The Value of Representative Populations for Accurate Inferences

Seattle Symposium

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Outline

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- Personal stories: consequences of research in non-representative populations
- Examples of population based research
- Solutions and challenges of big data related to convenience samples vs population based samples

Personal Perspective from Seeing Markers for Alzheimer's Disease

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Early studies focused on small samples form highly filtered specialty samples. Examples:

- Platelet membrane Fluidity (1992)
- Amyloid deposits in skin biopsies

Then rare mutations (App717, App 693 and PRIP gene mutations) 1991

Conclusions – there are clearly hazards using small samples from specialized populations. Can these be avoided with overwhelmingly large samples?

Differences in Community Populations

Populations from samples recruited from AMCs and specialty clinics are younger - generally have more severe disease with stronger “genetic’ finger print in comparison to more community-based samples:

- All community recruited populations are not equal - some are more representative than others.
- Populations and samples recruited from AMCs and Specialty clinics: Younger, have more severe disease, higher frequency of apoE e4 allele.
- "Population based" subjects (from ADPR/ACT) are older, have shorter duration of symptoms when identified, milder disease.

- Barnhart RL, et. al., Geographically overlapping Alzheimer’s disease registries: comparisons and implications. J Geriatri Psychiatry Neurol 1995:8:203-8
- Tsuang D, et. al., Impact of sample selection on apoE e4 allele frequency: a comparison of two Alzheimer’s disease samples. J Am Geriatr Soc 1996;44:704-7.
- Tsuang D, et. al, The utility of ApoE genotyping in the diagnosis of Alzheimer’s disease in a community-based case series. Arch Neurol 1999;56:1489-95.
- Brayne, C. [commentary] A population perspective on the IWG-2 research diagnostic criteria for Alzheimer’s disease [comment on Advancing research diagnostic criteria for Alzheimer’s disease: the IWG-2 criteria] . Lancet Neurol, 2014;13(6):532-4.

Strength of Associations and Diagnostic Performance Changes Based on Population: The Home Visit Issue (Crane, et. al., 2016)

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- Importance of home visit capacity in dementia studies (Alzheimer's and Dementia 2016;12:419-426)
- Unique opportunity presented when ACT study began to enroll subjects in "ACT+" – UW's ADRC which included NACC requirements.
- ACT (an epi study) supplements in clinic with home visits vs ADRC requires in clinic visit
- RESULTS: In "full data" Risk of AD ApoE 4 (1.66) vs. clinic only (2.28) p=.008 Neuropath Strength of association for Braak, HS, Cystic infarcts different
- Conclusion: "studies that only include research clinic data may lead to biased conclusion" Using data missing not at random (MNAR) can provide the wrong answer and you can't know direction of bias.

Population Based Studies in Life Course Epidemiology Provide Unique Insights – a Dementia Example

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Diagnostic accuracy will be less in everyday populations:

- THERE HAVE TO BE FALSE POSITIVES
- WHY? PERSONS SURVIVE INTO THEIR 90s with plaques and tangles and no dementia. (Sonnen et al., Arch Neurology 2011)
- Illustrates the complexity and overlap of brain aging and neurodegenerative diseases.

