

Comparing Alzheimer's risk in African Americans and the Yoruba



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Risk and Resilience to Alzheimer's Disease in African Americans
Thursday, June 22, 2023

Disclosure

None

Community Engagement in Practice!



3rd Annual Free Classic Car Show, Bar-B-Que, and Men's Health Fair



Promoting Awareness of Alzheimer's Disease, Heart Health, and Sexual Health for Men

at Messiah Baptist Church, 13-17 Oak Street, East Orange, NJ

Outline

- Introduction
- Indianapolis-Ibadan Study
 - Findings from Observational Studies*
 - Biochemical assessments*
 - Genetic Studies*
- Preliminary data from Newark-Nigeria Study
- Conclusion
- Acknowledgements

Benefits of cross-cultural Studies

- Much wider diversity of environmental exposures – (diet, climate, exposure to pathogens & cultural factors that lead to epigenetic adaptations)
- Unique opportunity for identifying risk factors
- Exploration of gene-environmental interactions



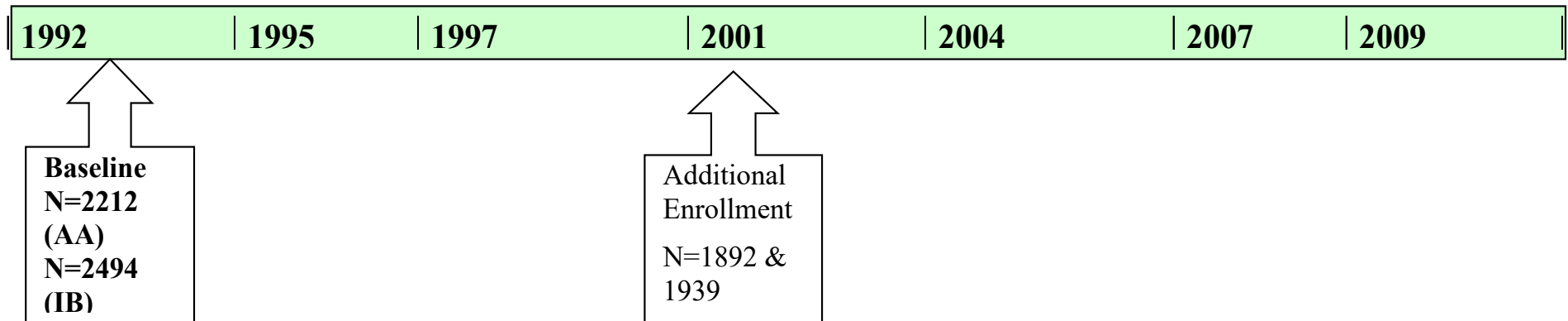
Indianapolis-Ibadan Study Hypothesis

- Identification of populations or communities with significantly lower or higher prevalence rates of AD could greatly enhance the search for environmental risk factors for AD”

Osuntokun et al (1992)



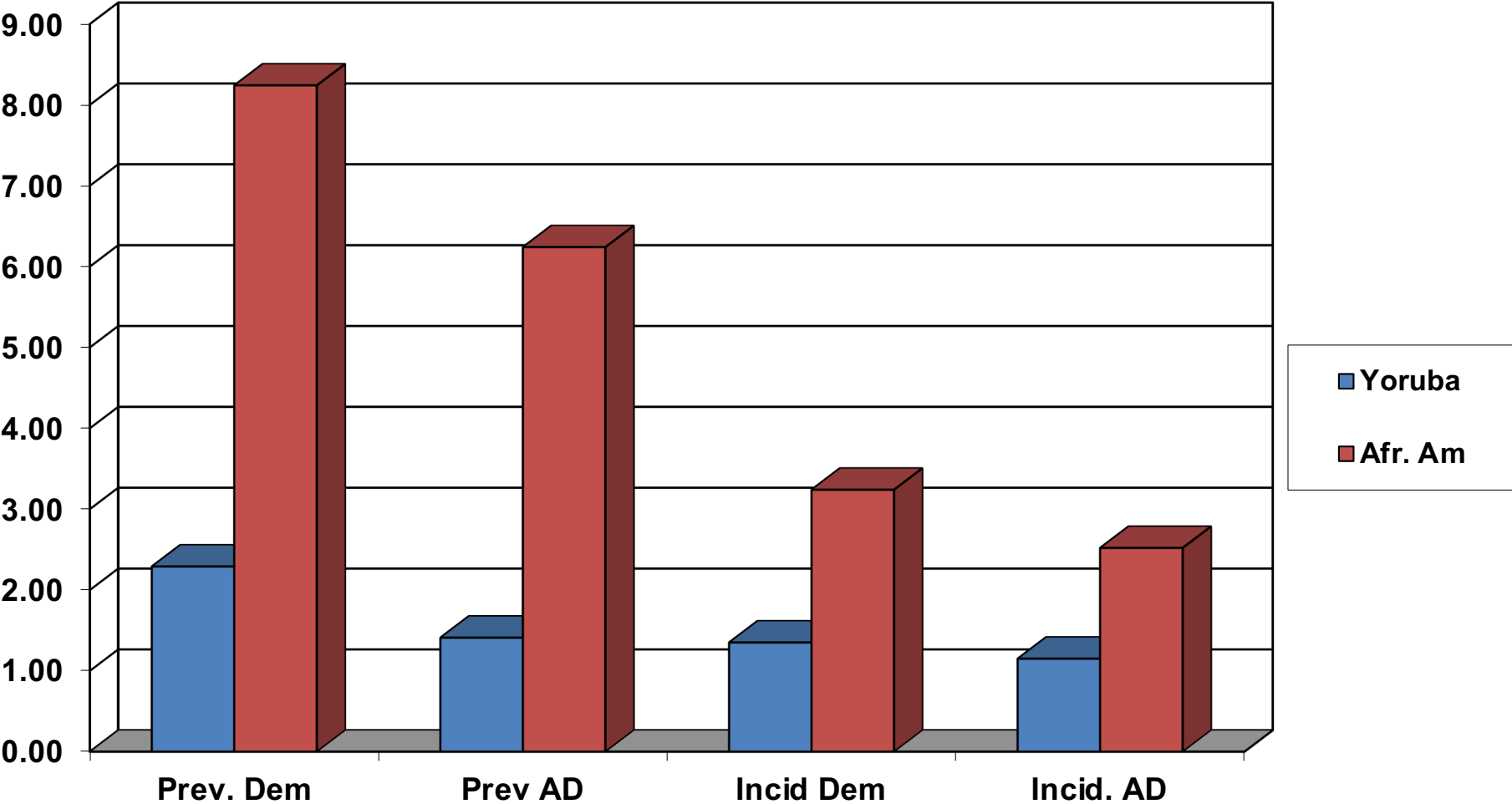
Project Timeline



- Total numbers of participants: 4104 African Americans
4433 Yoruba
- Up to 7 longitudinal evaluations over 19 years
- Two-phase sampling was used at each evaluation wave

