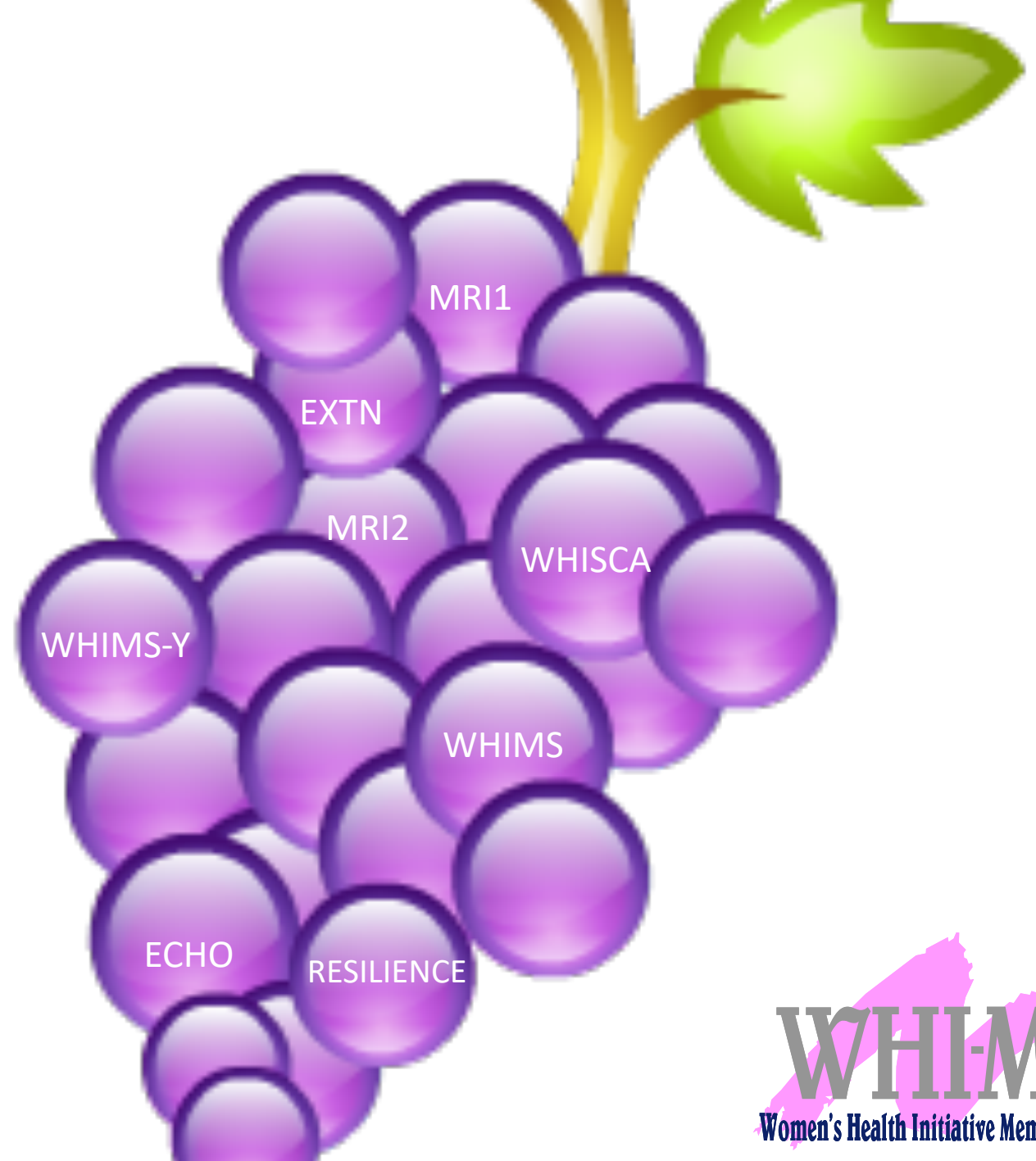


WHIMS 1996- 2020: The Harvest

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for the **WHIMS Team**



WHIMS
Women's Health Initiative Memory Study

Disclosures & Acknowledgements

DISCLOSURES

None

ACKNOWLEDGEMENTS

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WHIMS: Background

WHIMS Studies Aims over the years

- Effect of HT on.....
 - Incident dementia, MCI and global cog function (WHIMS, Extn, ECHO)
 - Specific cognitive functions (WHISCA)
 - Brain morphology (MRI1, MRI2)
- Predictors and course of cognitive aging
 - Cognitive impairment (dementia, MCI)
 - Specific cognitive functions
- Predictors and course of cognitive resiliency



