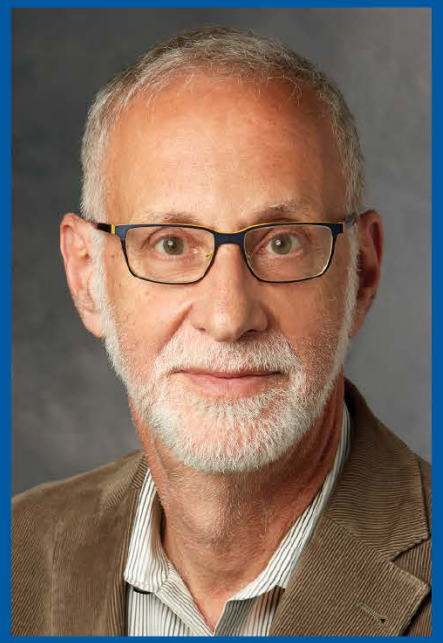
Lecture Series

2017
Genomics and Health Disparities

Exploring the Role of Genomics in Achieving Health Equity

Genomics: Will it help us address health disparities?



Mark Cullen, M.D.

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Director, Stanford Center for Population Health Sciences

Senior Associate Dean for Research

Stanford School of Medicine

Genomics: Will it Help Us Address Health Disparities?

NIH Conference on Genomics and Health Disparities
June 8, 2017

Mark R. Cullen M.D.
Stanford Center for Population Health Sciences

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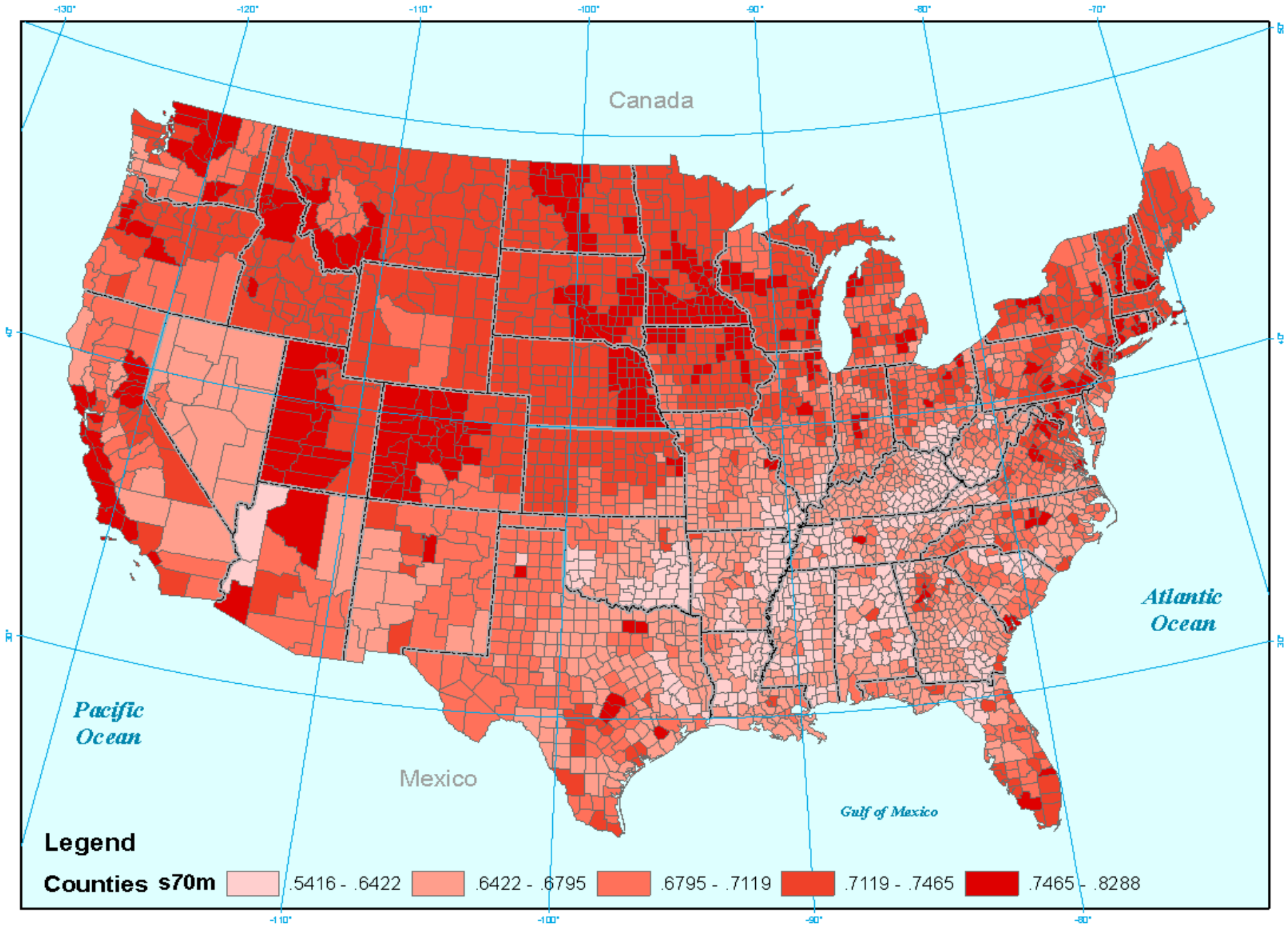
Reasons we shouldn’t go there

