000	5193	16	0·855
	13 269	40	0·070
	14 247	44	0·034
	15 156	46	0·025
	20 742	52	0·010
2001	20 742	58	0·007
	20 742	63	0·007
	21 432	64	0·007



Number of Vioxx prescriptions, England



- Merck settled the Vioxx lawsuits for $4.85 billion in the US//$21.8 million in Canada
- “Merck does not admit causation or fault”

The importance of research synthesis

ANALYSIS CMAJ

Managing evidence-based knowledge: the need for reliable, relevant and readable resources

Sharon Straus MD MSc, R. Bryan Haynes MD PhD

The sheer volume of research-based evidence is one of the main barriers to better use of knowledge. About 10 years ago, if general internists wanted to keep abreast of the primary clinical literature, they would have needed to read 17 articles daily.[6] Today, with more than 1000 articles indexed daily by MEDLINE, that figure is likely double. The problem is compounded by the inability of clinicians to afford more than a few seconds at a time in their practices for finding and assimilating evidence.[7] These challenges highlight the need for better infrastructure in the management of evidence-based knowledge.

Straus S et al. CMAJ 2009

Why bother with systematic reviews?

For informing policy:

Policy decisions involve both scientific and non-scientific concerns.

Systematic reviews may provide robust, reliable summaries of the most reliable evidence: a valuable backdrop of evidence on which decisions about policies can draw.

To support existing practice

Systematic reviews provide a key source of **evidence-based information to support and develop practice** as well as to support professional development –for example, by helping to identify new and emerging developments and gaps in knowledge.

Types of Review Articles

- Traditional, narrative review
- Systematic review
- Overview
- Meta-analysis
- Pooled analysis

Types of Reviews

Narrative reviews: usually written by experts in the field, are qualitative, narrative summaries of evidence on a given topic. Typically, they involve informal and subjective methods to collect and interpret information.

Systematic review: a review in which there is a comprehensive search for relevant studies on a specific topic, and those identified are then appraised and synthesized according to a predetermined and explicit method.

(Klassen et al., 1998)