Key Cognitive Variables Collected in WHIMS Suite of Studies

Adjudicated Cognitive Impairment

- **Mild Cognitive Impairment**
- **Dementia (all-cause)**

Global Cognitive Function

- **Modified Mini Mental State Exam (WHIMS, all ppts annually)**
- **Telephone Interview for Cognitive Status-modified (WHIMS-ECHO, WHIMS-Y all ppts annually)**
- **Composite scores**

Specific Cognitive Functions

- **CERAD Battery--WHIMS, 3MSE triggered, 10 yrs.**
- **WHISCA Battery--WHISCA sub-study, all ppts annually, 6 years**
- **Telephone Battery--WHIMS-ECHO, all ppts annually, 12+years**

Structural MRI

Cumulative
Adjudicated
Cognitive
Outcomes

Final Diagnosis	WHIMS	SCAP	ECHO	WHIMS-Y	TOTAL
NI	478 (38.5%)	169 (76.1%)	827 (38.9%)	87 (77%)	1561
MCI	533 (42.9%)	15 (6.8%)	764 (36.0%)	20 (17.7%)	1332
PD	232 (18.7%)	38 (17.1%)	533 (25.1%)	6 (5.3%)	809
TOTAL	1243	222	2124	113	3702

- **NI = No Cognitive Impairment**
- **MCI = Mild Cognitive Impairment**
- **PD = Probable Dementia**

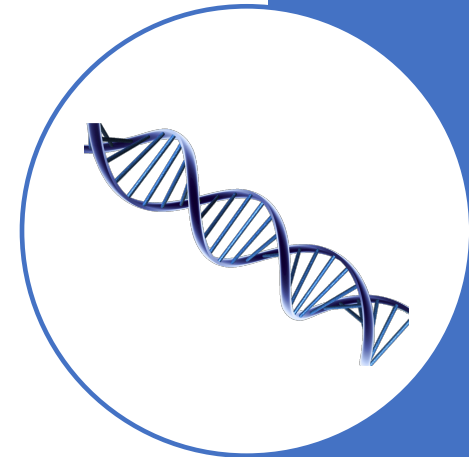
Specific Cognitive Functions from WHIMS

Study Acronym	N	Assessments											
		Global Cog Function	Visuo-spatial	Attention	Verbal Fluency	Verbal Knowledge	Exec Function	Episodic Memory	Figural Memory	Fine Motor Speed	Adjudicated MCI and Dementia	Brain MRI	DNA
WHIMS	7479	X	X*	X*	X*		X*	X*	X*		X	X	X
WHIMS-ECHO	2922	X		X	X		X	X			X	X	X
WHIMSY	1362	X		X	X		X	X			X		X
WHISCA	2304	X	X		X	X	X	X	X	X	X	X	X

*Obtained only for ppts who triggered cognitive screener (Modified Mini Mental State Exam; 3MSE)

WHIMS: Genetic data

- WHI Data: Common APOE genotypes ($\epsilon 2/\epsilon 2$, $\epsilon 2/\epsilon 3$, $\epsilon 2/\epsilon 4$, $\epsilon 3/\epsilon 3$, $\epsilon 3/\epsilon 4$, and $\epsilon 4/\epsilon 4$) in non-Hispanic whites
- Genetic Data Collection
 - Two SNPs used in APOE genotyping were imputed by the CCC in a genome-wide imputation
 - $R^2 = 0.98$ for each SNP in this study population
 - Genotypes based on the imputed SNPs were checked against direct genotyping in an available subset
- APOE genotypes in WHIMS Sub-Cohorts
 - WHIMS: $\sim N = 5,800$
 - WHISCA: $N = 1,900$
 - WHIMS MRI-1: $N = 1,200$
 - WHIMS MRI-2: $N = 600$
 - WHIMS Extension: $N = 3,200$
 - WHIMS-ECHO: $N = 2,400$