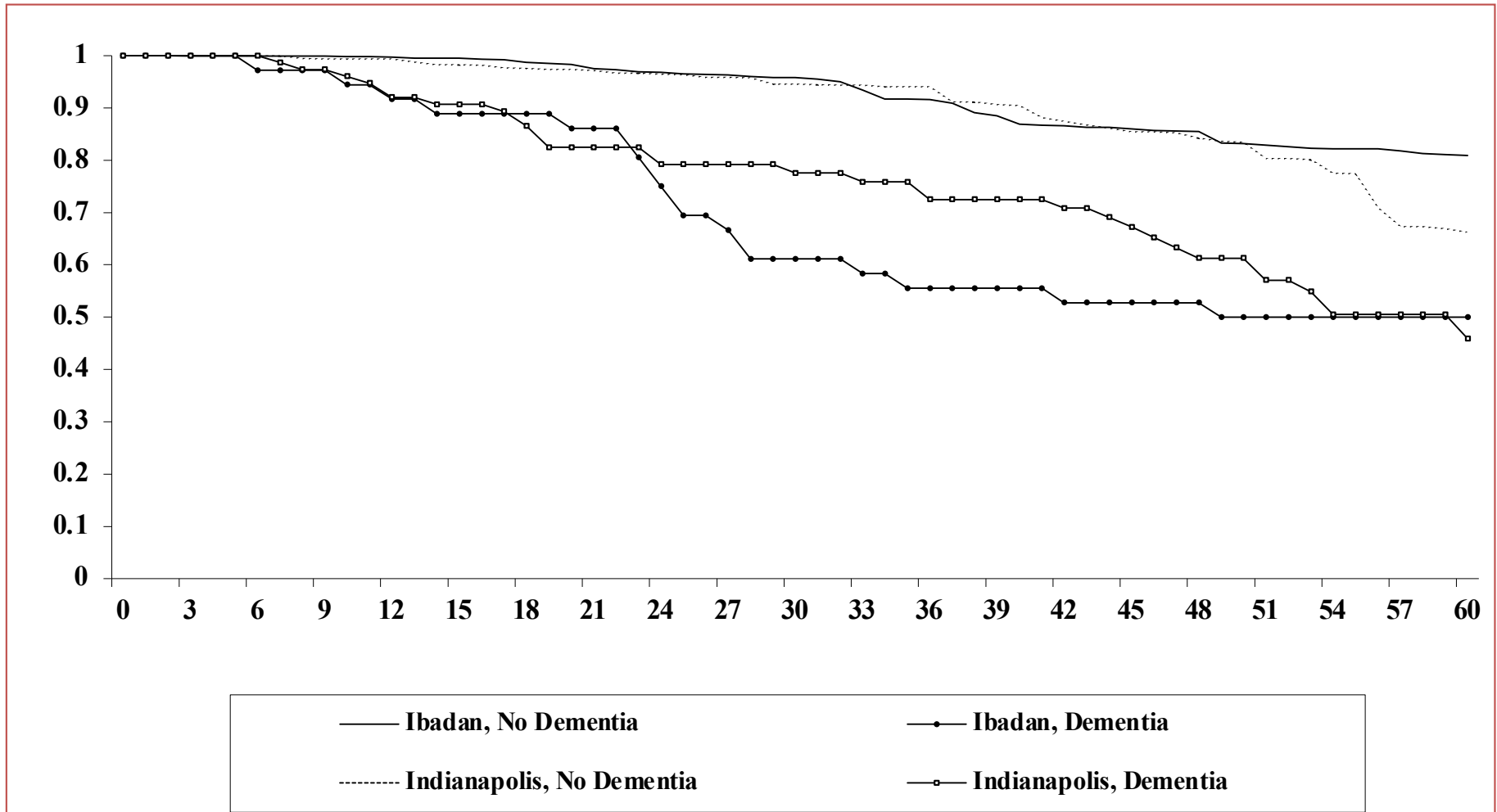
Incidence of dementia and Alzheimer disease in 2 communities: Yoruba residing in Ibadan, Nigeria, and African Americans residing in Indianapolis, Indiana. Hendrie HC, Ogunniyi A, Hall KS, Baiyewu O, Unverzagt FW, Gureje O, Gao S, Evans RM, Ogunseyinde AO, Adeyinka AO, Musick B, Hui SL. JAMA 2001 Feb 14;285(6):739-47.

Burden of Dementia in African Americans and Yoruba



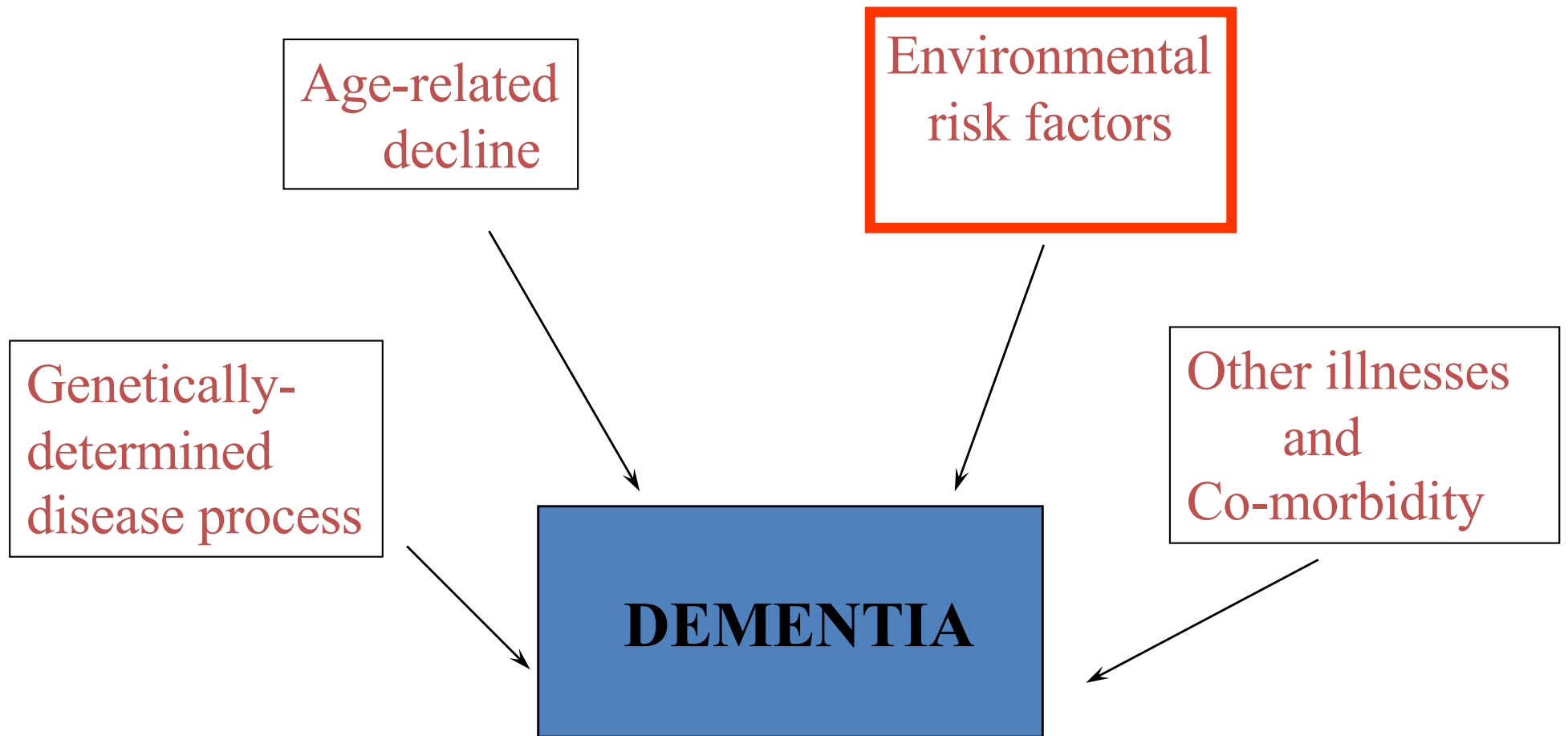
Hendrie 1995, 2001

Baseline Survivor Function by Site and Dementia Status



Risk of dying (Dementia cases vs. Normal): Indy 2.05; Ibadan 2.83

Processes influencing clinical expression of dementia



Focus on Gene-Environment interactions

- Environment – education, living experience
- Vascular factors
- Diet
- Genetic risk – APOE, GWAS