1. First things first

Reasons we shouldn’t go there



Survival to Age 70 (S_{70}) for White Male Pop. in 2000, *by county*

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Construct	Variable	Data Source	Metric
Low educational attainment	Education <12 years	Census	% of subgroup *10^{-2}
High educational attainment	Education >12 years		% of subgroup *10^{-2}
High occupational attainment	Managerial or professional job		% of subgroup *10^{-2}
Income	Household income per adult equivalent		Mean (Household income in$/adult equivalents) *$10^{-3}$
Poverty	Under the poverty line		% of subgroup *10^{-2}
Wealth (property)	Log of property value		Mean log (property value/5X10^{4}) among homeowners
Homeownership	Homeowner		% of subgroup *10^{-2}
Wealth (property) distribution	Gini coefficient on property values		Coefficient between 0 and 1
Immigrant status	Not a US citizen		% of subgroup *10^{-2}
Living without a partner	Divorced, separated or never married		% of subgroup *10^{-2}

Personal SES Variables

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County Level Environmental Variables

Construct	Variable	Data Source	Metric
Between race disparity in (property) wealth	Mean Black/Mean White property value	Census	Sex-specific quotient
Urban county	Metro by census definition		Dummy (yes/no)
Part urban	Part metro by census definition		Dummy
In the south	Southern by census definition		Dummy
Population growth rate	Population growth rate between 1990-2000		%change $X10^{-2}$
Proportion of county population that is black	Proportion of adults self-reported as black		% $*10^{-2}$
Black population in surrounding area	Proportion of adults in the State, excluding county, that is black		% $*10^{-2}$
Availability of fast food	Proportion of food sales classified as from limited service establishments	Economic census	% sales $*10^{-2}$
Quality of acute care	Proportion of acute MI patients getting beta-blockers	Ref	% hospitals* 10^{-2}
Cold climate	Mean January temperature		Degrees F$*10^{-2}$
Warm climate	Mean July temperature		Degrees F$*10^{-2}$
Air pollution	County mean conc. of fine particulate $PM_{2.5}$	EPA website	$PM_{2.5}$ in mg/M^3

