What is EPIDEMIOLOGY, and what does it offer for understanding, treating, and preventing Alzheimer's?

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OVERVIEW

- What is Alzheimer's?
- What is epidemiology?
- Major functions
  - Assess and forecast the magnitude of the problem *(brief intro to Dr. Langa's talk)*
  - Understand risk and protective factors and their potential role in prevention *(brief intro to Dr. Yaffe's talk)*
  - Put clinical findings in a population context
  - Assess and improve methods for observational studies

WHAT IS ALZHEIMER'S?

Alzheimer's disease (AD) dementia is a type of *dementia* caused by a specific *neuropathology*--amyloid plaques and neurofibrillary tangles

Confusingly, AD is used both to refer to the *pathology* and the *clinical syndrome* caused by the pathology

Dementia and *Mild Cognitive Impairment* (MCI) are clinical diagnoses based on cognitive and functional status and can be caused by AD pathology or other pathologies

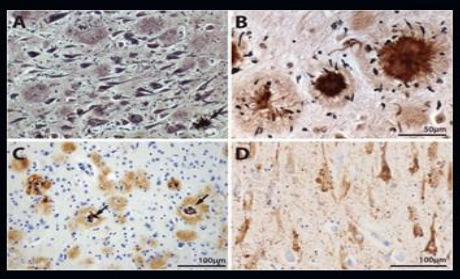
Also confusingly, AD and dementia are sometimes used interchangeably, in part because AD is the most common form of dementia

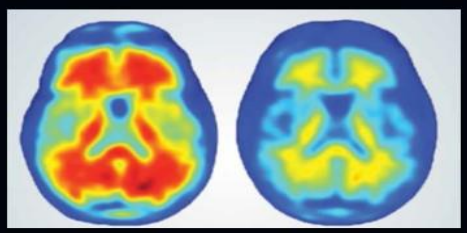
Clinical vs. pathological diagnosis

A definitive diagnosis of AD requires evidence of AD pathology from biomarkers or autopsy, but diagnosis in clinical and population studies is often based on symptoms alone

Whether this matters depends on the purpose

Fine for understanding disease burden or costs, but problematic for targeted clinical trials, and complicates the interpretation of epidemiologic and genetic studies



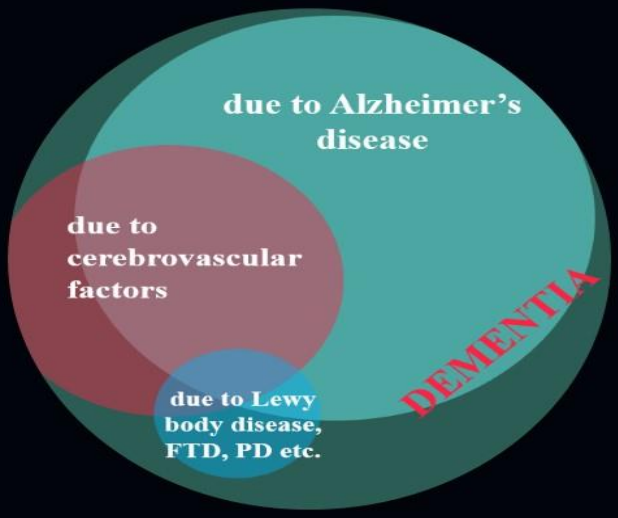


Additionally complicating the interpretation of research findings . . .

AD pathology often co-occurs with other pathologies, particularly cerebrovascular pathology

The effects of these different pathologies are at least additive and may interact

At later ages, mixed dementia is very common, and additional pathologies likely remain to be identified

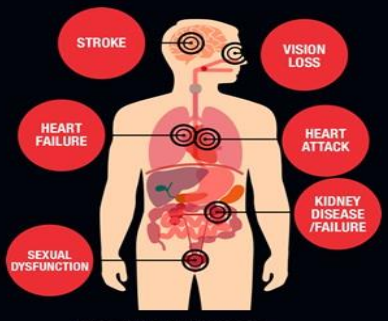


Graphic courtesy of Dr. Jennifer Weuve

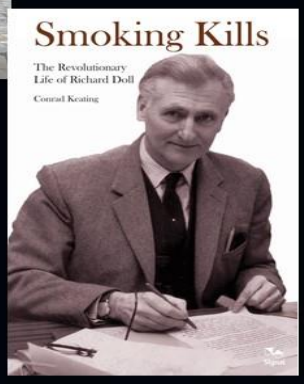
WHAT IS EPIDEMIOLOGY?