Search for environmental risk factors



Living Alone: Indianapolis 53.6%, Ibadan 7.4%

Bassuk Involvement Score

Presence of a spouse

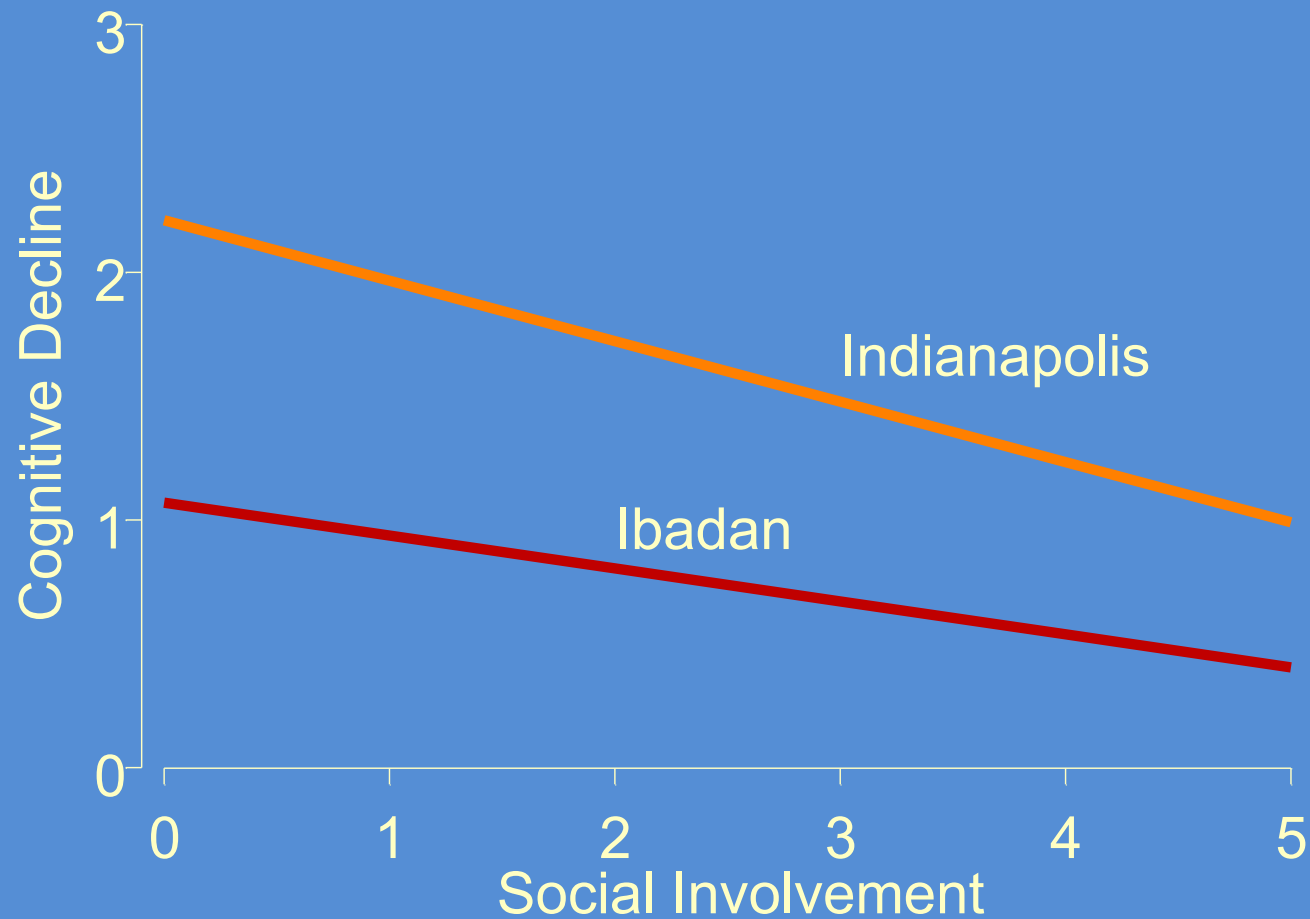
Visits with at least 3 relatives or friends per month