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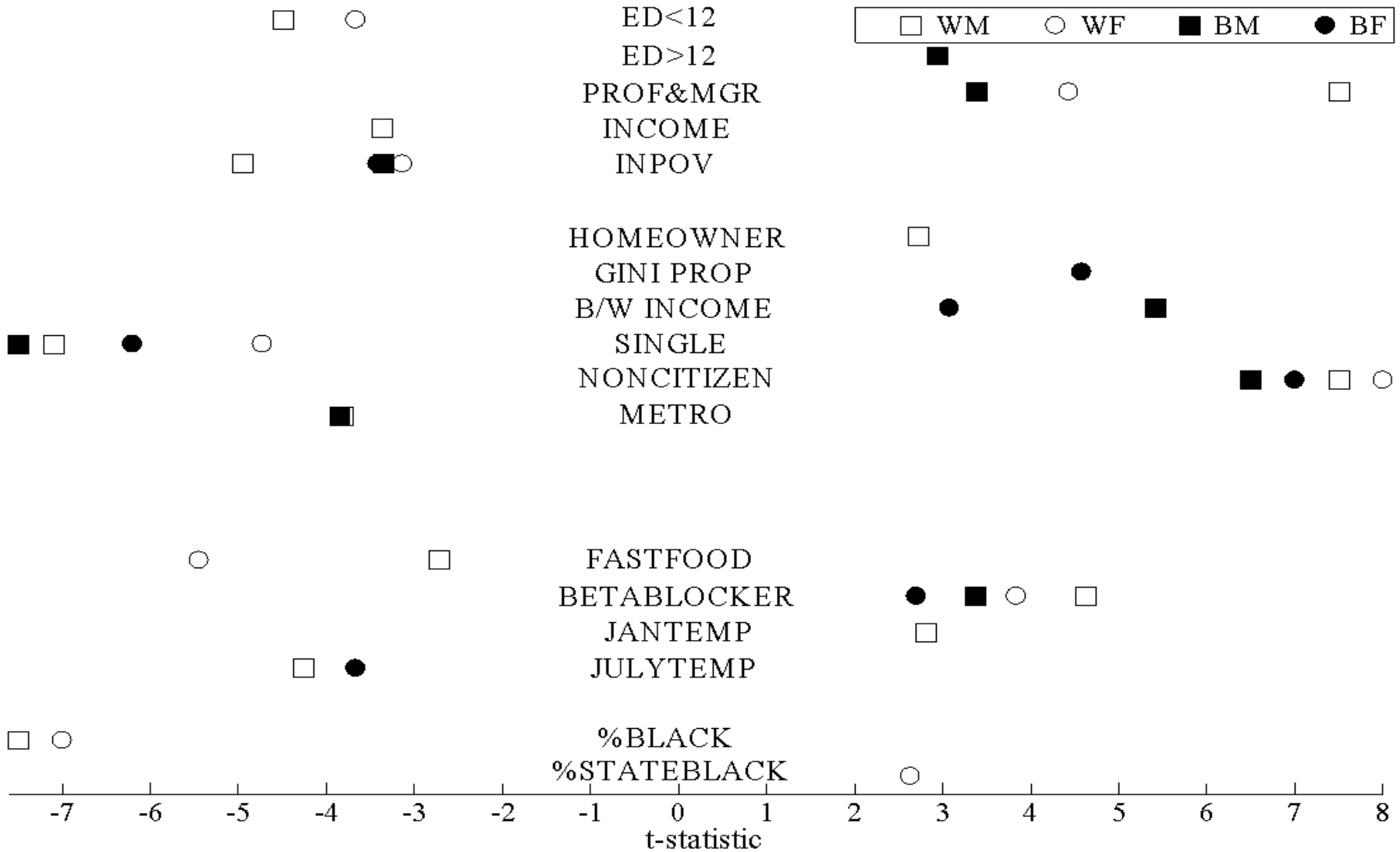
T-statistics for each significant predictor variable