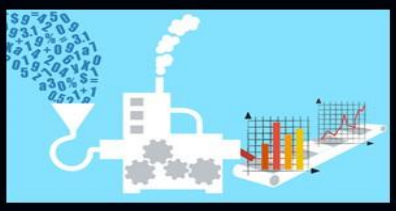
Initial focus on infectious disease--surveillance, containment, etc.

Later parallel focus on chronic disease--to understand disease burden, patterns over time and space, and understand risk factors



Health Threats From High Blood Pressure





What do epidemiologists do?

Quantify disease in the population overall, according to demographic factors, and across time and space

Use patterns of association and careful statistical analysis to understand risk and protective factors, offering insight into mechanism and prevention

Assess whether findings from clinical studies hold up in the general population, with implications for screening and real world impact of interventions

Assess and develop optimal methods for observational studies, with implications for clinical trials, screening, and health services

DESCRIPTIVE EPIDEMIOLOGY: Magnitude and patterns

How many people have the disease now? (*Prevalence*)

How many new cases can be expected . . . (*Incidence*)

- at a given age or in a given time window?
- cumulatively until a certain time ?
- over a lifetime?

How do the above numbers change across demographic factors, geographic regions, and birth cohorts?

Descriptive Epidemiology: Magnitude and patterns

Provides estimate of disease burden to inform care planning, policy, and research priorities

Big picture suggests rising rates overall despite apparent fall in age-specific incidence* --and that's why we are here today!

Stay tuned: *Details from Dr. Langa*

RISK AND PROTECTIVE FACTORS

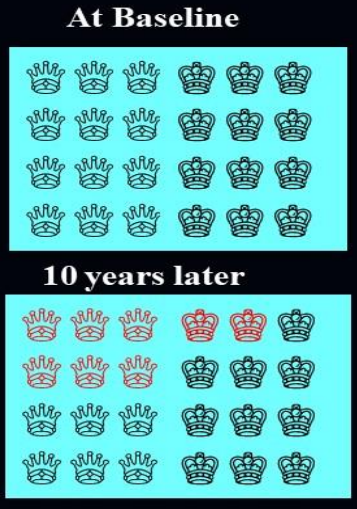
Use associations to discover factors that increase or decrease disease risk

Risk and protective factors can be genes or diet , activities, medical conditions, or local environment

Can identify high risk populations or select intervention strategies for clinical trials

Can be translated into individual health recommendations and population health policy

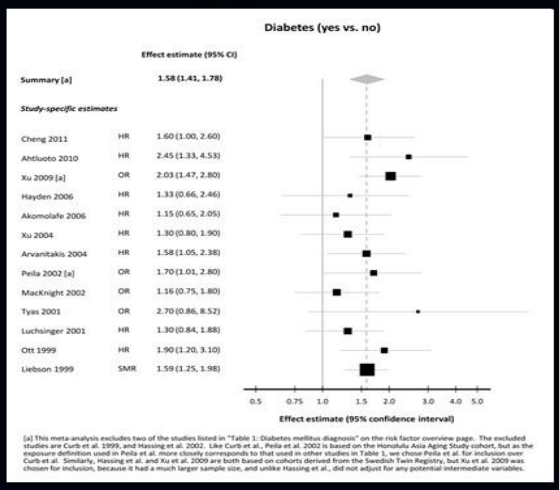
Can help understand mechanism and drug development



Spiky crown may be a risk factor for turning red after 10 years

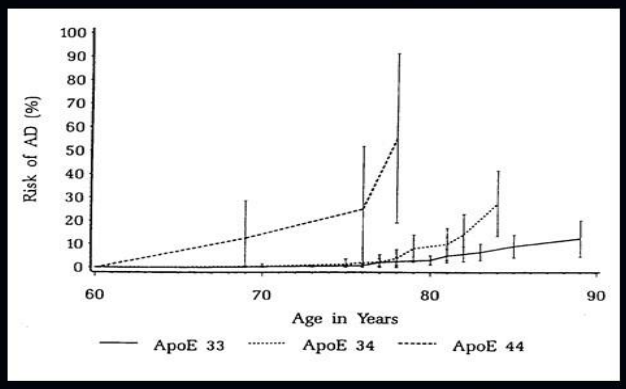
Examples

Systematic Review of risk of dementia with diabetes



Weuve et al., AlzRisk, Alzheimer Research Forum, www.alzrisk.org

Cumulative incidence of dementia by *APOE*-4 dose: Framingham Study



Myers et al., Neurology, 1996

Stay tuned: *Details from Dr. Yaffe*

PUT CLINICAL RESEARCH AND EXPERIENCE INTO A POPULATION CONTEXT

Patients **are more impaired than average for the same diagnosis (e.g., MCI, because symptoms drive care-seeking), and also have more other illnesses that may unmask decline, increase contact with doctors, etc.**

