Predicting and Measuring Progression in Early AD
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Risk Factors for MCI Development and for MCI Progression: *Are They The Same?*

Mary Ganguli, MD, MPH
Professor of Psychiatry, Neurology, and Epidemiology
University of Pittsburgh
Pittsburgh, PA, USA

Conflicts

- No actual or potential conflicts of interest to disclose.

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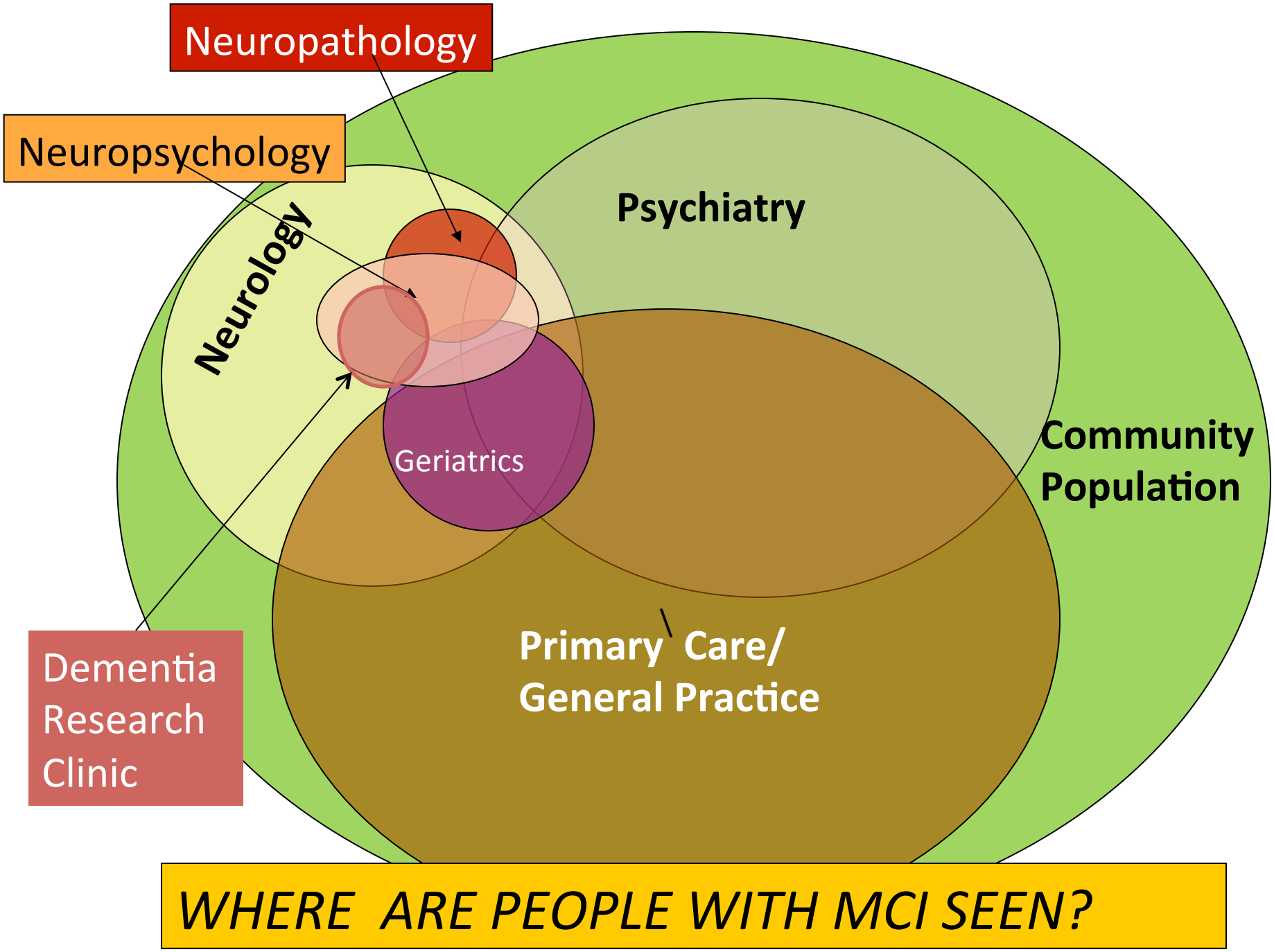
Mild Cognitive Impairment