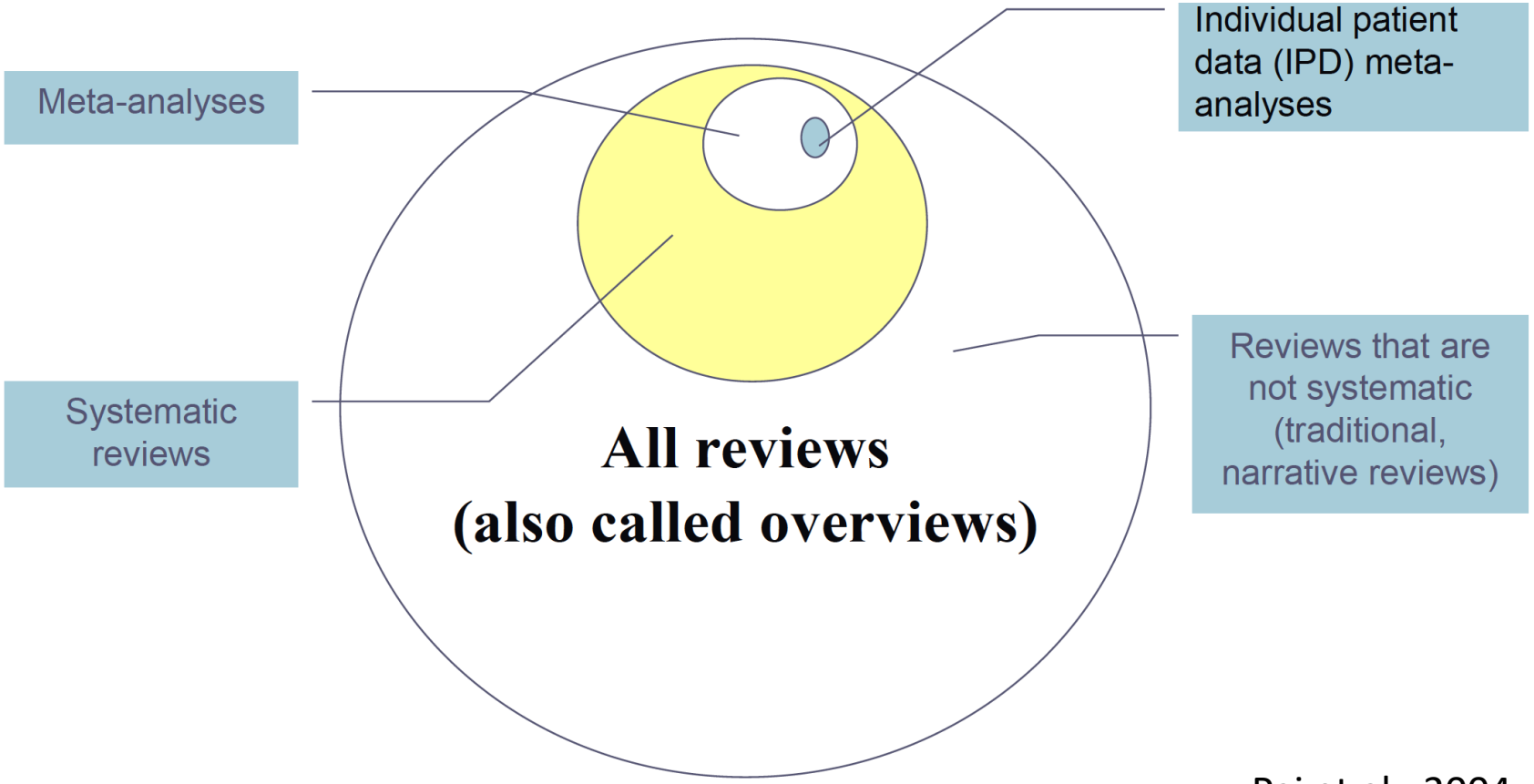
Types of Reviews

Meta-analysis: Statistical combination of at least two studies to produce a single estimate of the effect of the healthcare intervention under consideration

Individual patient data meta-analyses: Involves obtaining raw data on all patients from each trial or study directly and re-analyzing the data

Klassen et al., 1998

Types of Reviews



Pai et al., 2004

Narrative vs. Systematic Reviews

Narrative Reviews	Meta-analysis
Addresses broad questions	Addresses focused questions
Vague methods, search strategy	Very specific criteria, search strategy pre-specified, multiple reviewers
No quality assessment	Quality assessment/subgroup analyses
