Identifying early AD: Data from a community-based study

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Background

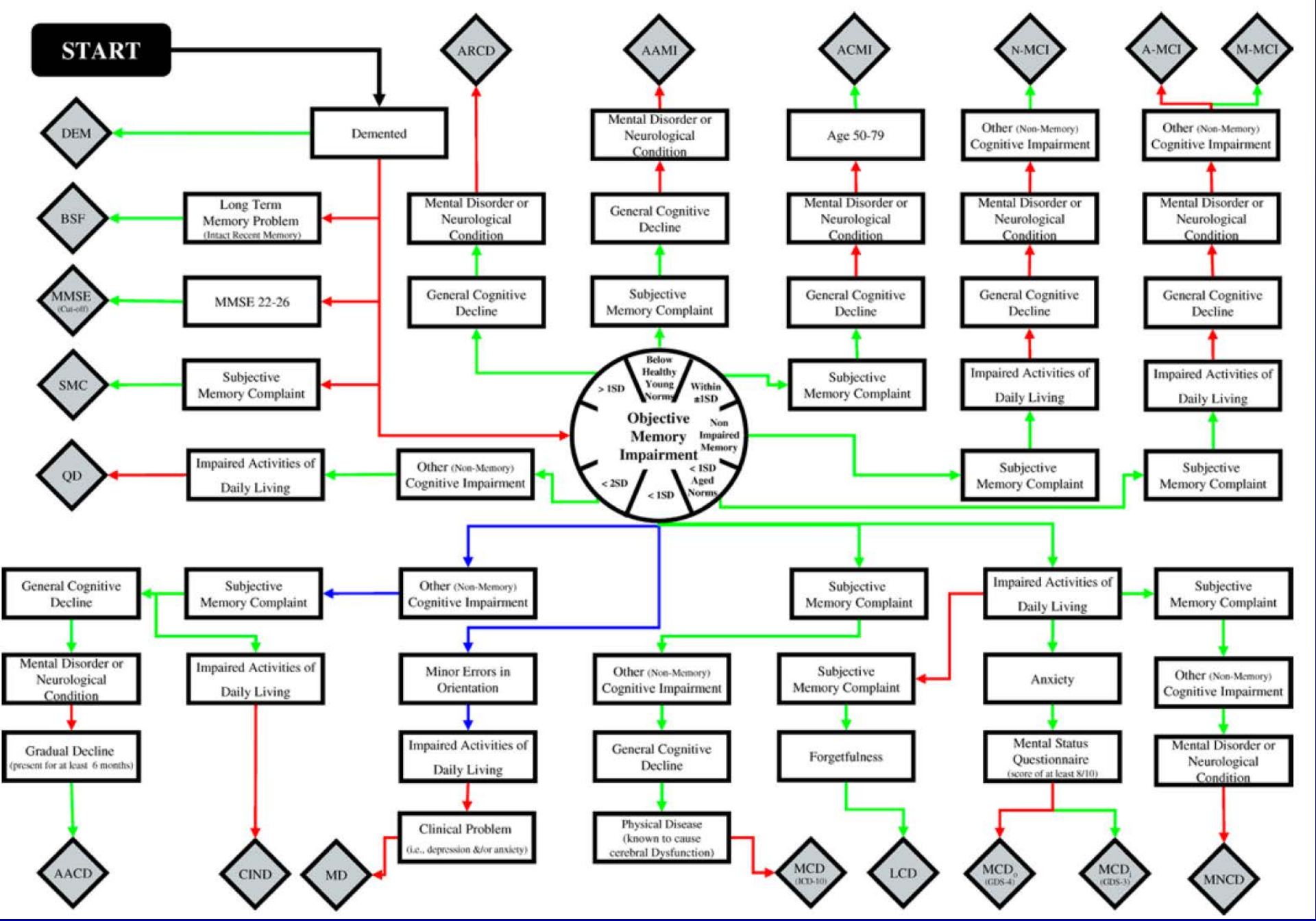
- AD is a progressive neurodegenerative condition
- Pathological processes thought to be irreversible by the time symptoms are severe enough to be reliably distinguished from “normal”
- Rationale very clear for intervention strategies to start earlier
  - “Prodromal” phase (“early symptoms before specific symptoms occur”)
  - “Silent” phase (no symptoms at all)