- ***Patients*** **are also more educated, more affluent, and have other attributes that increase access to care**
- **However, screening programs, publicity, or the availability of early intervention can bring those with milder illness into care**

Research volunteers **are often highly educated, and more likely to have family history, subclinical symptoms, etc.**

NACC vs. population samples

Study	NACC	FHS	Rotterdam
Description	US volunteer, 80% white	US pop, 1° ly white	European pop, white
N	5073	4078	6399
mean (sd) age (yrs)	68.7 (4.30)	62.0 (1.71)	65.4 (4.18)
% male	33.6%	43.2%	45.2%
mean (sd) educ (yrs)	15.79 (2.99)	13.20 (*)	12.94 (*)
E-4 allele freq	0.178	0.117	0.150
% w/ family history	58.3%	N/A	21.7%
% w/ memory concerns	24.9%	N/A	43.1%
mean (sd) MMSE	29.0 (1.3)	28.5 (1.0)	28.8 (1.4)

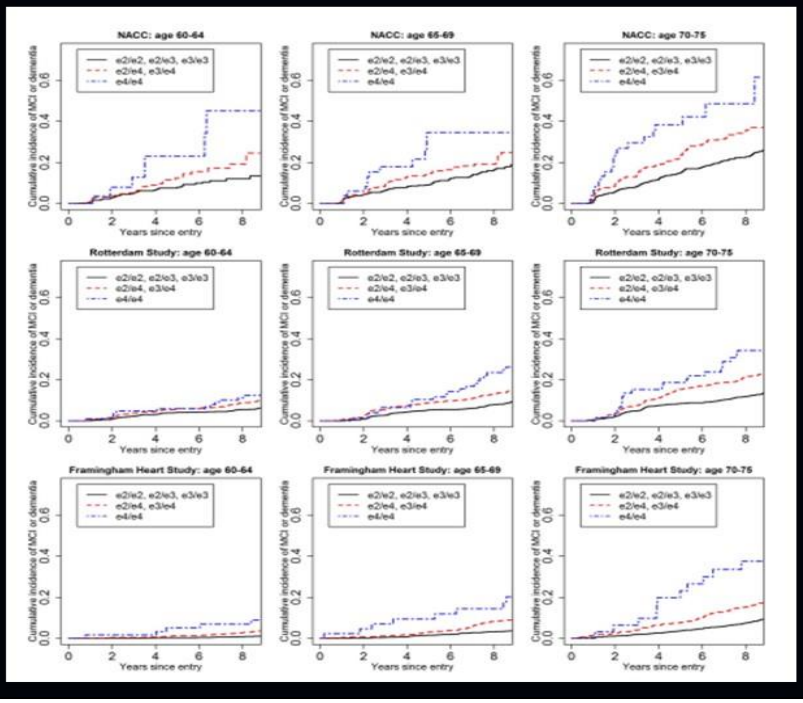
Cumulative Incidence of MCI/dementia by *APOE* dose

Alzheimer Centers (NACC)

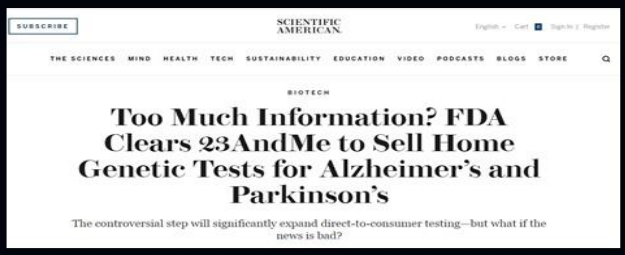
Rotterdam Study

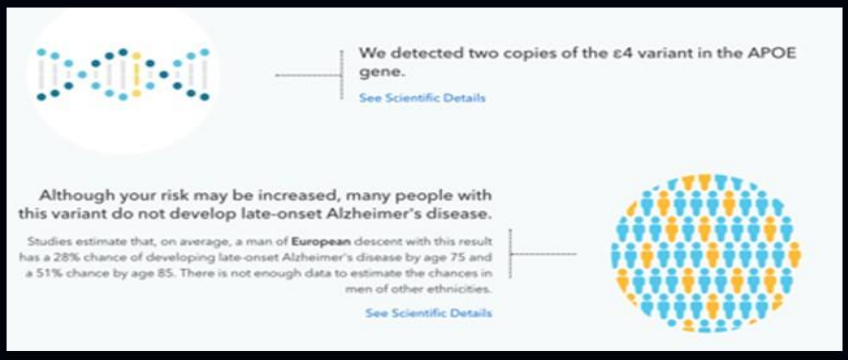
Framingham Heart Study

Qian et al, PLoS Medicine, *2017*



Example: 23andMe *APOE* Testing





Sample report courtesy of Robert Green and Debby Tsuang

Importance of Population Context

23andMe's risk estimates are too high (likely because they're based on data from clinical/volunteer samples)