WHIMS-ECHO Cohort Characteristics

WHIMS-ECHO Cohort Characteristics

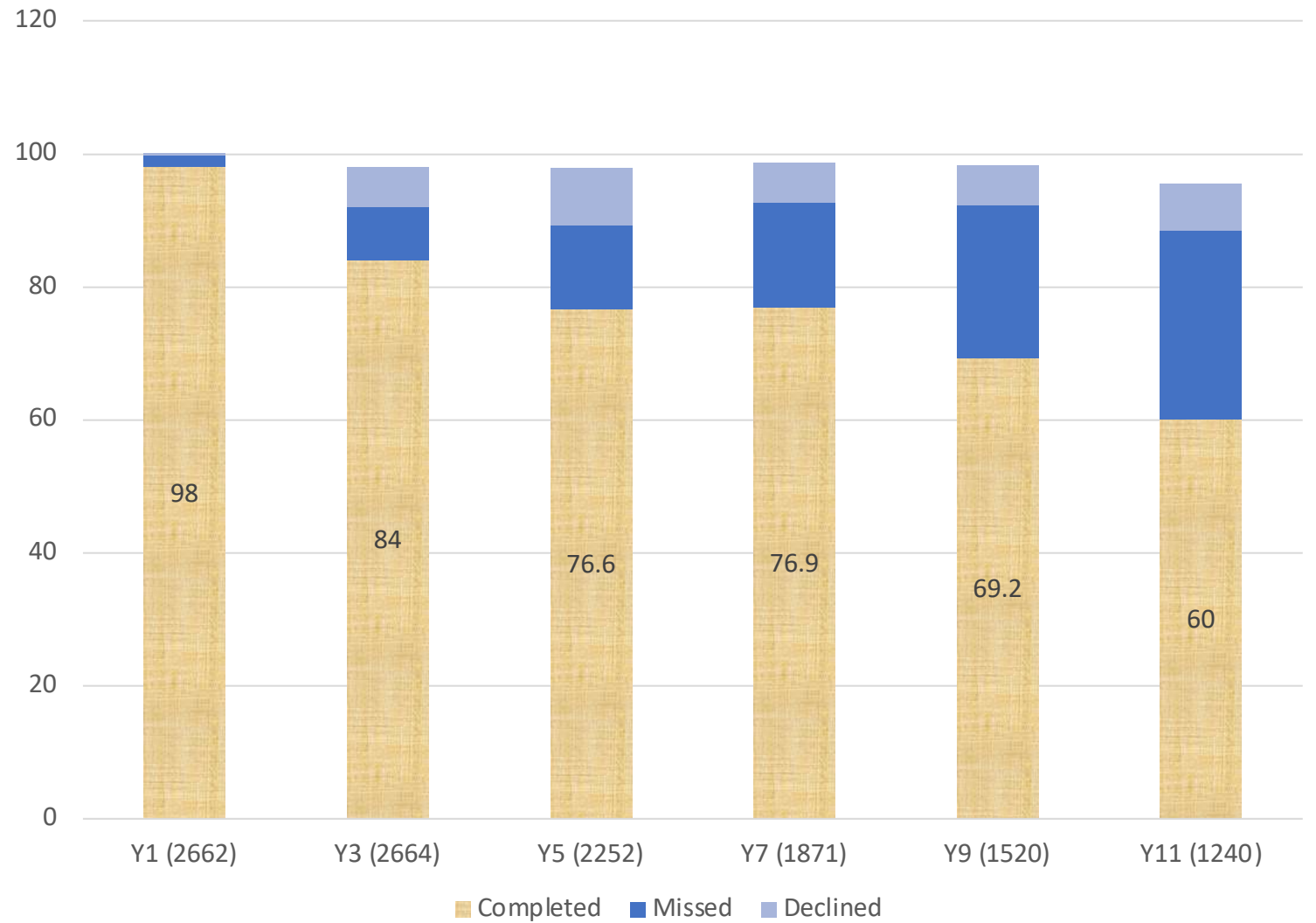
CHARACTERISTIC	N (%) Enrollment (2008)	N (%) Current (4/30/2020)
Active Ppts	2922	1240
WHI-HT Treatment Assignment		
E-Alone Placebo	543 (18.6)	216 (17.4)
E-Alone	530 (18.1)	229 (18.5)
E+P	894 (30.6)	367 (29.6)
E+P Placebo	955 (32.7)	428 (34.5)
Age at Enrollment		
64-69	1531 (52.4)	789 (63.6)
70-74	1028 (35.2)	371 (29.9)
75-80	363 (12.4)	80 (6.5)
Age as of April 30, 2020		
85-89		371 (29.9)
90-94		658 (53.1)
95-99		198 (16.0)
100+		13 (1.1)