Size and magnitude

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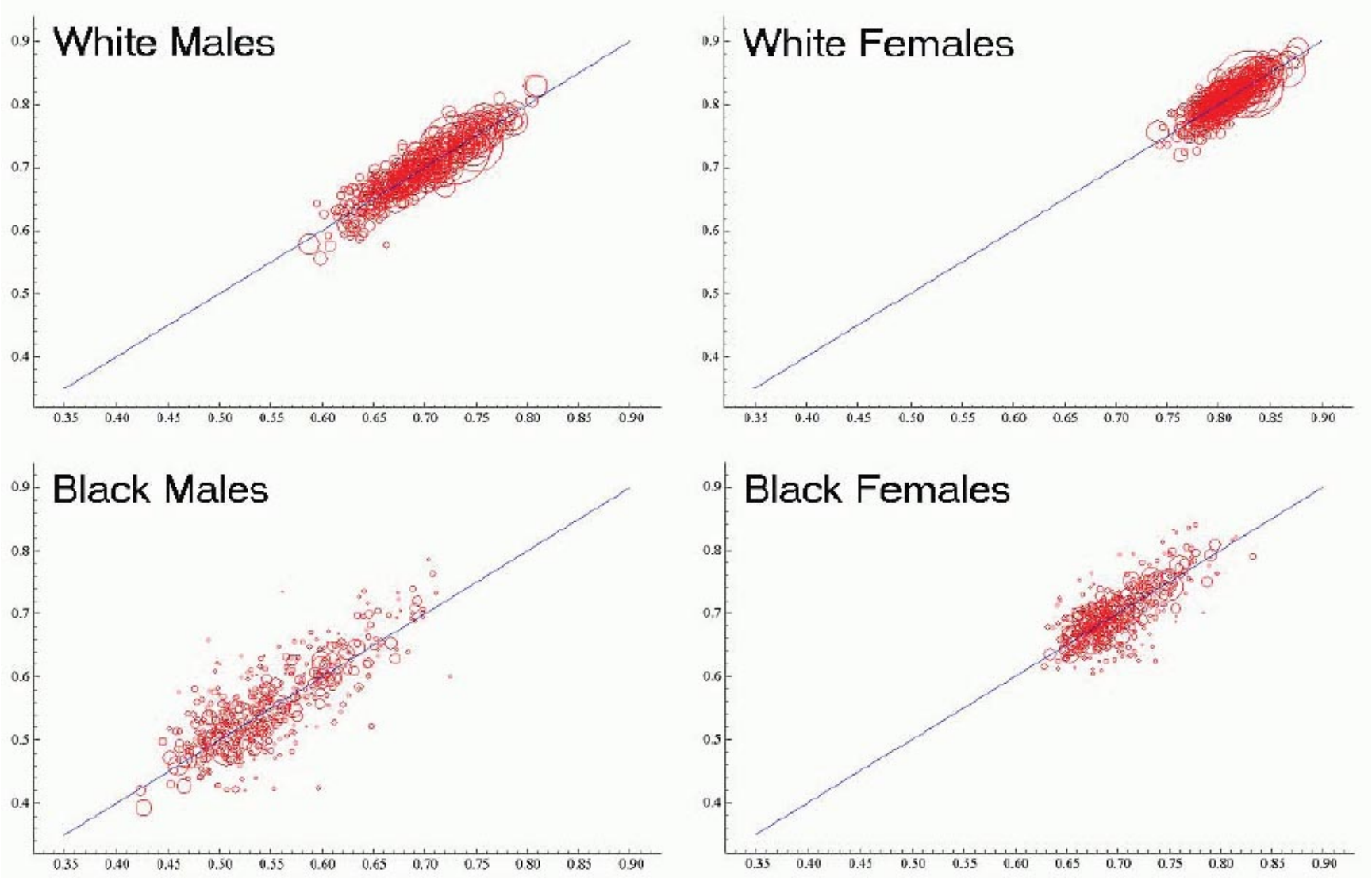
Actual and predicted S_{70}