- A cognitive state **intermediate** between normal cognition and dementia.
- *"Intermediate" ≠ "Transitional"*
- In memory clinics, MCI progresses to dementia at the rate of 12-15% per year.
- At the population level, of people meeting MCI criteria:
  - The majority remain mildly impaired;
  - Some progress to dementia;
  - Some get better.


Neuropathology
Neuropsychology
Neurology
Psychiatry
Geriatrics
Community Population
Primary Care/ General Practice
Dementia Research Clinic
WHERE ARE PEOPLE WITH MCI SEEN?

Course and Outcome of Amnestic MCI: *Clinical Research Series*

Mayo series: 12% of amnestic MCI progress (or "convert") to AD annually.

Petersen et al., 1999

Washington University series: 100% with CDR =0.5 progress to AD over 9.5 years.

Morris et al., 2001

Harvard series: volunteer panel: 18.7% with CDR= 0.5 progress to AD over 3 years.

Daly et al., 2000

Course and Outcome of Amnestic MCI: Community Cohorts

Progression to dementia/AD:

11.1% over 3 years: Eugeria study *(Ritchie et al., 2001)*

8.3% over 2 years: PAQUID study *(Larrieu et al., 2002)*

10-17% over 2 years: MoVIES study. *(Ganguli et al, 2004)*

Reversion to normal:

40% over 2 years: PAQUID study

33-56% over 2 years: MoVIES study

Stable MCI (no change):

11-21% at 2 years: MoVIES study

Meta-analysis:

The majority of individuals meeting MCI criteria in population studies will not progress to dementia over ten years.

(Mitchell et al., IGJP 2008)

Why the discrepancy in results?