WHIMS-ECHO Cohort Characteristics (cont.)

CHARACTERISTIC	N (%) Enrollment	N (%) Current (4/30/2020)
Active Ppts	2922	1240
Baseline 3MSE		
< 90	100 (3.4)	34 (2.7)
90-94	435 (14.9)	166 (13.4)
95-100	2329 (79.7)	1015 (81.9)
Race/Ethnicity		
Amer Indian/Alaskan Native	6 (0.2)	1 (0.1)
Asian/Pacific Islander	42 (1.4)	21 (1.7)
Black/African American	188 (6.4)	92 (7.4)
Hispanic/Lantinx	47 (1.6)	19 (1.5)
White	2595 (88.8)	1087 (87.7)

WHIMS ECHO Cohort Over Time

% of Due Completed, Missed & Declined



WHIMS Achievements

Selected Paper Topics Using Data from WHIMS Suite of Studies

Clonal hematopoiesis & AD

Whole genome sequence of AD-TOPMed

Whole genome & AD in Welllderly-TOPMed

Cholesterol & APOE genotype

Sex-specific genetic architecture & AD

Gene X environment in brain aging

Candidate gene & dementia

Cog resilience among APOE-4 carriers

Optimism & dementia

Work & risk of dementia

Hearing loss, HT & cog decline/impairment

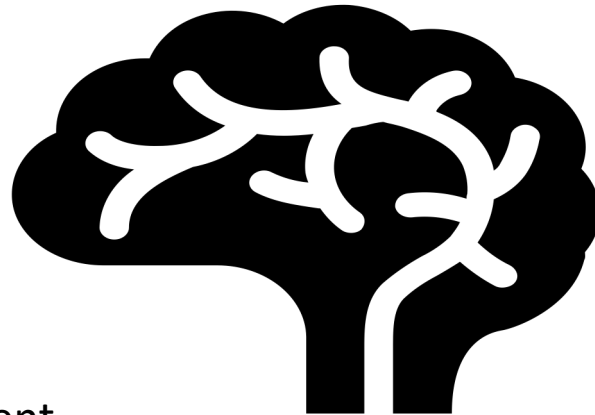
Subjective memory complaints & cog imp

Optic nerve cupping & cog decline/imp

Anemia & cog function

Air pollution & small vessel dz; memory,
depressive sx; neuroanatomic risk AD

Neighborhood & cog decline



Statin use & dementia

Magnesium & cog decline

Chocolate & cog function