Problem: differentiation

- When AD has progressed to a diagnosable state, its symptoms are readily distinguished from other conditions (such as normal variability often found in aging)
- Before that, almost by definition, it is not distinguishable from other conditions
  - A prodrome would be marked by symptoms, but non-specific symptoms
  - A silent / asymptomatic phase would be marked by no symptoms at all
- Huge ethical considerations when considering risks and benefits of interventions that have some potential harms
  - Hippocratic oath
  - Contrary to the themes of personalized medicine

MCI et al.

- Numerous efforts to characterize an earlier state of AD
  - At least to identify a high-risk subgroup
  - Optimally to identify specific individuals destined to develop AD
- And I do mean numerous



Matthews FE, Stephan BCM, Bond J, McKeith I, Carol Brayne on behalf of the Medical Research Council Cognitive Function and Ageing Study (2007) Operationalisation of Mild Cognitive Impairment: A Graphical Approach. PLoS Med 4(10): e304.

Specialty clinics vs. community-based studies

- MCI seems a different beast in specialty clinic settings
  - Conversion rate higher
- Convenient for pharmaceutical companies to enroll highest risk people
- Once a drug gets licensed for “MCI”, though, most of its sales will be among people not in specialty clinics
- Crucial to understand the implications of definitions in community-based samples

“Screening” modalities

- “Prodromal” phase – non-specific symptoms
  - at least there is some symptom to work-up
- “Silent” phase – NO symptoms
  - To detect the condition, would have to apply the categorization procedure to all relevant people
- Many modalities are expensive
  - MRI, SPECT, PET
- Some modalities are (also) invasive
  - LP for CSF
  - Even a small infection rate will lead to mortality associated with the screening procedure when applied to tens of millions of asymptomatic elderly
- Cognitive testing seems an appropriate relatively inexpensive, relatively well tolerated, and non-invasive modality

Data from a community-based study

- Adult Changes in Thought based in Group Health Cooperative in Seattle
  - E Larson, PI
- Participants 65+ at baseline, evaluated for dementia every 2 years
- MCI study: additional testing to identify people with prevalent and incident MCI
  - S Craft, PI
- Many more identified than planned
- Supplement to follow-up everyone regardless of scores – “the first 200”

Assessment of MCI

- Neuropsychological battery
- Two different benchmarks: published norms and Shipley estimated ability
- Two different thresholds: 1 and 1.5 SD
- Two different approaches: ANY test within a domain and AVERAGE across all tests within a domain
- Petersen criteria for MCI presence and subtypes

2-year follow-up data

- 136 participants returned and were evaluated
- Similar procedures used
- Again categorized as normal, MCI, or dementia (n=14)
- Data tables reviewed
- Focus on reversion to normal (left) and progression to dementia (right)