Qualitative 'vote counting' synthesis strategy	Meta-analysis gives higher weight to more precise studies, calculate pooled/weighted effect measures
Qualitative approach to heterogeneity	Graphical and statistical methods to address heterogeneity
Cumulative systematic biases/opinions	Less influenced by biases/opinions

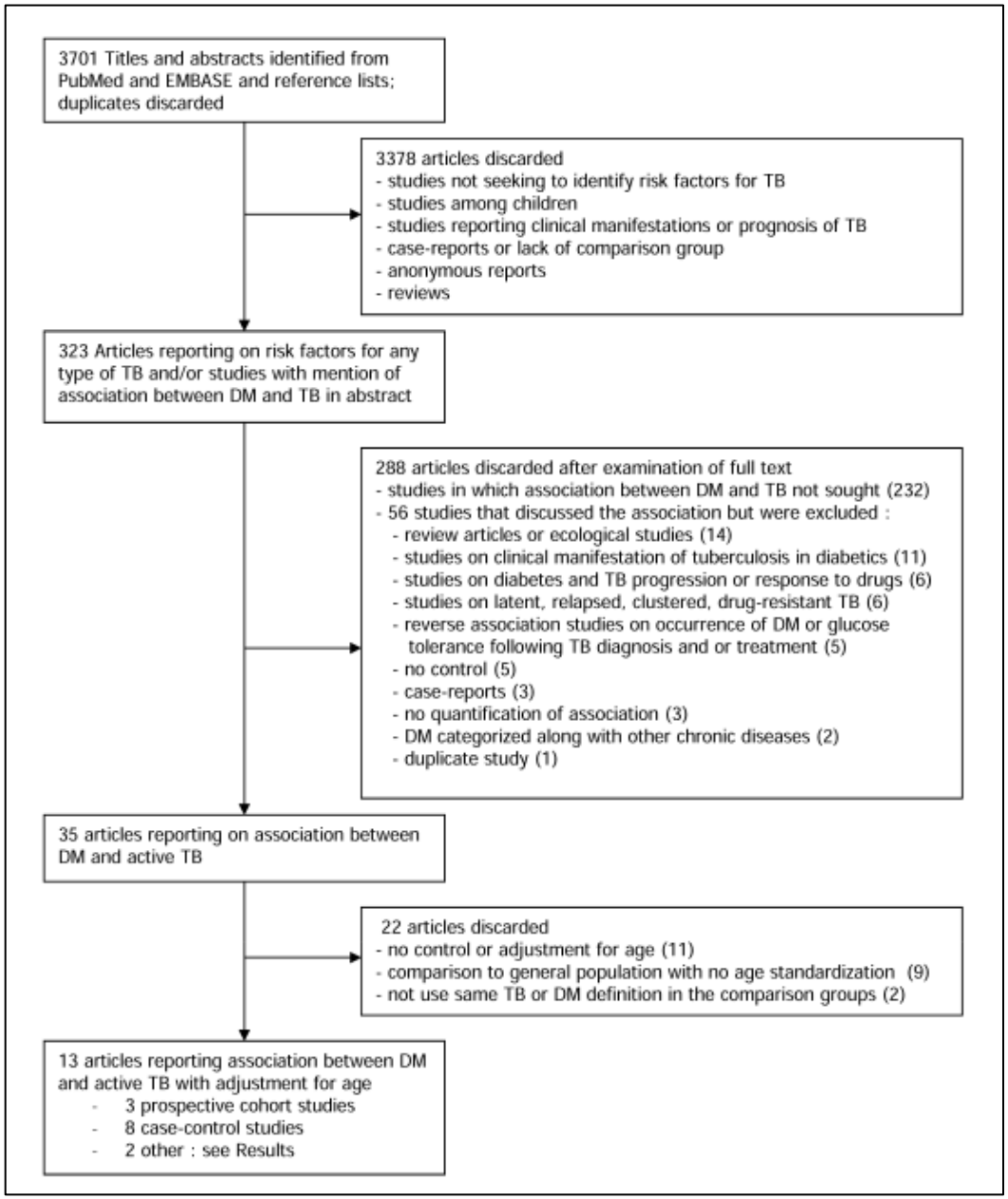
"… it is always appropriate and desirable to systematically review a body of data, but it may be sometimes inappropriate, or even misleading to statically pool results from separate studies. Indeed, it is our impression that reviewers often find it hard to resist the temptation of combining studies even when such meta analysis is questionable or clearly inappropriate"