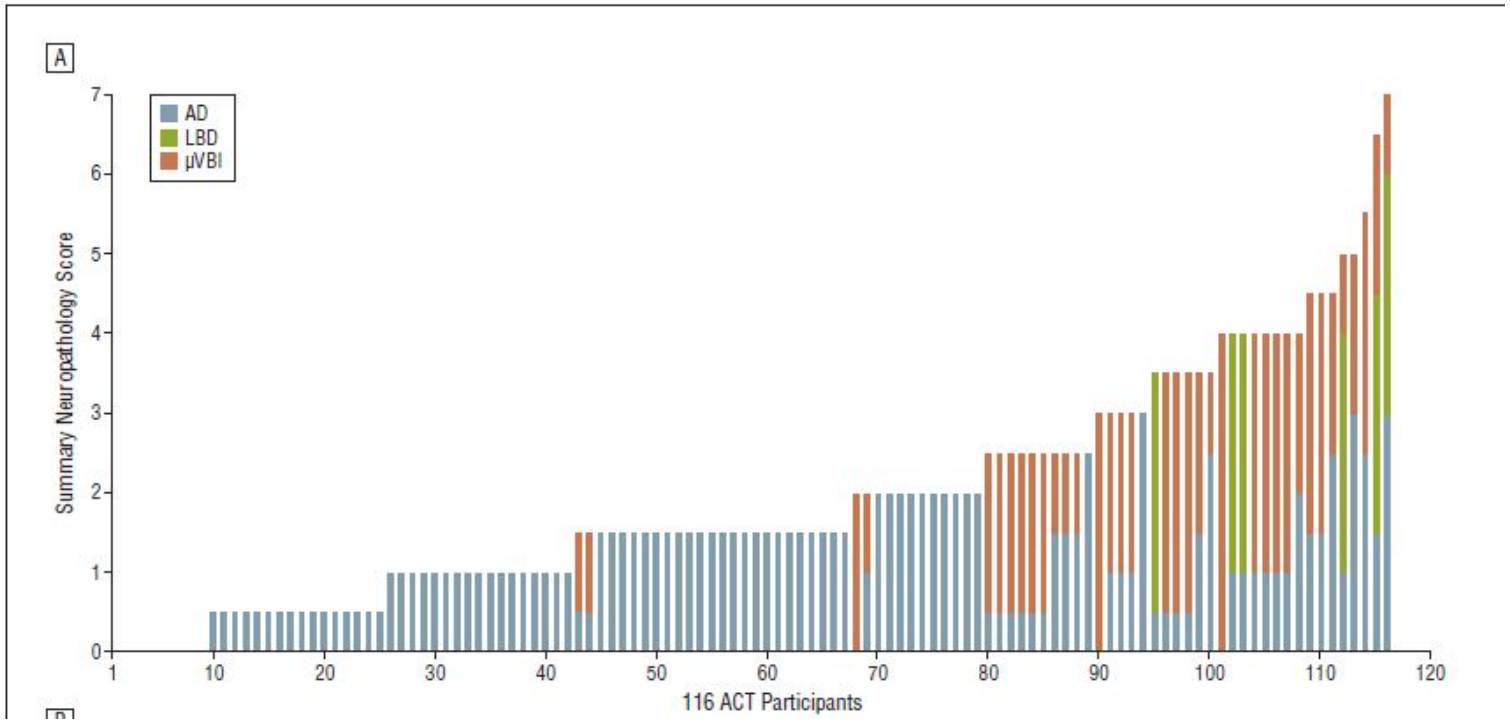

Figure 1. Brain autopsy results from 336 cognitively normal individuals expressed as summary neuropathology scores (range, 0-9) ranked from lowest to highest. Each stacked bar shows an individual's burden of Alzheimer disease (AD) (blue), Lewy body disease (LBD) (green), and microvascular brain injury (µVBI) (red). A, One hundred sixteen Adult Changes in Thought study (ACT) participants. B, One hundred six Nun Study (NS) participants. C, Fifty-nine Honolulu-Asia Aging Study (HAAS) participants. D, Fifty-five Oregon Brain Aging Study (OBAS) participants.

Diagnostic Accuracy Likely Overrated

Diagnostic accuracy will be less in everyday populations:

- THERE HAVE TO BE FALSE POSITIVES
- WHY? PERSONS SURVIVE INTO THEIR 90s with plaques and tangles and no dementia. (Sonnen et al., Arch Neurology 2011)
- Illustrates the complexity and overlap of brain aging and neurodegenerative diseases.

WILL THERE ALSO BE FALSE NEGATIVES?

For a condition with a prevalence of 50% and more in the fastest growing segment of the population this is a difficult question but the answer must be YES.

Recent Lessons Learned

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- Population based samples allow for assessment of selection bias in autopsy based research. (Tsuang D, et al., Evaluation of selection bias in an incident based dementia autopsy case series. Alzheimer Dis Assoc Disord 2005;19:67-73)
- Using inverse probability weighting to adjust for selection bias and bootstrap techniques to assess uncertainty one can assess generalizability of autopsy based inferences to general population from which sample was drawn and adjust associations based on differences between autopsy sample and reference population. (Haneuse S, et al., Adjustment for selection bias in observational studies with application to the analysis of autopsy data. Neuroepidemiol 2009;32(3):229-39)

Examples of GHRI Work

Group Health /UW Alzheimer's disease patient registry now Adult Changes in Thought

- A 30 year journey: 1986 – today – 2021
- A source for many companion projects and shared data

Living Laboratory

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New News from the Adult Changes in Thought (ACT) study:

A long standing living laboratory of aging funded for five more years

Authors: Eric B. Larson, Erin J. Bowles, Rod L. Walker, Melissa L. Anderson, Darlene White, KatieRose Richmire, William W. Lee, Steven L. Balch, Andrea LaCroix, Dori Rosenberg, Sascha Dublin, Paul K. Crane

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Background

Increasing number of older people with multiple chronic conditions

Research on multiple chronic conditions benefits from practical, clinical evidence from everyday populations