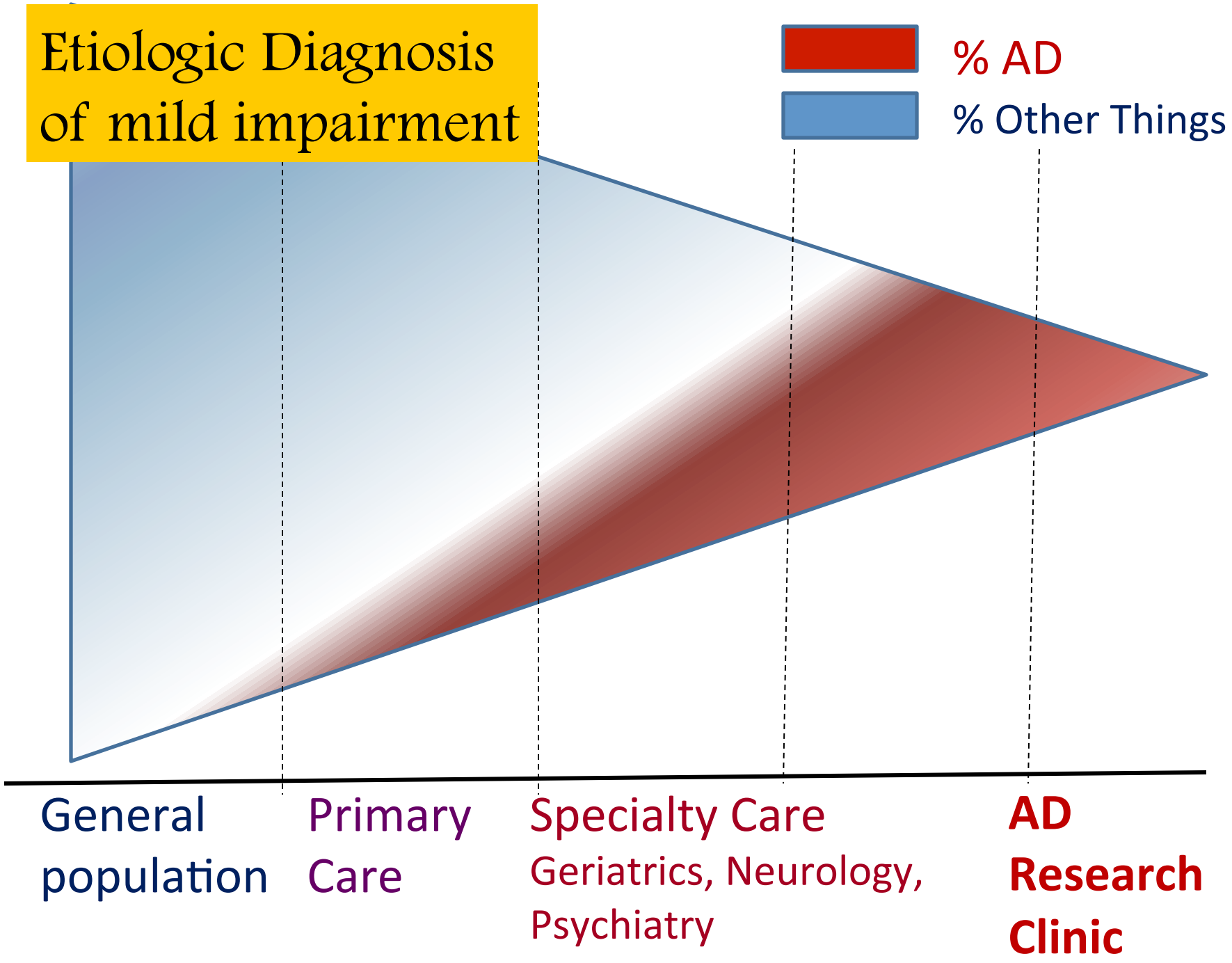
- Different samples:

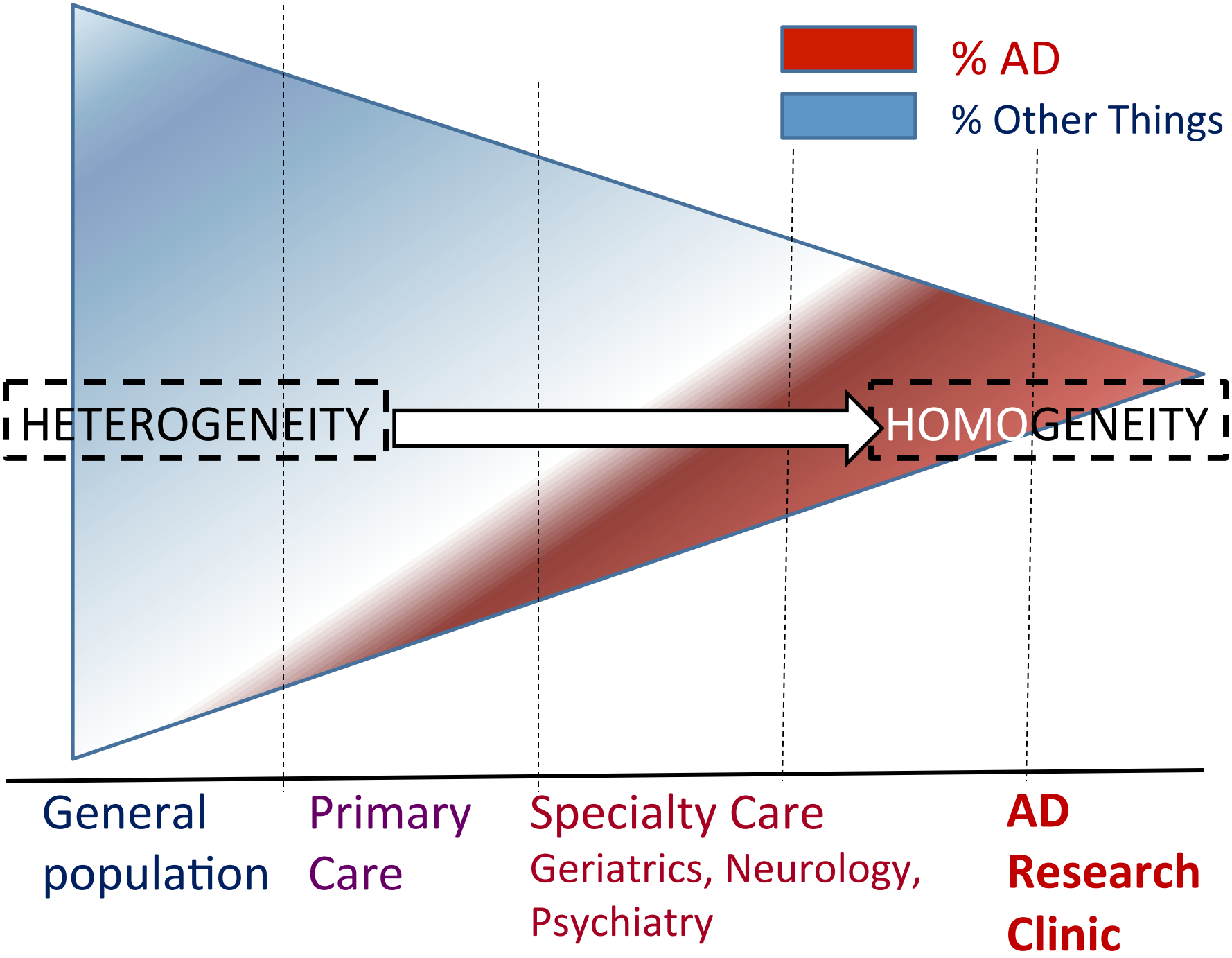
(patients seeking specialist care for memory loss *versus* people in the community who happen to have some memory problems.)

- Different study aims and designs.
- Different methods to operationalize criteria.
- "Complaints" spontaneous *vs*. elicited.
- "Clinical judgment" *vs*. standardized assessment.

2 sources of heterogeneity

1. **Mild impairment** is more etiologically heterogeneous than **severe impairment/ dementia** (because more conditions can cause mild impairments, some of which are non-progressive).
2. **Community/primary care settings** are more heterogeneous than **specialty care settings** (because some selection is involved in people going to specialty care.)


Etiologic Diagnosis of mild impairment
% AD
% Other Things
General population
Primary Care
Specialty Care
Geriatrics, Neurology, Psychiatry
AD Research Clinic


% AD
% Other Things
HETEROGENEITY
HOMOGENEITY
General population
Primary Care
Specialty Care
Geriatrics, Neurology, Psychiatry
AD Research Clinic

If MCI is etiologically heterogeneous

- Different “kinds” of MCI would have different outcomes;
- Different kinds of MCI would have different risk factors;
- Since the majority of individuals with MCI at autopsy have degenerative as well as vascular pathology,
- Maybe we should look for vascular risk factors for MCI.

Vascular Markers and MCI

- Various markers of vascular disease and inflammation in cross-sectional studies are associated with concurrent MCI and dementia.
- Some of these factors also predict progression from MCI to dementia, in longitudinal studies.
- Few studies have reported true risk factors predicting the incidence of new-onset MCI in individuals who were previously cognitive intact.
- Would they all be the same?

Should We Assume…

…that a risk factor that gets you from normal to MCI would necessarily also get you from MCI to dementia?