	Normal	MCI	Dementia	Total
Normal				
MCI				
Total			14	136

Results: Standard norms

1.0 SD

Any

	Normal	MCI	Dementia	Total
Normal	34	14	0	48
MCI	20	54	14	88
Total	54	68	14	136

Avg

	Normal	MCI	Dementia	Total
Normal	39	15	0	54
MCI	18	50	14	82
Total	57	65	14	136

1.5 SD

	Normal	MCI	Dementia	Total
Normal	64	21	3	88
MCI	18	19	11	48
Total	82	40	14	136

	Normal	MCI	Dementia	Total
Normal	77	18	4	99
MCI	12	15	10	37
Total	89	33	14	136

Results: Individualized norms

Any

1.0 SD

	Normal	MCI	Dementia	Total
Normal	16	8	1	25
MCI	17	81	13	111
Total	33	89	14	136

1.5 SD

	Normal	MCI	Dementia	Total
Normal	36	14	3	53
MCI	20	52	11	83
Total	56	66	14	136

Average

	Normal	MCI	Dementia	Total
Normal	21	9	1	31
MCI	16	76	13	105
Total	37	85	14	136

	Normal	MCI	Dementia	Total
Normal	40	19	3	62
MCI	19	44	11	74
Total	59	63	14	136

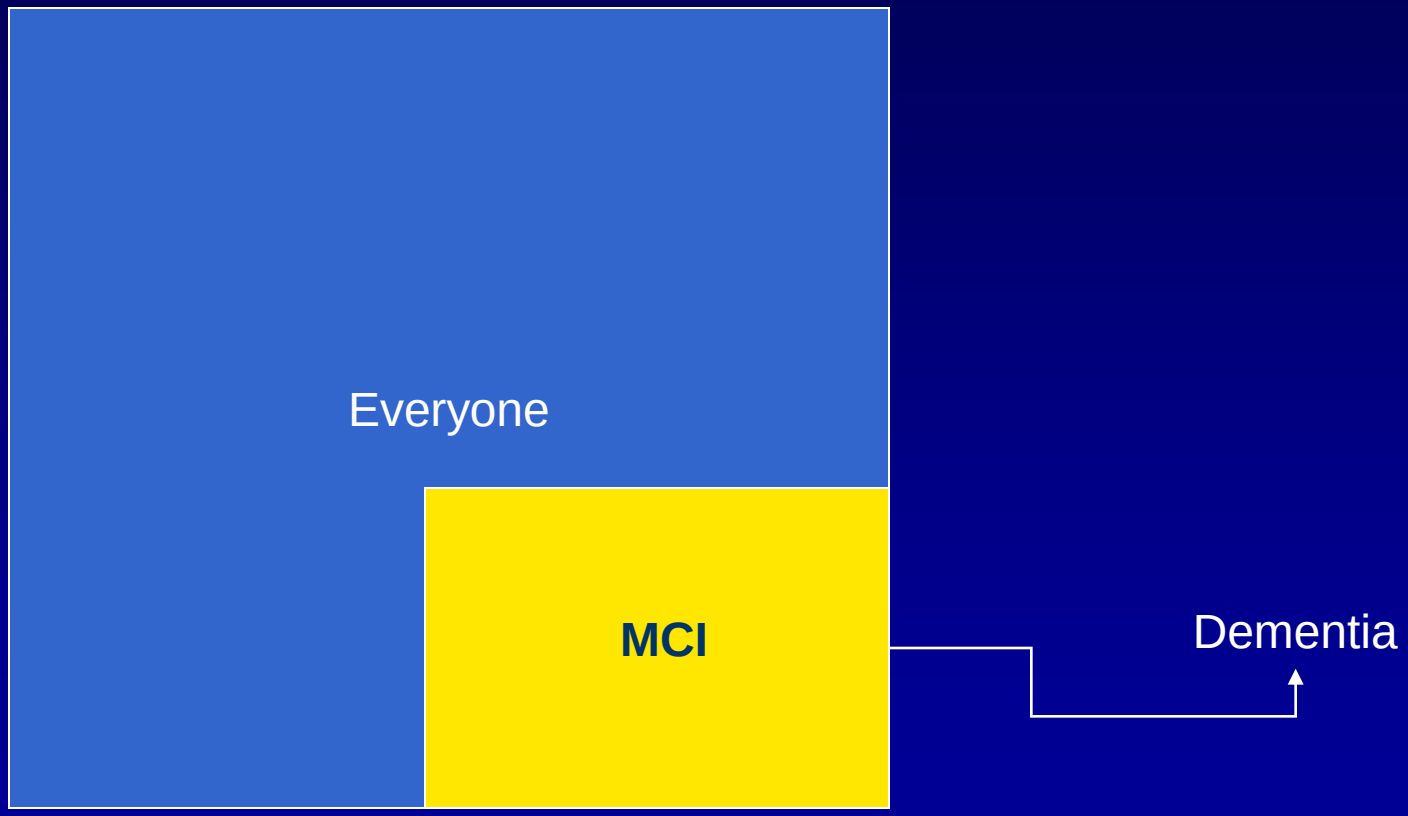
Discussion

- In each of 8 operational definitions of objective cognitive impairment among people who did not have dementia, the two year reversion rate was higher than the two year conversion rate
- Limitations: only considering objective cognition here, not considering imaging, biomarkers, subjective complaints
- These data limited to the “first 200”; results from the entire cohort currently being analyzed and may produce different results
- Results are from 2 year follow-up; Results at other time points may be different
- Strengths: community-based cohort, prospective study, established protocols for identifying dementia, dementia evaluations independent of MCI tests

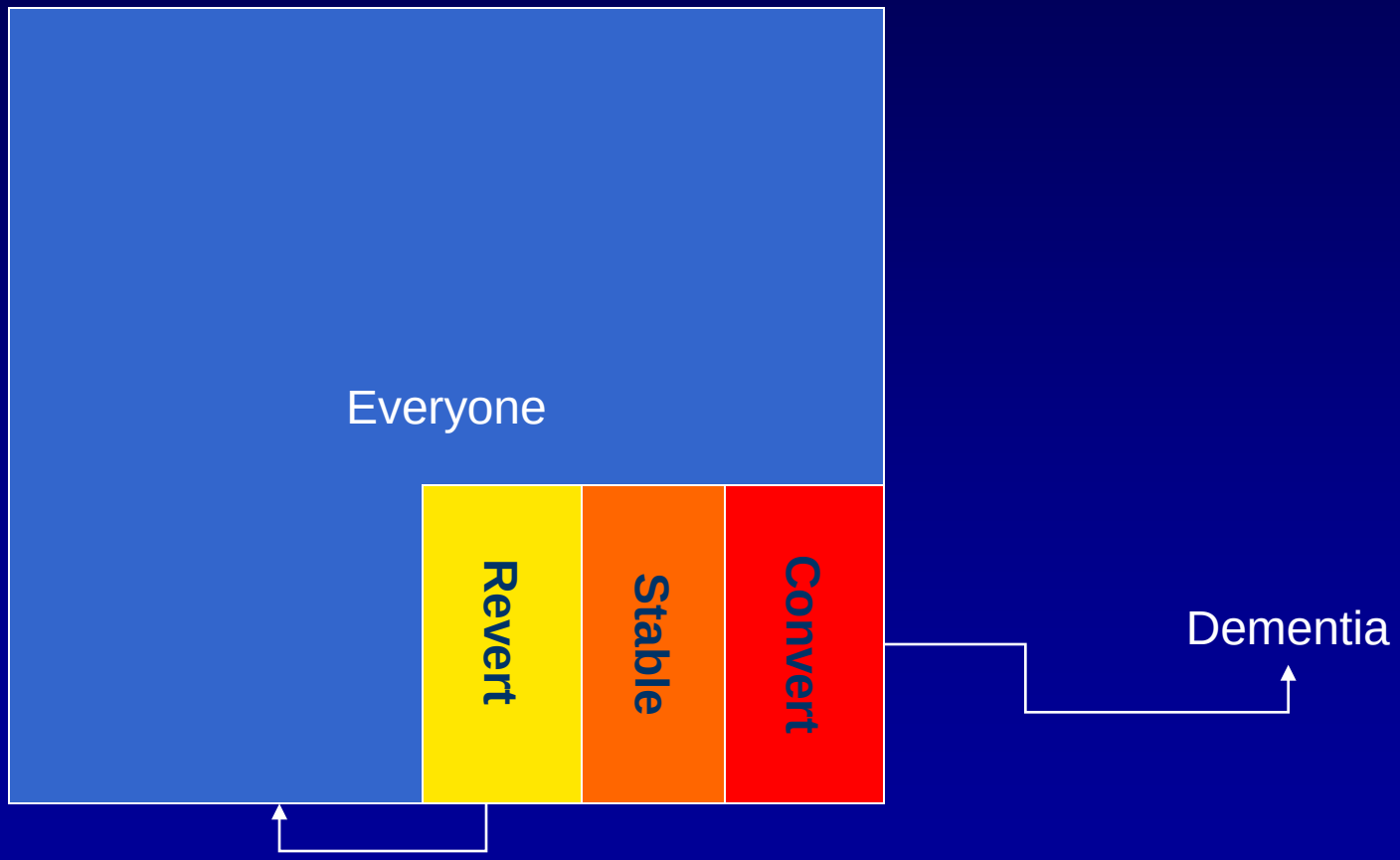
Reversion to normal: an inconvenient truth