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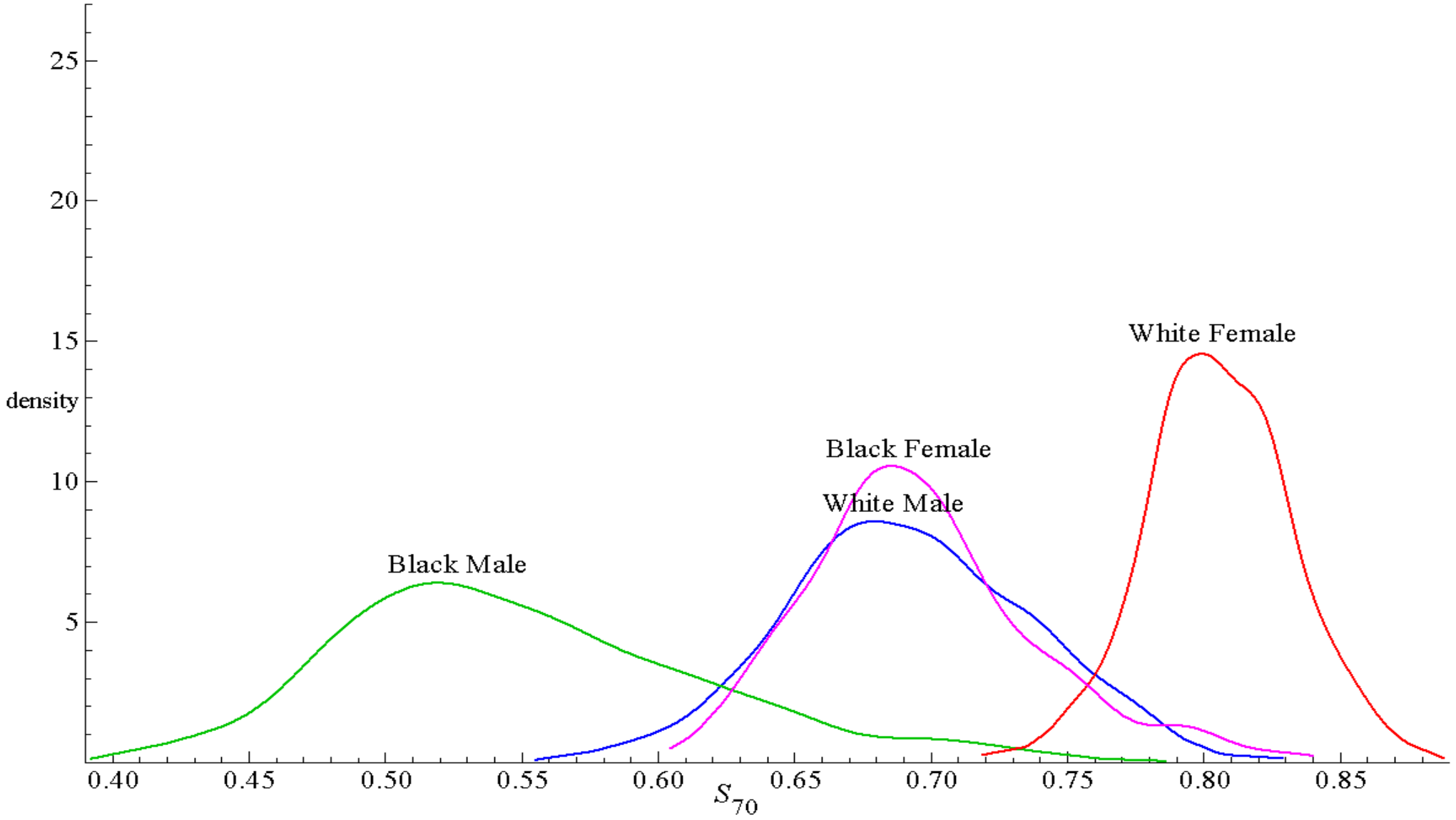
Frequency distribution *(kernel plot)* for S_{70}