Artificially sweetened beverages & mortality

Diabetes & cog function

BP variability & brain morphology

Heart failure & cog decline

Insulin resistance & death from AD

Proinflammatory diet & dementia

Low fat diet & dementia

MIND diet & cog function

Neuroanatomical risk of AD

Machine learning prediction & cog imp

Predicting cog resilience w ML

Harmonizing measures of global cog function

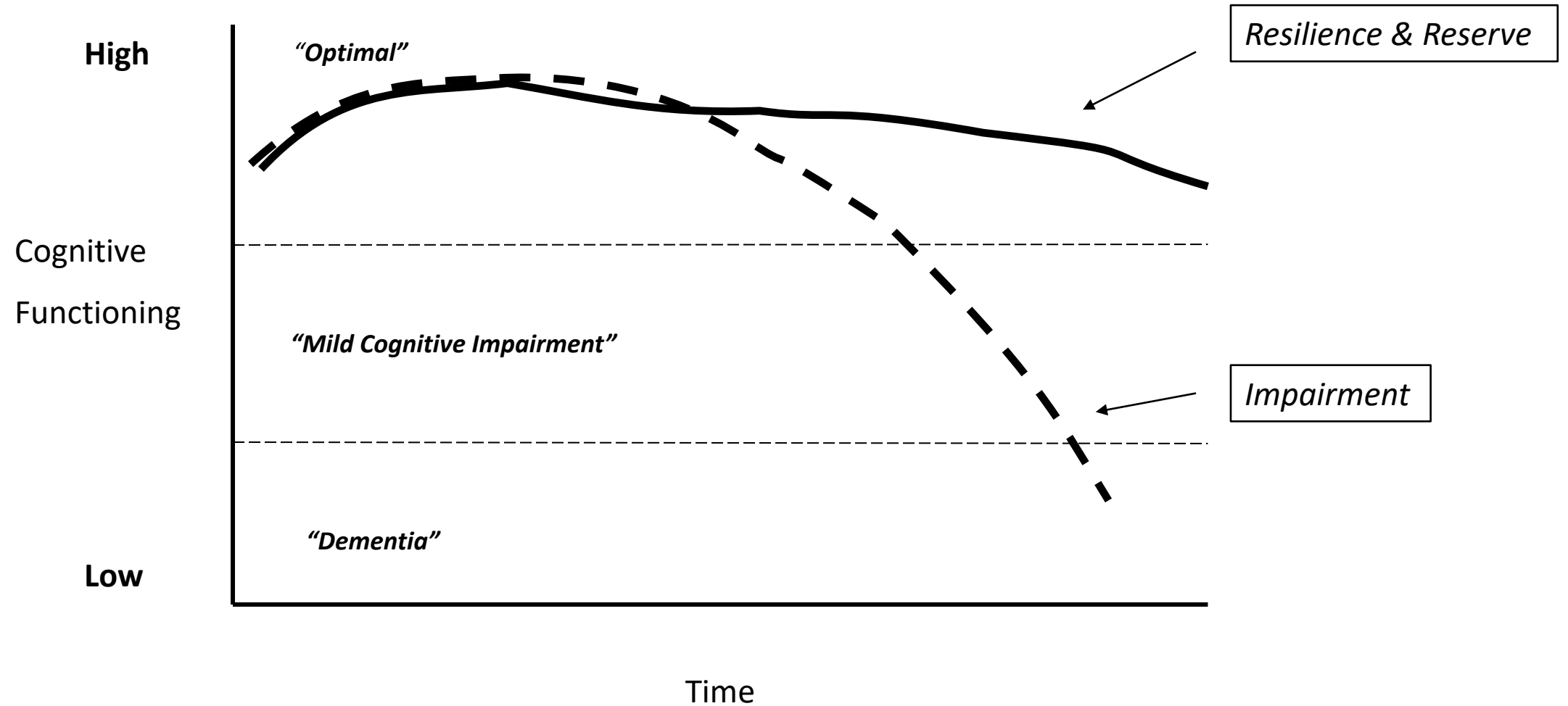
Validation of telephone cog battery

Supplemental Case Ascertainment Protocol

Performance w/2 measures of cog function

Cognitive reserve & cog impairment

WHIMS: From Impairment to Resilience & Reserve



Investigating the Biology of Cognitive Resilience Among APOE ϵ 4 Carriers in WHIMS (AS615, AS637)

NIA Intramural Team

Susan Resnick, PI

Josephine Egan

Luigi Ferrucci

Ruin Moaddel

Abhay Moghekar

Madhav Thambisetty

Ranjan Sen

Dimitrios Kapogiannis

Measures

- ❖ **Insulin Resistance, IGF-1 and its binding proteins** (Josephine Egan)
- ❖ **Olink proteomics** (Luigi Ferrucci/Ruin Moaddel/Abhay Moghekar)
- ❖ **Simoa assays – NF-Light, IL-6, $A\beta_{40}$, $A\beta_{42}$, *Total Tau*** (same)
- ❖ **Targeted metabolomics** (Madhav Thambisetty)
- ❖ ***Autoantibody signatures*** (Ranjan Sen)
- ❖ ***Exosomes (subset of participants)*** (Dimitrios Kapogiannis)