Egger et al., 2001

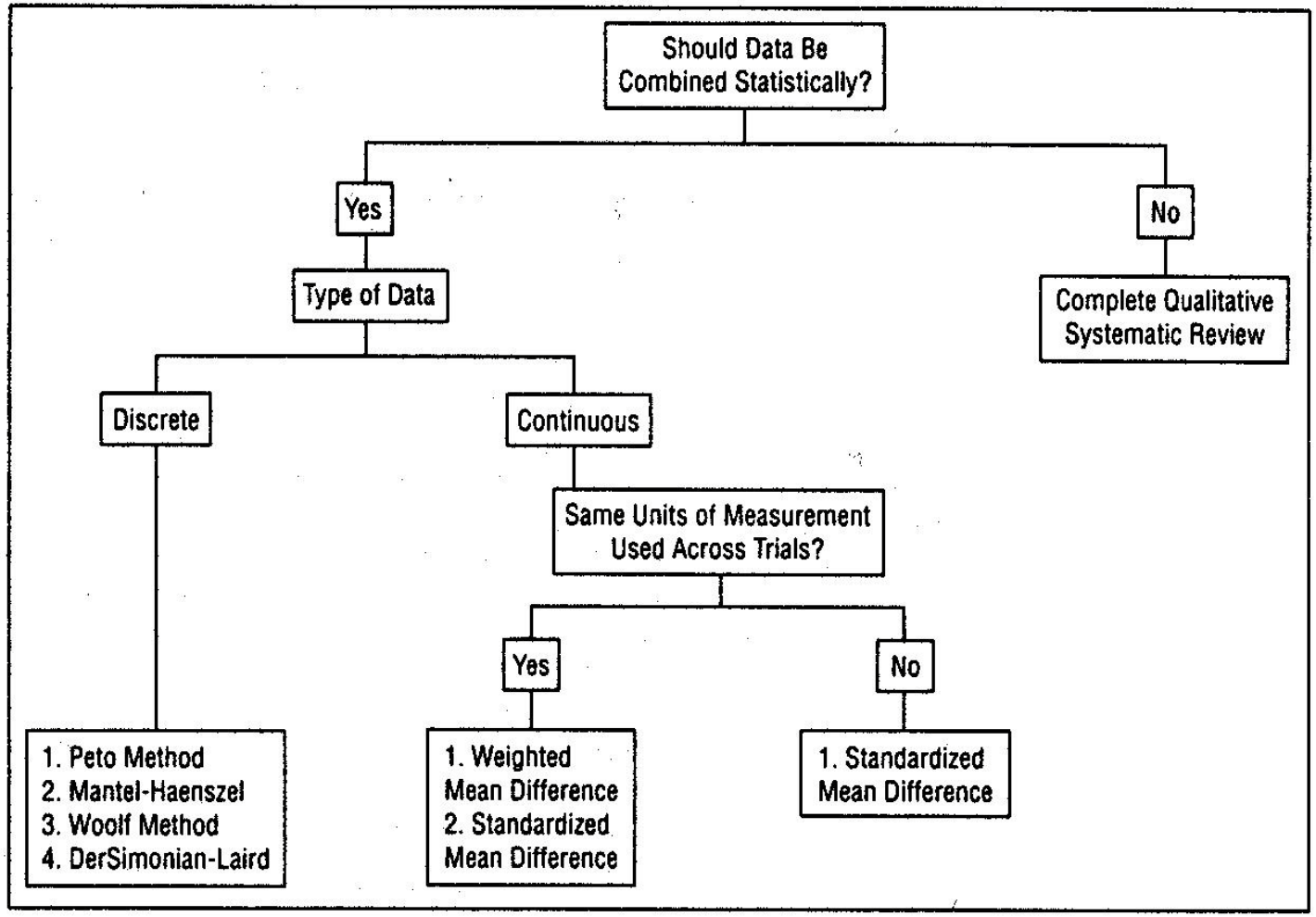
Elements of a systematic review

- Formulate a question and write research protocol
- Search for and include primary studies
- Assess study quality
- Extract data
- Analyze results
- Interpret results and write report

Flow Chart of Literature Search



When to do a meta-analysis



Algorithm of statistical choices available to systematic reviewers.

(Moher, 1998)

Meta-Analyses

- Each study is considered an ‘observation’
- To perform a meta-analysis we compute an effect size and variance for each study, and then compute a weighted mean of these effect sizes.
- To compute the weighted mean we generally assign more weight to the more precise studies, but the rules for assigning weights depend on our assumptions about the distribution of true effects.

Systematic reviews are used to judge the quality of evidence

Box 2 | Quality of evidence and definitions

High quality— Further research is very unlikely to change our confidence in the estimate of effect

Moderate quality— Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate

Low quality— Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate

Very low quality— Any estimate of effect is very uncertain

Factors in deciding on quality of evidence

Factors that might decrease quality of evidence

- Study limitations
- Inconsistency of results
- Indirectness of evidence
- Imprecision
- Publication bias
- Factors that might increase quality of evidence
- Large magnitude of effect
- Plausible confounding, which would reduce a demonstrated effect
- Dose-response gradient

Assessing Study Quality

ANALYSIS

RATING QUALITY OF EVIDENCE AND STRENGTH OF RECOMMENDATIONS

GRADE: an emerging consensus on rating quality of evidence and strength of recommendations

Guidelines are inconsistent in how they rate the quality of evi
recommendations. This article explores the advantages of the
being adopted by organisations worldwide

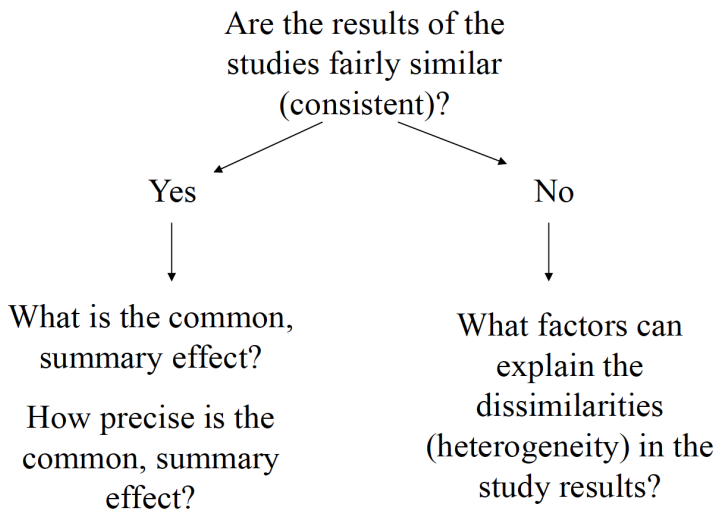
Factors in deciding on quality of evidence

Factors that might decrease quality of evidence

- Study limitations
- Inconsistency of results
- Indirectness of evidence
- Imprecision
- Publication bias

- Factors that might increase quality of evidence
- Large magnitude of effect
- Plausible confounding, which would reduce a demonstrated effect
- Dose-response gradient

Heterogeneity



If heterogeneity is present, a common summary effect measure is hard to interpret

Important to understand the difference between statistical vs. clinical heterogeneity

- Patient population
- Intervention used
- Outcomes
- Study design (follow-up)
- Random error
- Biases