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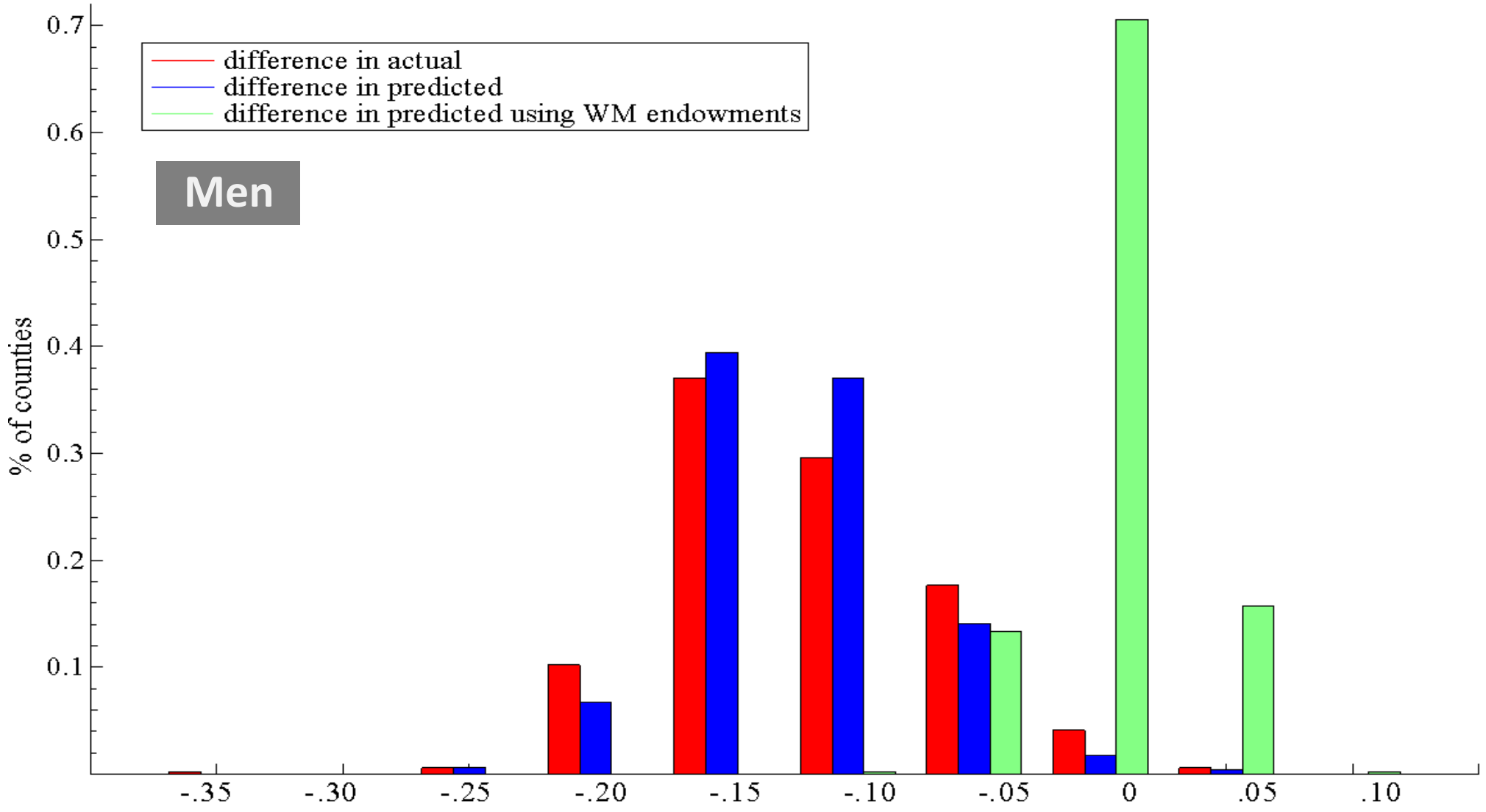
Percent of counties with actual & predicted race differences in S_{70}