- Not only “not getting worse” but actually “getting better”
- Distinct ethical implications for intervention studies
  - You are at increased risk for developing AD
  - You are also at increased risk of reverting to normal
- Difficulties counseling individual people even now
- These difficulties will be enhanced when (we hope!) we have actual disease modifying therapies to offer
  - Complex risk/benefit discussion, depending on the toxicities associated with the therapy
- Whether “risk” (?) of reversion is stressed as much as risk of conversion to dementia in clinical encounters is not well studied
  - Possible that our current evidence-based medicine delivery focuses only on the half of the evidence that fits with a nice story

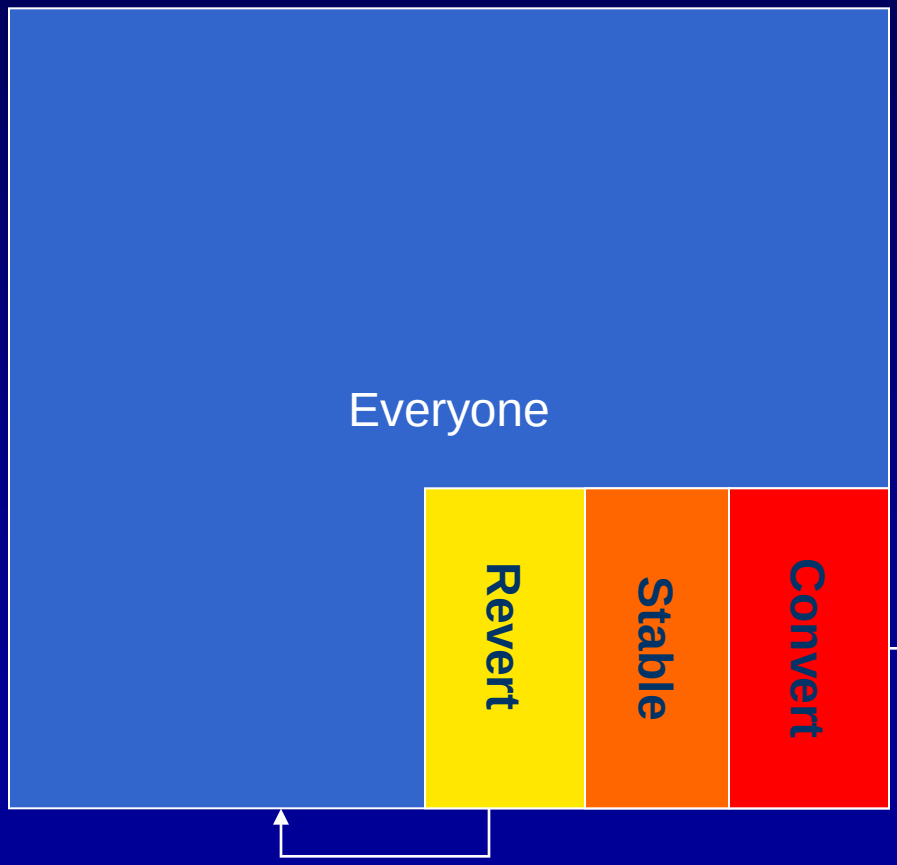
Model not quite consistent with data



Model more consistent with data



And the problem is



We don’t know how to identify people in these groups

Conclusions

- More work needed to develop criteria that are reliable enough for individual-level decision making
- Community-based studies uniquely positioned to evaluate thought experiments on the consequences of strategies that are being developed