Investigating the Biology of Cognitive Resilience in WHIMS: Planned Analyses

- Extreme Groups
 - e4 impaired ≤ 80 vs. e4 resilient > 80
 - e4 impaired ≤ 80 vs all 80+
- Time to onset of impairment
- Age at onset of impairment
- Association with 3MSE

Additional Considerations

- Need for Replication:
 - WHI: COSMOS-MIND, WHISPER, WHISH

Specific Assays

Egan - Glucose and Insulin Resistance
(Through existing data and Olink)

Insulin

IGF-1

IGF-1 binding proteins

Ferrucci /Moaddel/Moghekar

Olink proteomics

Quanterix Simoa

IL-6

NF-light

Neurology 3-Plex A, AB40, AB42, Ttau

Thambisetty - Targeted Metabolomics

AbsoluteIDQ® p500 HR assay – Biocrates

Sen – Antibodies

Autoantibody Profiles

Kapogiannis – Exosomes

SIMOA - p181-tau

SIMOA - A β 42

SIMOA - A β 40

MSD - pSer312-IRS-1

MSD - Py-IRS-1

AKT signaling panel - total and phospho-proteins

3 Synaptic proteins

EV-Associated Clusterin

EV-Associated ApoE

Micro RNAs

Investigating the Biology of Cognitive Resilience in WHIMS (N = 1625)

	Age ≤ 80 e4/* and cognitive impaired	Age > 80 e4/* and no assessment met criteria	Age > 80 e4/* cognitively impaired	Age ≤ 80 e3/e3 and cognitive impaired	Age > 80 e3/e3 and no assessment met criteria	Age > 80 e3/e3 and cognitively impaired
N	115	345	218	105	04	438
Age at Enrollment	70.7 (3.4)	70.5 (3.6)	72.5 (3.8)	71.1 (3.6)	70.5 (3.6)	72.2 (3.8)
Age at impairment or last non-impairment record	76.2 (2.8)	86.1 (3.6)	85.4 (3.5)	76.0 (2.9)	86.7 (3.6)	86.2 (3.6)
APOE						
e3/e4	99 (86.1)	328 (95.1)	197 (90.4)			
e4/e4	16 (13.9)	17 (4.9)	21 (9.6)			
e3/e3				105 (100)	404 (100)	438 (100)
Education						
< High school	7 (6.1)	15 (4.4)	9 (4.1)	17 (16.2)	9 (2.2)	23 (5.3)
HS/GED	34 (29.6)	62 (18.0)	50 (22.9)	23 (21.9)	71 (17.6)	95 (21.7)
Some college	41 (35.7)	142 (41.2)	86 (39.5)	44 (41.9)	160 (39.6)	164 (37.4)
=>4 yrs. college	33 (28.7)	126 (36.5)	73 (33.5)	21 (20.0)	164 (40.6)	155 (35.4)
Missing						1 (0.2)