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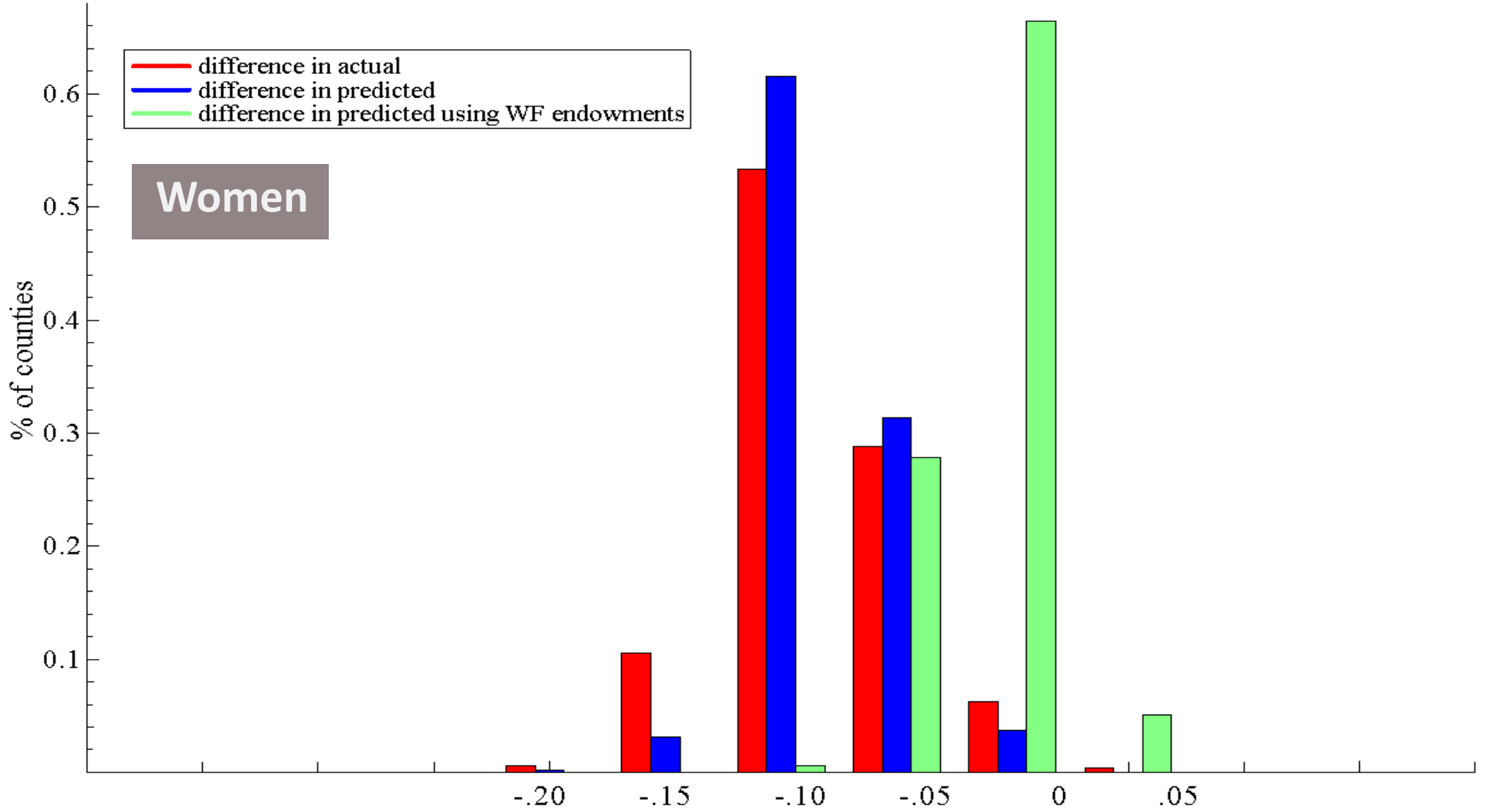
Percent counties with actual & predicted race differences in S_{70}