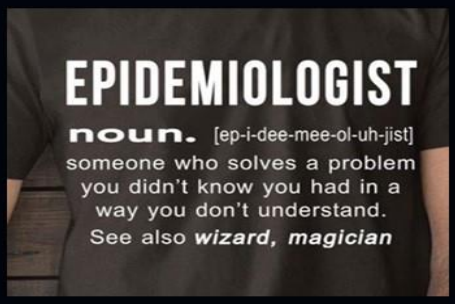
Similar issues apply for imaging, biomarkers, and clinical symptoms tested in clinical/volunteer settings

Critical issue whenever findings from one setting are applied in another; examples:

- **The MCI trial of donepezil turned to community recruiting when clinical recruiting ran short, but lower onset rate of dementia in community participants reduced the study's power**
- **Expected rates of developing dementia based on biomarker data from clinical samples of MCI will be lower if a new treatment becomes available, as that would drive less impaired individuals to seek care**

ASSESS AND IMPROVE METHODS FOR OBSERVATIONAL AND OTHER CLINICAL RESEARCH

Caveat Auditor



Epidemiology focuses on observational research, so has developed careful methods to guard against and quantify potential false or distorted conclusions

The importance of these details depends on the question

Causal questions are particularly vulnerable to biases, and are critically important to translational applications

Key issues that can lead to bias

Measurement error: over or under-calling dementia or MCI outcome, noise in measuring cognitive or functional status, mismeasurement of risk factors

Sampling issues: impact of entry criteria and operational definition of non-demented at baseline, age at entry and survival bias, participant burden, and autopsy consent

Confounding: something related to both your outcome and to your putative risk factor that creates a spurious association between the two–age and education are major confounders in AD research

Reverse causation: an effect masquerading as a cause

Will illustrate by raising some questions about whether cognitive activity really reduces risk of dementia

Measurement Error

A particular concern for cognitive testing, MCI, and any diagnosis in claims or health records; mostly adds noise and reduces power, but can lead to biased findings if differentially affects each side of the question at hand

For understanding the role of cognitive activity in risk for dementia, typical cognitive activity surveys focus on activities of the highly educated, which could make high levels of activities look protective when education is actually providing the benefit

Counted

Not counted

Sampling bias

In the examination of cognitive activity and risk of dementia, because there is a broad perception that cognitive activities are desirable, those who are inactive may be reluctant to participate (or may over-report their activity—see measurement error), or those who are very active may be too busy

Survival bias could also distort the relationship if those with greater levels of cognitive activity live longer, as might be expected given the association of longevity and education

Confounding

Age and education are major confounders that affect measurement, care seeking, and multiple risk factors

For cognitive activity and risk of dementia, the big concern is education, which is associated with greater cognitive activity, but contributes to dementia risk in multiple other ways

Or, early life cognitive activity might build protective "brain reserve," and later effects might be observed simply because those habits persist over time

Reverse causation

risk factor → dementia VS. dementia → "risk" factor

Given insidious onset of dementia, incipient cognitive decline can lead to changes in physiologic state (weight, BP) or lifestyle, which can in turn be mistaken for causes

Decline in cognitive activity in the face of early cognitive decline is highly plausible, and careful bias analysis cannot rule out reverse causation driving the apparent lower risk of dementia

Graphic courtesy of Dr. Jennifer Weuve

Parting words on the value of epidemiological methods

ELSEVIER

Alzheimer's & Dementia 11 (2015) 1098-1109

Alzheimer's & Dementia

Review Articles

Guidelines for reporting methodological challenges and evaluating potential bias in dementia research

Jennifer Weuve[a,1], Cécile Proust-Lima[b,1], Melinda C. Power[c,1], Alden L. Gross[c,d], Scott M. Hofer[e], Rodolphe Thiébaut[b,f,g], Geneviève Chêne[b,f,g], M. Maria Glymour[h,i,2], Carole Dufouil[b,f,g,*,2], for the MELODEM Initiative[3]

Full report

Executive summary

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