Adult Changes in Thought (ACT) study recently awarded 5 more years of funding
- One of the longest, continually funded studies on aging

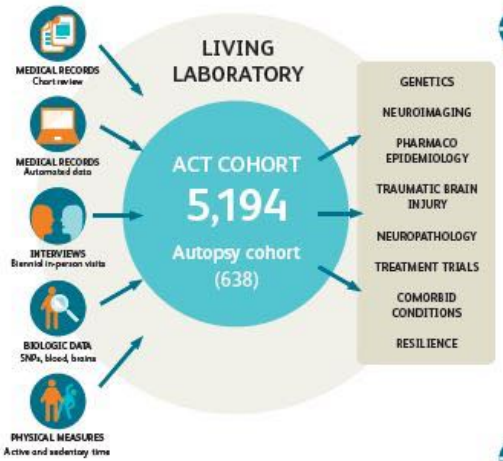
Methods

RECRUITMENT
- Cohort of randomly selected people over age 65 without dementia
- Established 1994
- Since 2004, maintain a constant cohort of approximately 2000 living persons
- Follow participants every 2 years
- Replace participants who die, become demented, or are lost to follow-up

DATA
- Biobank with extensive genome-wide single nucleotide polymorphism (SNP), exome sequence, and gene expression data
- Neuropathology biobank with neuroimaging data
- Cognitive and functional measures from Cognitive Abilities Screening Instrument and other tests
- Extensive chart abstraction data on clinical care
- Laboratory and pharmacy records from GH automated data and medical record review
- activPAL (thigh worn) and Actigraph (waist worn) to capture valid measures of sitting, standing, sit-to-stand transitions, and physical activity

PARTICIPANT CHARACTERISTICS
- Current enrollment 5,194
- 1,088 cases incident dementia (>60% Alzheimer's disease (AD) type)
- 2,711 participants lived to age 85
  - 1,044 still alive
  - 40,481 person-years of follow-up
- 638 autopsy cases with extensive frozen tissues

STUDY OUTCOMES
- Dementia and AD (based on cognitive testing and consensus review)
- Cognitive functioning (CASI score, CASI trajectories)
- Neuropathology measures (neurofibrillary tangles, neuritic plaques, cerebral microinfarcts, cystic infarcts, amyloid angiopathy)
- Resilience (avoidance of cognitive decline and frailty in late life)



Feasibility of measuring physical and sedentary activity related to cognitive health in older adults

N=307 Mean age: 84 years 72% female

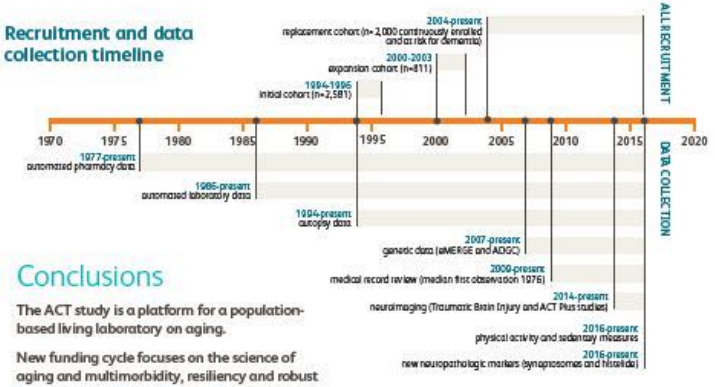
Physical/sedentary activity	Mean	Cognitive tests	Mean times to completion
Accelerometer wear time	5.7 days, 13.6 hrs per day	Visual search and perceptual speed (Trails A)	54.4 seconds
Measured sedentary time	8.6 hours per day	Working memory and task switching (Trails B)	148.6 seconds
Self-reported sedentary time	11 hours per day	Executive function (Trails B – Trails A)	94.1 seconds
Measured moderate-to-vigorous activity time	8.7 minutes per day		

From Rosenberg D, et al. Independent associations between sedentary behaviors and mental, cognitive, physical, and functional health among older adults in retirement communities. J Gerontol A Biol Sci Med Sci, 2015, 1-6.

Study Aims

1. **MULTIMORBIDITY** – evaluating the effects of cardiovascular risk factors and their treatments on the aging brain
2. **RESILIENCE** – determining the impact of physical and sedentary activity on cognitive trajectories and physical performance; identifying factors associated with robust aging; and evaluating whether neuropathologic findings are associated with resilience
3. **LIVING LABORATORY** – improving ACT infrastructure to continue to share high quality scientific data for research

Recruitment and data collection timeline



Conclusions

The ACT study is a platform for a population-based living laboratory on aging.