Monongahela-Youghiogheny region

- Allegheny County.
- Southwestern PA.
- Former steel manufacturing area.
- Stable population (low in- and out-migration).
- 17% aged 65+.
- Voter registration is the most comprehensive publicly available list.

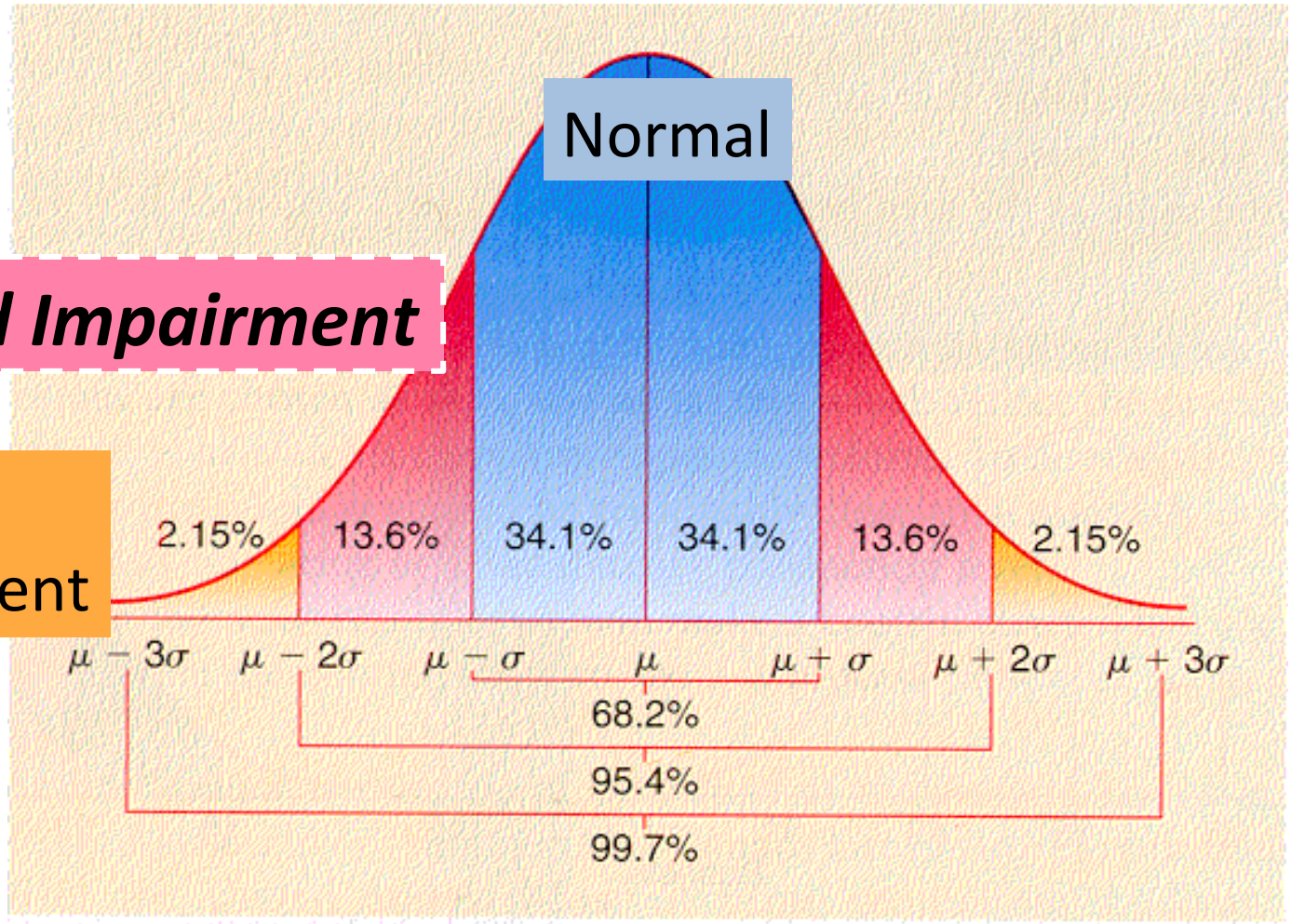
Monongahela-Youghiogheny Healthy Aging Team (MYHAT)