Attendance at religious services once or more per month

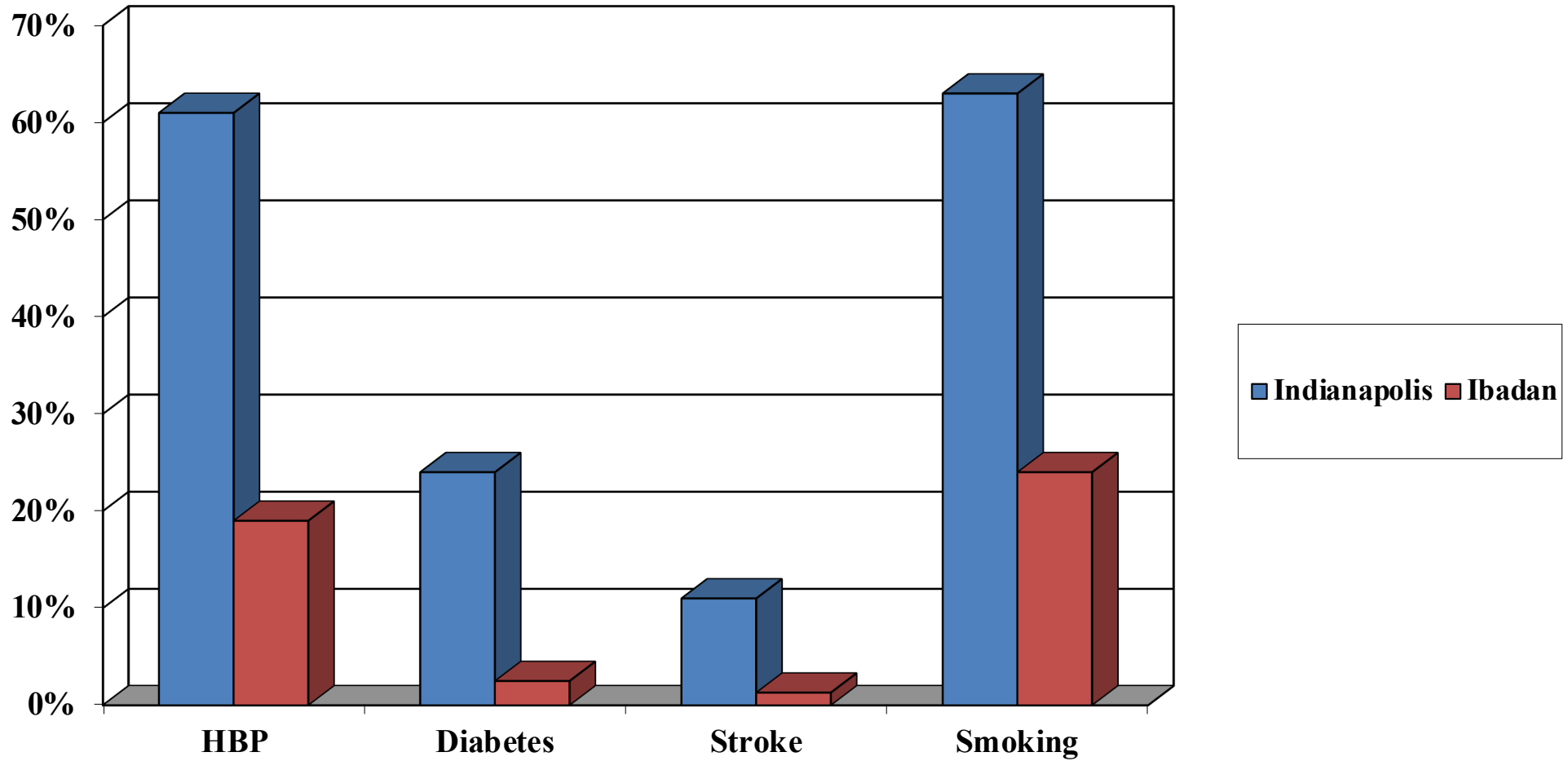
Group membership

Regular recreational/social activities

The Association of Social Involvement and Cognitive Decline at 7-Year Follow Up



Frequencies of self-reported vascular risk factors



Comparison of baseline vascular factors

	Ibadan	Indianapolis
Systolic BP (mm Hg)	135	146
Mean Cholesterol (mg/dl)	166	221

Ref. Ogunniyi et al, 2000; Hendrie et al. 2004

Means & Standard Deviations for Blood Pressure in Both Sites

	Indianapolis		Ibadan	
	Mean \pm SD		Mean \pm SD	
Males	Systolic BP	Diastolic BP	Systolic BP	Diastolic BP
65 – 74	148.49 \pm 20.89	82.03 \pm 12.46	149.48 \pm 29.34	85.39 \pm 15.81
75 – 84	145.53 \pm 21.41	80.26 \pm 11.84	146.27 \pm 27.23	82.70 \pm 15.00
85+	146.21 \pm 25.39	75.06 \pm 12.51	145.75 \pm 30.81	80.30 \pm 13.63
Females				
65 – 74	144.27 \pm 21.78	79.83 \pm 11.60	152.76 \pm 32.53	85.71 \pm 15.48
75 – 84	144.90 \pm 21.66	77.78 \pm 11.16	154.43 \pm 32.54	84.64 \pm 15.46
85+	147.81 \pm 25.79	76.97 \pm 14.00	157.04 \pm 31.94	82.82 \pm 15.08

73.41% of African Americans take anti-hypertension medications

Lipid measurements

Lipids (mg/dL)	Indianapolis	Ibadan
Cholesterol*	186.7	174.8
LDL*	112.8	106.7
HDL	51.2	50.0
Triglycerides*	113.4	89.5

P < 0.05

* Significant interaction with APOE ε4 allele

Daily Diet of the Elderly Yoruba and African Americans: A Preliminary Analysis

	% Carbohydrates	% Fat	% Protein
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Yoruba

78.4

9.5

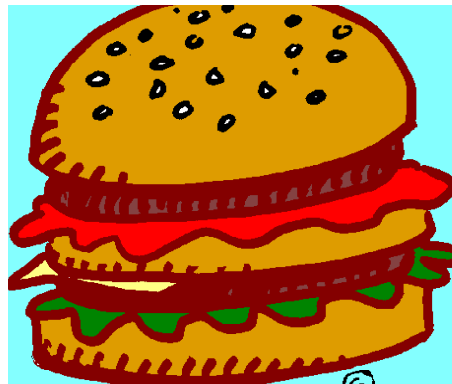
12.1

African Americans

52

34

15



Approach through disease mechanisms

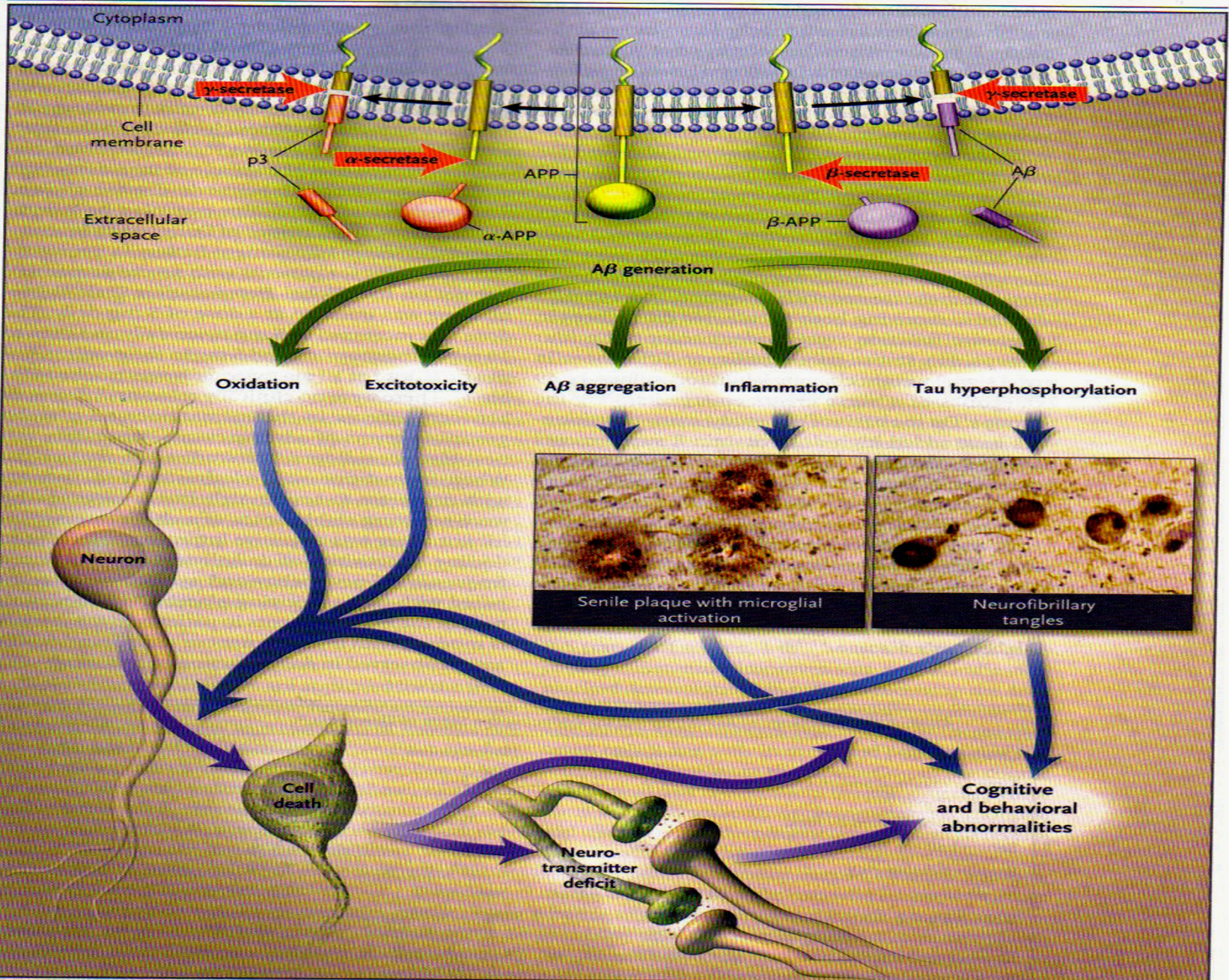


Figure 2. Putative Amyloid Cascade.

This hypothesis of the amyloid cascade, which progresses from the generation of the beta-amyloid peptide from the amyloid precursor protein, through multiple secondary steps, to cell death, forms the foundation for current and emerging options for the treatment of Alzheimer's disease. APP denotes amyloid precursor protein, and A β beta-amyloid.