New funding cycle focuses on the science of aging and multimorbidity, resiliency and robust aging, and data sharing.

Effective partnerships, including widespread data and specimen sharing, are foundational and critical for optimal success.

CONTACT FOR DATA REPOSITORY:
ACTproposals@ghc.org

Funding: National Institute of Aging, 2 U01 AG006781

ACT Living Laboratory of Aging and Brain Aging

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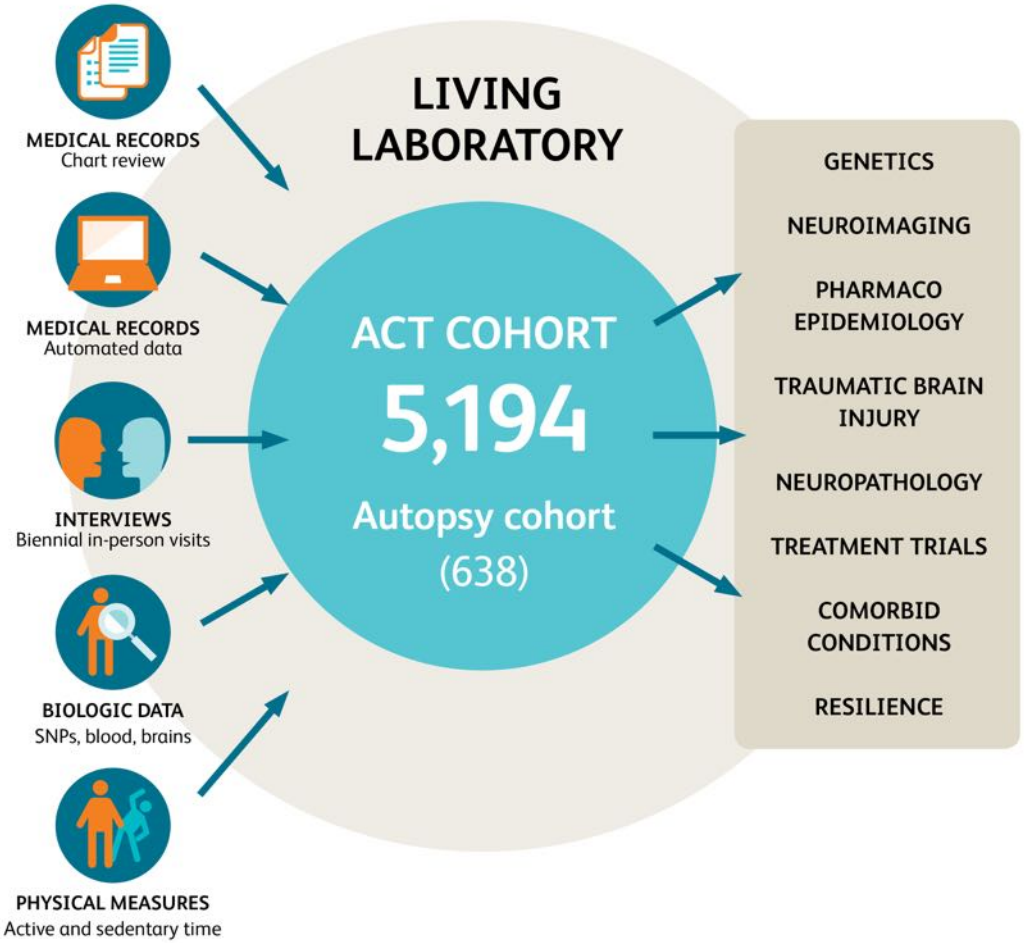

Examples of GHRI Work, cont.

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- eMERGE – Electronic Medical Records and Genomics – based on existing medical records and biobanks
- Sources: ACT and NW institute for Genomics Medicine (NWIGM)
- NWIGM is a population based sample of persons randomly selected over 50 – 65 to complement the ACT subjects who were recruited age 65+
- Our eMERGE is very different from others – offers more complete EMR data capture and possibility of life course epidemiology; Unique opportunities to understand phenotyping from EMR including using NLP
- Long history of using registries in other areas

Some Issues

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- The most ideal approach: population based samples and a life course epidemiology approach

- To what extent can challenges to external validity of findings be overcome simply by having giant populations, albeit convenience and in the case of PMI volunteers who may have a health use bias?

- How can we come up with statistical techniques that could help detect data missing not at random and more robust methods to address this issue.

Conclusions

- Ideally research is set in populations recruited from a known population base and followed over time with complete availability of relevant outcomes
- We need to know generalizability of very large convenience samples
- Methods work in this area will be valuable

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QUESTIONS?