- New cohort study funded in Sept 2005 by NIA.
- Objectives:
  - Identify older adults who are cognitively normal or only mildly impaired.
  - Identify those who progress from normal cognition to MCI, and from MCI to dementia.
  - Identify predictors of progressing to MCI and to dementia.

Measuring Cognition

COGNITIVE DOMAIN	NEUROPSYCHOLOGICAL TESTS	
Attention	Trailmaking A	Digit Span
Executive function	Trailmaking B Letter Fluency	Clock Drawing
Language	Boston Naming Animal Fluency	Token Test
Memory	Logical Memory, imm. Logical Memory, del.	Visual Memory, immed Visual Memory, delayed Fuld Object Memory Test
Visuospatial	Block Design	

Norms-based Approach



Cognitive Classification

- **Normal cognition:**
  - Neuropsychological test scores within ± 1.0 *S.D.* of the mean for the individual's age/gender/education
- **Mild cognitive impairment:**
  - Neuropsychological test scores 1.0 – 2.0 *S.D.* below the mean for the individual's age/ gender/ education.
- **Severe impairment**
  - **Neuropsychological** test scores > 2.0 *S.D.* below the mean for the individual's age/ gender/ education.

Clinical Dementia Rating (CDR)

Hughes et al, 1982

	Memory	Orientation	Judgment & Problem-solving	Community Affairs	Home & Hobbies	Personal Care
0		x		x	x	x
0.5	x		x			
1						
2						
3						
	x	**x**	**x**	**x**	**x**	**x**

Algorithm-based summary CDR score weighted towards memory.
CDR 0 = no dementia, *CDR 0.5*= very mild/questionable dementia,
CDR 1 =mild dementia, *CDR 2* =moderate dementia

"MCI" is CDR=0.5 *(Morris et al 2001)*

Two Definitions of MCI

- **"Cognitive MCI"** (based on cognitive classification, purely neuropsychological, norms-based).

- **"Functional MCI"** (based on CDR, cognitively-driven everyday function, self-report and rater assessment, not based on neuropsychological data).

Vascular /Metabolic Risk Factors

Risk factor	Measure	Risk Factor	Measure
Stroke	History	Smoking, before	History
Coronary disease	History	Smoking, now	History
Heart failure	History	Alcohol, before	History
Arrhythmia	History	Alcohol, now	History
Hypertension	History or SBP	*APOE*4*	genotype
Diabetes	History or HbA1c	Inflammation	C-Reactive Protein
Hypercholest-erolemia	History or total cholesterol	Atherosclerosis/ renal function	Cystatin-C
HDL	HDL or ApoA1	Homocysteine	Hcy
LDL	LDL or ApoB	Lipoproteins	ApoB:ApoA1 ratio

Participants included in this analysis

Total cohort at baseline: 2036

- Full assessments: 1982
- Cognitively Normal: 1190
- CDR=0 1413

Over 5 assessments (4 years of followup):

- "Cognitive MCI": 460
- "Functional MCI (CDR=0.5): 265
- Lost to followup (death, illness, dropout): xxxx

Risk and Protective Factors for Cognitive MCI

- Unpublished data will be shown

Risk and Protective Factors for Functional MCI (CDR=0.5)

- Unpublished data will be shown

Summary and Conclusions

Various indicators of vascular disease and vascular risk increase:

(a) The risk of developing MCI.

(b) The risk of MCI progressing to dementia.

Controlling vascular risk has potential for

(a) Preventing or delaying MCI.

(b) Preventing or delaying dementia.