Comparison of Biomarkers: AA vs. Yoruba

Mechanism	Test	AA	Yoruba	P value
<u>Endothelial Dys.</u>	E-selectin	44.5 (23.6)	37.9 (34)	<0.001
	PAI-1	21.9 (27.5)	39.5 (31.9)	<0.001
	Homocysteine	17.4 (7.4)	17.4 (6.9)	0.9
<u>Oxidation</u>	CRP	14.81 (26.6)	8.1 (18.9)	<0.001
	8-Isoprostane	586.3 (1283)	1270.3 (1585.5)	<0.001
<u>Insulin Res.</u>	Metabolic Synd.	27%	7%	
	HOMA-IR	7.16	0.91	<0.001
<u>Atherogenesis</u>	Cholesterol	188.5 (38.6)	174.7 (40.9)	<0.001
	Triglycerides	104.7 (47)	89.5 (36.4)	<0.001
<u>DNA synthesis</u>	Folate	9.81 (8.4)	5.87 (6.7)	<0.001
	Vit B12	612.6 (352.7)	785.5 (310.2)	<0.001

PAI-1 – Plasminogen Activator Inhibitor-I; CRP – C-Reactive Protein;

HOMA-IR- Homeostasis Model Assessment (HOMA-IR); AA – African Americans

Deeg M et al. 2008

Homocysteine levels and dementia risk in Yoruba and African Americans

Hugh C. Hendrie,^{1,2,3} Olusegun Baiyewu,⁴ Kathleen A. Lane,⁵ Christianna Purnell,² Sujuan Gao,⁵ Ann Hake,⁶ Adesola Ogunniyi,⁷ Oye Gureje,⁴ Frederick W. Unverzagt,³ Jill Murrell,⁸ Mark A. Deeg⁹ and Kathleen Hall³

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ABSTRACT

Background: High levels of homocysteine have been associated with increased risk for dementia although results have been inconsistent. There are no reported studies from the developing world including Africa.

Methods: In this longitudinal study of two community-dwelling cohorts of elderly Yoruba and African Americans, levels of homocysteine, vitamin B12 and folate were measured from blood samples taken in 2001. These levels were compared in two groups, participants who developed incident dementia in the follow-up until 2009 (59 Yoruba and 101 African Americans) and participants who were diagnosed as cognitively normal or in the good performance category at their last follow-up (760 Yoruba and 811 African Americans). Homocysteine levels were divided into quartiles for each site.

Results: After adjusting for age, education, possession of ApoE, smoking, and time of enrollment the higher quartiles of homocysteine were associated with a non-significant increase in dementia risk in the Yoruba (homocysteine quartile 4 vs. 1 OR: 2.19, 95% CI 0.95–5.07, $p = 0.066$). For the African Americans, there was a similar but non-significant relationship between higher homocysteine levels and dementia risk. There were no significant relationships between levels of vitamin B12 and folate and incident dementia in either site although folate levels were lower and vitamin B12 levels were higher in the Yoruba than in the African Americans.

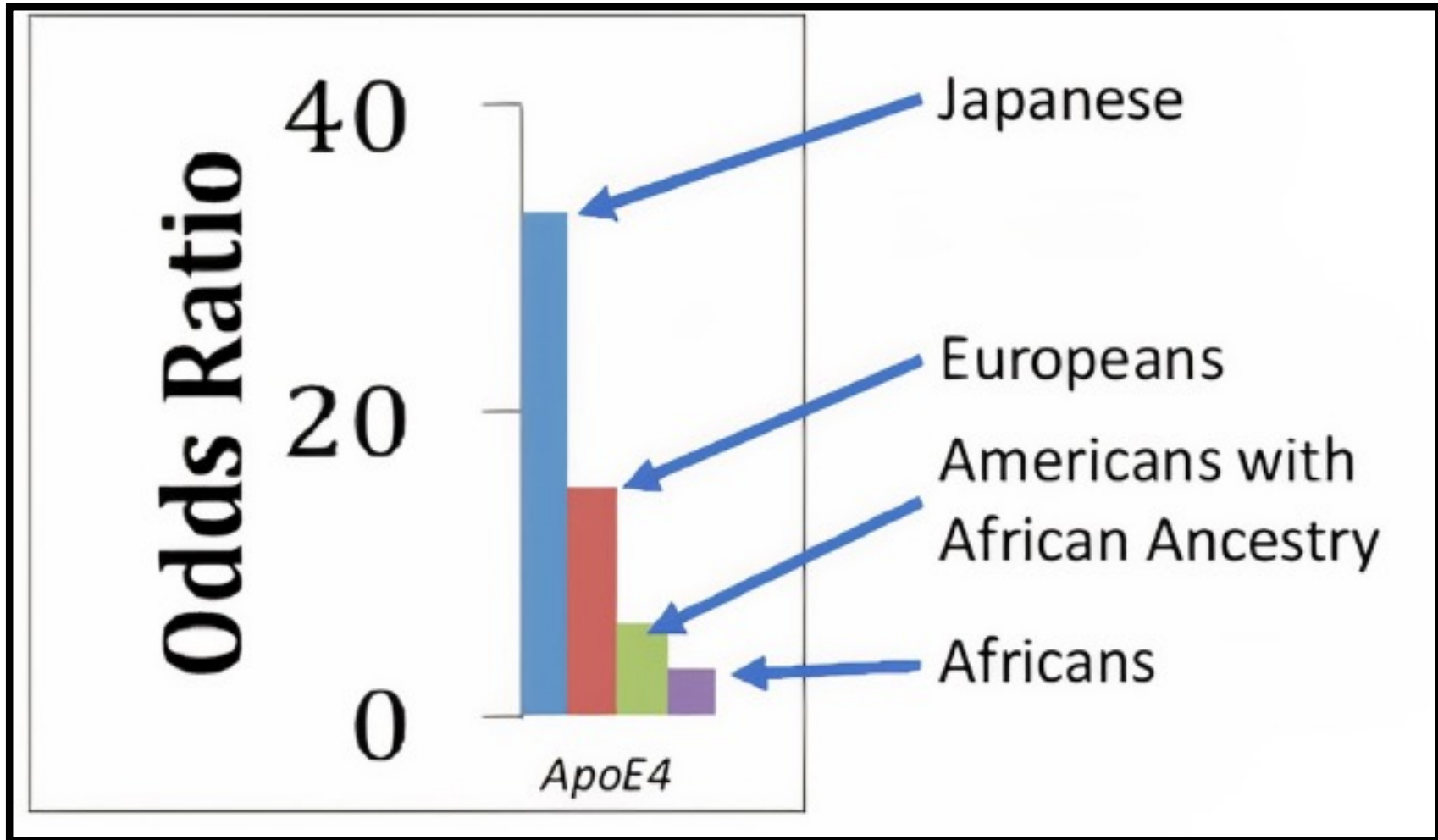
Conclusions: Increased homocysteine levels were associated with a similar but non-significant increase in dementia risk for both Yoruba and African Americans despite significant differences in folate levels between the two sites.