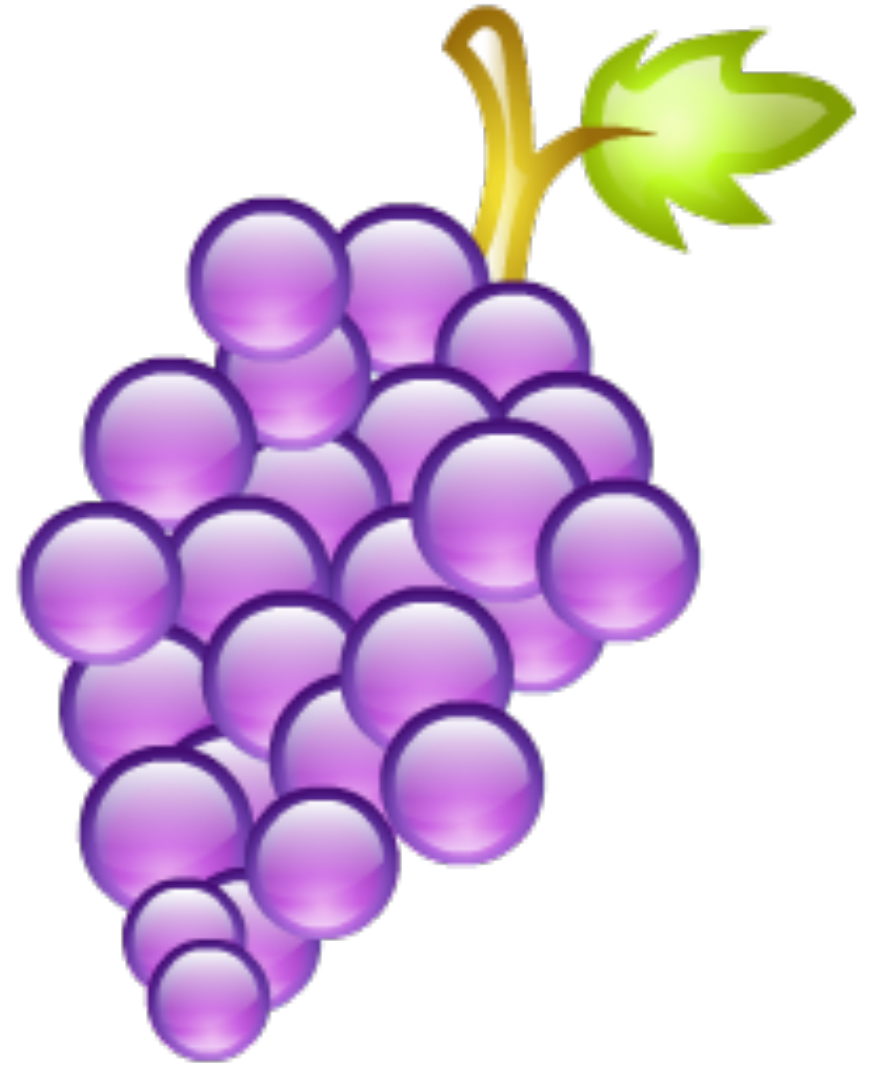
Future directions

Number of
WHIMS
Participants
in LLS,
OPACH

Ancillary Study	N	LLS Overlap	OPACH Overlap
WHIMS	7875	1523	1897
WHIMS-ECHO	2880	1577	1383
WHIMS MRI-1	1365	896	588
WIMS-MRI-2	730	610	421
WHISCA	2266	1043	734
WHIMS-Younger	1178	0	188
Cog Resilience (615/637)	2053/1725	778/454	668/376

Future Directions

- WHIMS-ECHO through 2021
- Cognitive function/impairment being considered in new ancillary studies:
 - CHIP
 - WHISH Extn
 - Sensory Impairment
 - Neuroimaging
 - LILAC-2
 - WHISPER-2



Thank you

Supplemental slides

WHIMS-ECHO (2008-2021)

- **11 years completed; 13 years planned**
- **Annual assessment** with full battery for each participant
- **>25,000 telephone assessments** completed
- Cognitive domains assessed: **Attention, Memory, Working Memory, Executive Function, Verbal Fluency**
- Additional assessments: **depressive symptom severity, insomnia**
- **Proxy reports:** Dementia Questionnaire
- **Adjudicated outcomes** Probable Dementia, Mild Cognitive Impairment

WHIMS

- N =
- 1996-2007
- Annual Modified Mini Mental State Exam on all ppts
- Detailed clinical work-up on all positive 3MSE
- Adjudication of NI, MCI, PD

WHIMS-ECHO

- N = 2914
- 2008-2021
- Annual telephone cognitive battery on all ppts
 - Memory, language, attention, executive function,
 - Depression, sleep prob,
- Adjudicated NI, MCI, PD
- 18,302 telephone assessments completed to date

WHIMS-Younger

- N=1362
- 6 years
- Telephone cognitive battery
 - Memory, language, attention, executive function,
 - Depression, sleep prob,
- Adjudicated NI, MCI, PD
- 5,590 telephone assessments

SCAP

- Supplemental Case Ascertainment Protocol
- Deceased + Proxy Only
- Dementia Questionnaire to Proxy
- Adjudicated NI, MCI, PD