Key words: dementia, Alzheimer's disease, homocysteine, African Americans, Yoruba

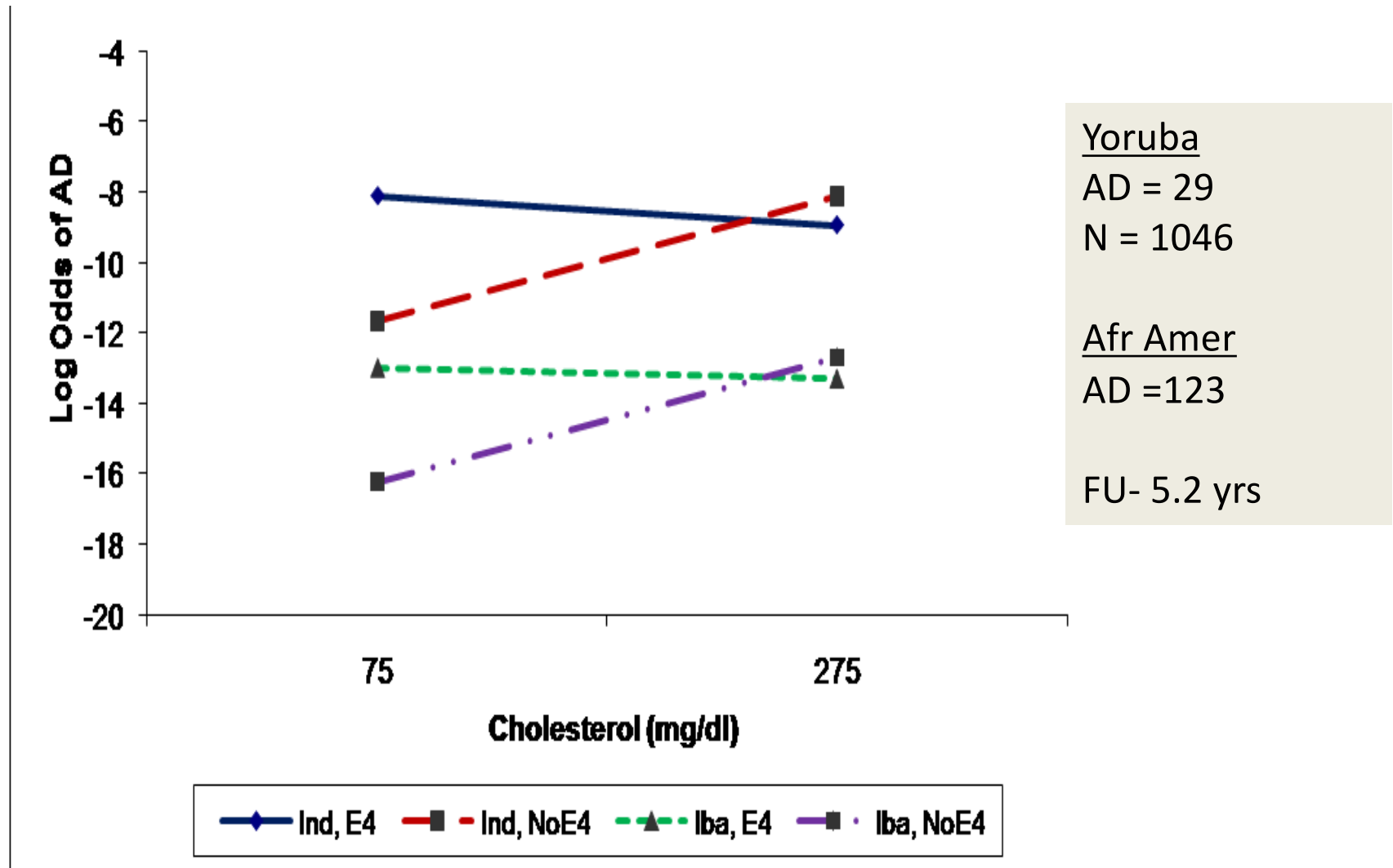
Interim Summary

- Prevalence of Dementia and AD higher in African Americans than in Yoruba
- Social involvement slows cognitive decline in both populations
- Vascular factors appear to have some role to play in disease pathogenesis but biomarker studies were inconclusive

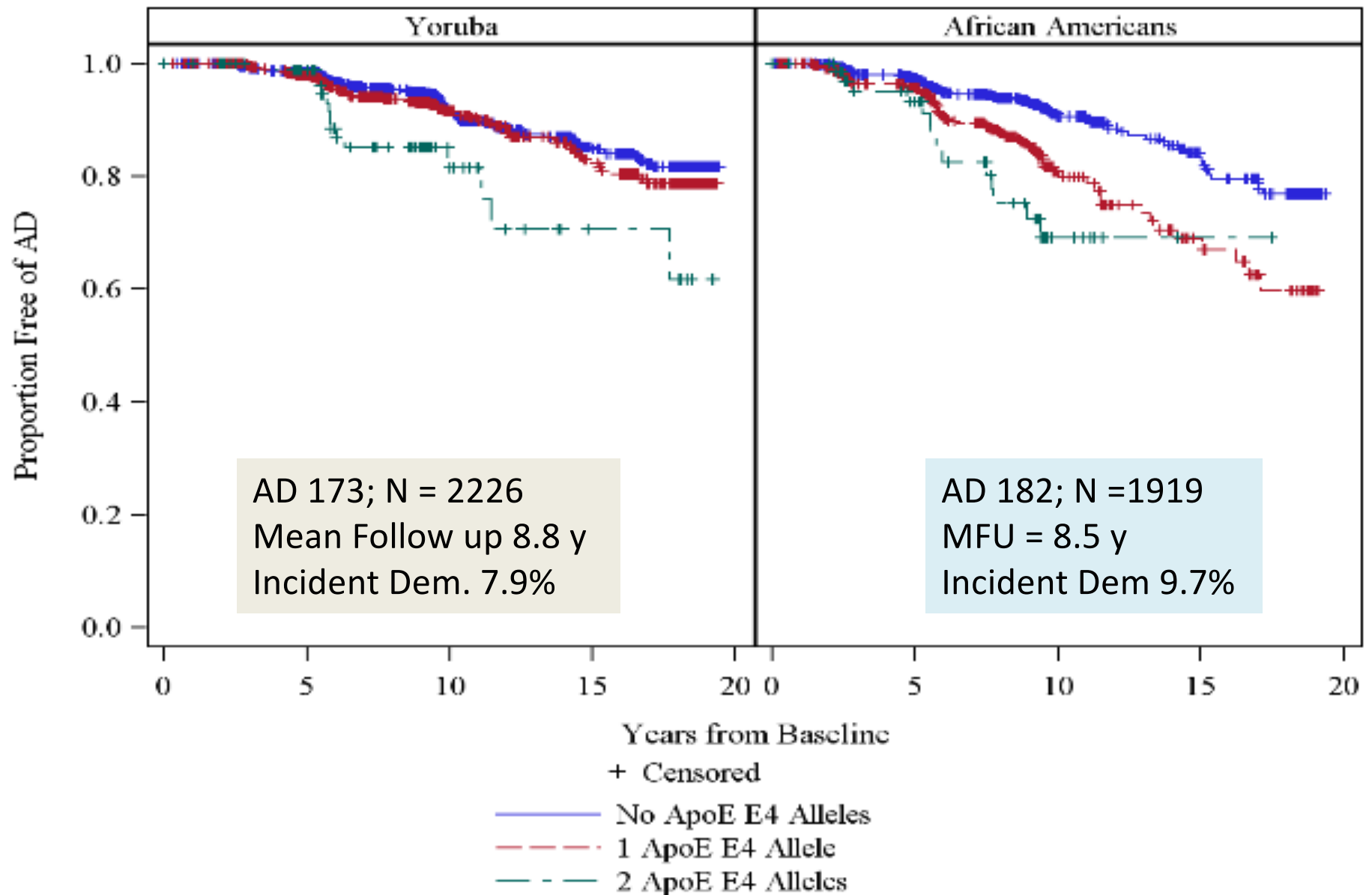
APOE and AD



ApoE ϵ 4 Genotype and Cholesterol Interaction Effects on AD in Indianapolis and Ibadan



Association between APOE and AD



APOE and AD Risk

	Yoruba		African Americans		Caucasian*	
	HR	95% CI	HR	95% CI	OR	95% CI
Number of APOE ε4 alleles						
2 vs. 0	2.95	1.67-5.19	4.12	2.33-7.28	12.5	8.8-17.7
1 vs. 0	1.21	0.88-1.67	2.31	1.70-3.14	2.7	2.2-3.2

Hendrie HC, Murrell J, Baiyewu O, et al. APOE epsilon4 and the risk for Alzheimer disease and cognitive decline in African Americans and Yoruba. *Int Psychogeriatr* 2014;26:977-985.

* Farrer LA, Cupples LA, Haines JL, et al. Effects of Age, Sex, and Ethnicity on the Association Between Apolipoprotein E Genotype and Alzheimer DiseaseA Meta-analysis. *JAMA*. 1997;278(16):1349–1356.

Interim Summary

- APOEε4 has a significant but weaker effect on incident AD in Yoruba than in African Americans.
- Although both have African ancestry, it appears that African Americans and Yoruba have different genes associated with AD risk.
- Environmental and genetic interactions are considered to be highly plausible but further research is needed to explore biological pathways underlying these associations.

Observed Phenotypic Variation

<i>Genes</i>	<i>+Environment</i>	<i>+Gene/Gene</i>	<i>Gene/Environment</i>
APOE ϵ 4	Vascular risk HBP	Other Genes involved	APOE ϵ 4/Lipid
? Other genes	Diet Social interaction	APOE ϵ 4 Expression	

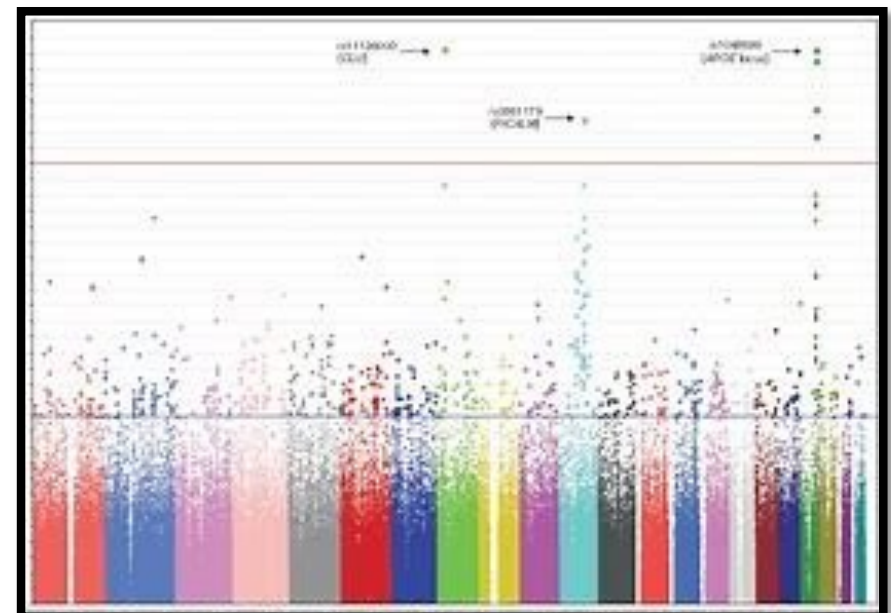
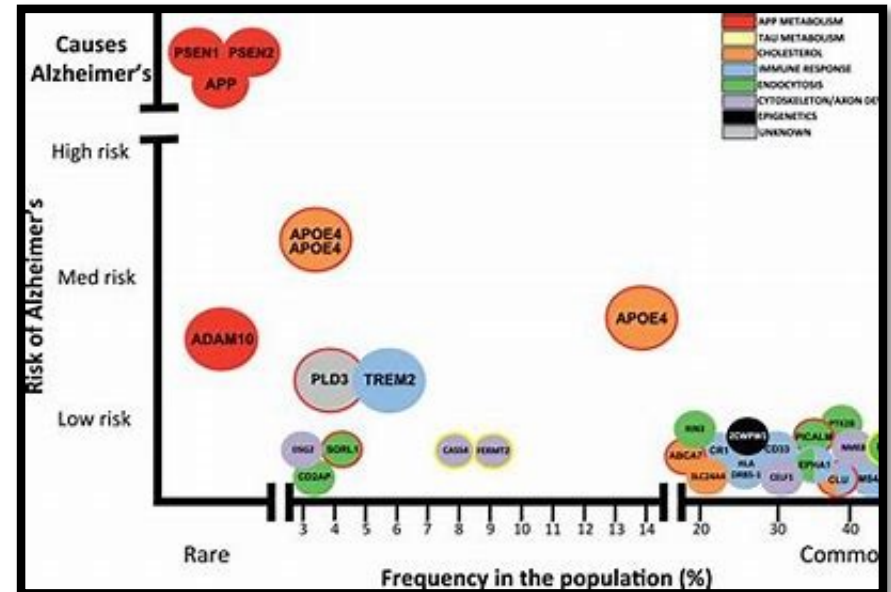
Are there differences in genes associated with AD?

Associations of Targeted Genetic Variants with Alzheimer's Disease in African Americans and Nigerians



GWAS for AD Genes

- Genome-wide association studies (GWAS) are useful for associating specific genetic variations with particular diseases through scanning the genomes from many different people and looking for genetic markers that can predict the presence of a disease
- No GWAS Data from Africa

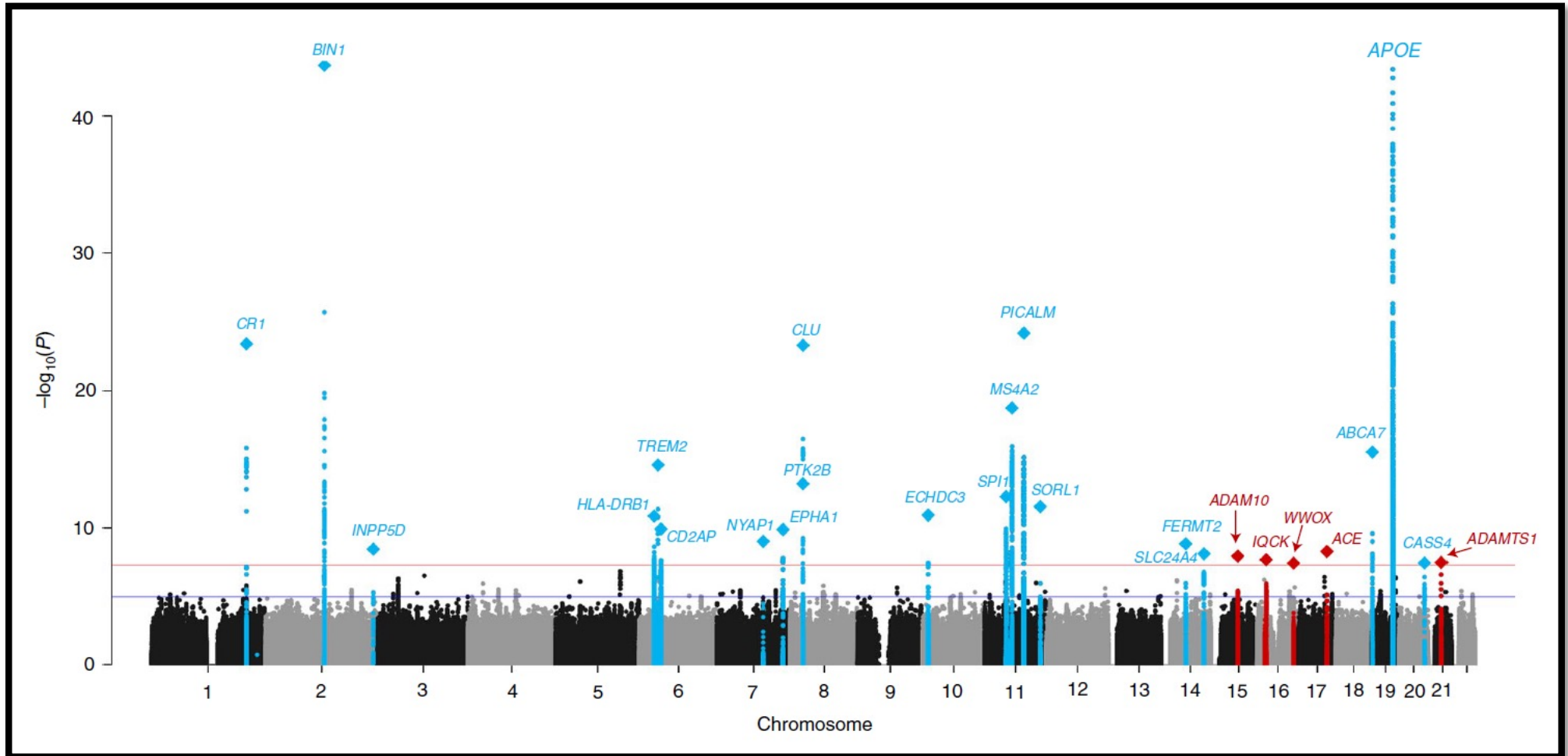


Hazard Ratio (HR) Estimates Adjusting for Age, Sex, Education and APOE.

SNPs	Closest Gene	African Americans			Yoruba		
		HR	95% CI	p-value	HR	95% CI	p-value
rs3752246	ABCA7	1.84	1.06 - 3.21	0.0306	--		
rs4147929	ABCA7	2.06	1.21- 3.50	0.0077	--		
rs9331949	CLU	0.59	0.29 - 1.20	0.1435	2.05	1.22 - 3.45	0.0069
rs10498633	SLC24A4 /RIN3	0.87	0.58 - 1.30	0.4854	1.55	1.02 - 2.36	0.0401
rs12881735	SLC24A4	0.88	0.59 - 1.32	0.5437	1.55	1.04 - 2.32	0.0316

ABCA – ATP-Binding Cassette Subfamily 7
 CLU – Clusterin; SLC – Solute Carrier Family 24

Risk Genes for AD



RESEARCH ARTICLE

A locus at 19q13.31 significantly reduces the *ApoE* ϵ 4 risk for Alzheimer's Disease in African Ancestry

Farid Rajabli¹, Gary W. Beecham^{1,2}, Hugh C. Hendrie³, Olusegun Baiyewu⁴, Adesola Ogunniyi⁴, Sujuan Gao⁵, Nicholas A. Kushch¹, Marina Lipkin-Vasquez¹, Kara L. Hamilton-Nelson¹, Juan I. Young^{1,2}, Derek M. Dykxhoorn^{1,2}, Karen Nuytemans^{1,2}, Brian W. Kunkle^{1,2}, Liyong Wang^{1,2}, Fulai Jin⁶, Xiaoxiao Liu⁶, Briseida E. Feliciano-Astacio⁷, Alzheimer's Disease Sequencing Project, Alzheimer's Disease Genetic Consortium, Gerard D. Schellenberg⁸, Clifton L. Dalgard⁹, Anthony J. Griswold^{1,2}, Goldie S. Byrd¹⁰, Christiane Reitz¹¹, Michael L. Cuccaro^{1,2}, Jonathan L. Haines¹², Margaret A. Pericak-Vance^{1,2}, Jeffery M. Vance^{1,2*}

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OPEN ACCESS

Citation: Rajabli F, Beecham GW, Hendrie HC, Baiyewu O, Ogunniyi A, Gao S, et al. (2022) A locus at 19q13.31 significantly reduces the *ApoE* ϵ 4 risk for Alzheimer's Disease in African Ancestry. *PLoS Genet* 18(7): e1009977. <https://doi.org/10.1371/journal.pgen.1009977>

Summary

- In the African American sample, two variants in the adenosine triphosphate-binding cassette subfamily A member 7 (ABCA7) gene had significant associations with earlier AD onset. These ABCA7 variants were not observed in the Yoruba sample.
- In the Yoruba sample, one variant in the Clusterin gene (CLU) and two variants in the Solute Carrier family 24 member 4 gene (SLC24A4) were significantly associated with earlier AD onset.
- In the Yoruba sample, rs10498663 in SLC24A4 was significantly associated with higher levels of triglycerides

Cross-validation of risks for
Alzheimer's disease in African
Americans with Yoruba people of
West Africa: Newark-Nigeria
Dementia Study

AIMS OF THE STUDY

- To evaluate how variation in physical fitness is correlated with cognitive function and how this association is mediated by various health and lifestyle variables.
- To cross-validate the risk factors for AD in African Americans and in Yoruba people.

Cognitive Test Battery*

- MMSE (Mini-Mental State Examination)
- Wechsler Adult Intelligence Scale 4th Version (WAIS IV)
- Digit Span (Forward, Backward, & Sequencing)
- Rey Auditory Learning Test (RAVLT)
- GDS (Geriatric Depression Scale – 15 items)
- Trail making A and B tests (Stick Design)
- STROOP (Color Naming, Color Interference and Word Reading) and Delayed recall (RAVLT after 20 minutes)
- Clock drawing
- Controlled Word Association (CWA) - Naming
- Pittsburgh Sleep Quality Index
- Lifestyle, Physical Fitness and Activity Assessments
- **Grit and Resilience**
- Midlife Development Inventory (MIDI)

Other assessments

- Color Vision Testing
- Blood Pressure, Height, Weight measurement
- Rutgers Generalization Test
- Get Up and Go, 6-Minute Walking tests
- Pulse Oximetry
- Blood for Malaria Parasites; Plasma Glucose
- Sputum for genetic studies

Preliminary Results

- Total enrolled: 124 (51 Male (41.1%))
- Mean Age: 70.1 (7.2) years
- Any education: 89.5% (including 29% with 3⁰ education)
(Previous I-I D Study: Indy Literacy 97.9%; Ibadan 15.2%)
- Widowed/Separated: 37.9%
- Presently working: 43.5%
- MMSE score \geq 24: 90.3%
- Frequencies: Hypertension: 42.7% (51% of them on treatment)
Diabetes Mellitus 15.5%; Smoking: 1.6%
Previous Stroke 1.6%

Frequencies of Selected Midlife Personality Traits

Traits	Frequency (%)
Organized, Helpful, Responsible, Self-disciplined, Sympathetic, Thorough	100
Friendly	99.2
Adventurous	64.5
Outgoing	57.3
Talkative	51.6
Worrying	49.2
Impulsive	35.5
Careless	28.2
Moody	14.5
Reckless	10.5

Concluding Remarks



“Demography is not Destiny”

Mark Gluck

Conclusion contd.

- Lower dementia burden in the Yoruba
- Some differences in dementia risk in the two populations – vascular, genetic, etc.
- Resilience is worth exploring through clinical, imaging, neurobiobanking and “omic” studies

Members of the Indianapolis-Ibadan Research Teams



In loving memory



Benjamin O. Osuntokun
(1935-1995)



Kathleen S. Hall
1944-2022

Acknowledgement contd.



Acknowledgements

- The Indianapolis-Ibadan Dementia Project (Hendrie/Hall)
NIH R01 AG09956
- Indiana ADC (Saykin) NIH P30 AG 10133
- Alzheimer's Association/F.M. Kirby Foundation (Pilot
Research Grant IRG-95-084)
- Longitudinal interactive vascular exposure and Alzheimer
Disease (LiveAD) (Gao) NIH R01 AG0145350
- Risk Factors for Future Cognitive Decline and Alzheimer's
Disease in Older African Americans (Gluck)
R01AG053961-05S2 (supplement)