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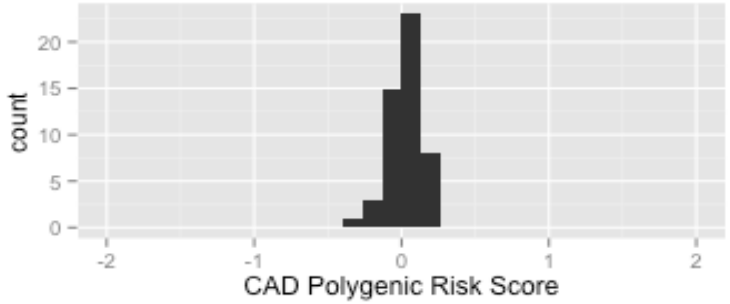

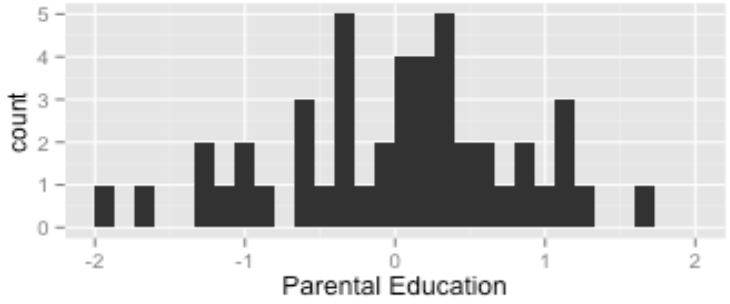

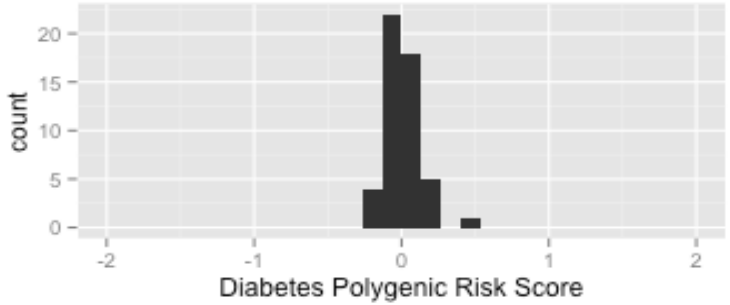

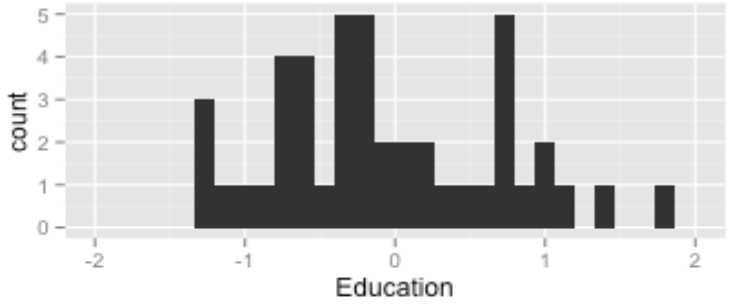

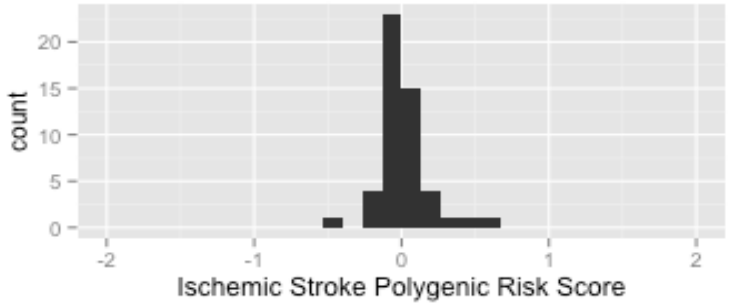

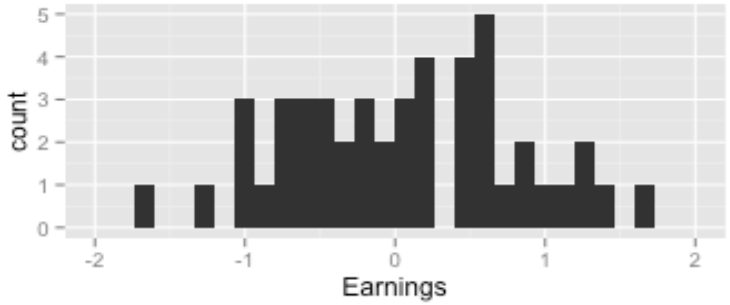

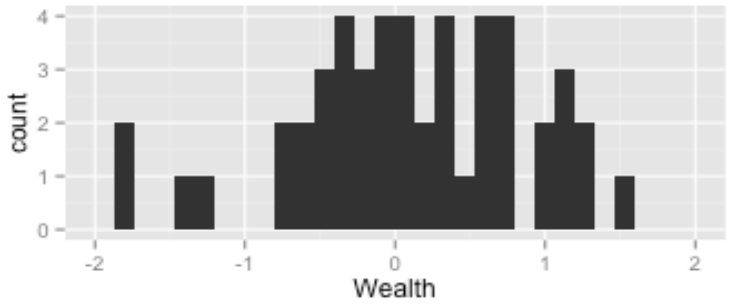

Risk distribution based on genetic and environmental factors

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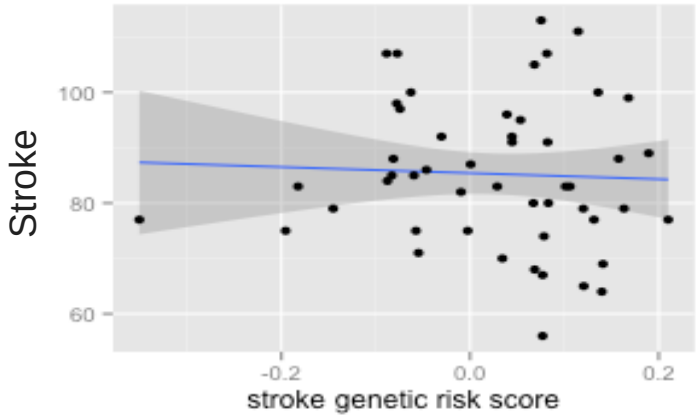

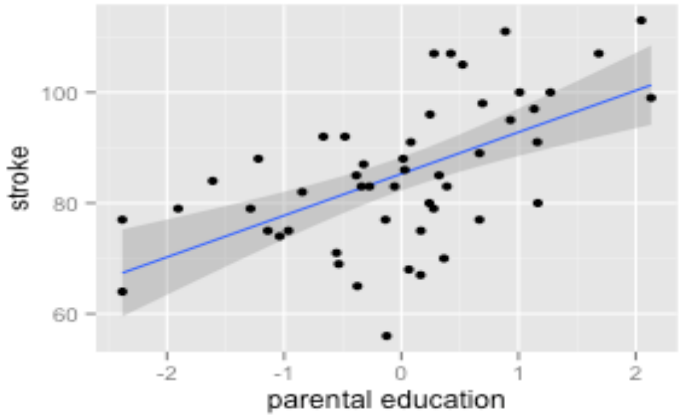

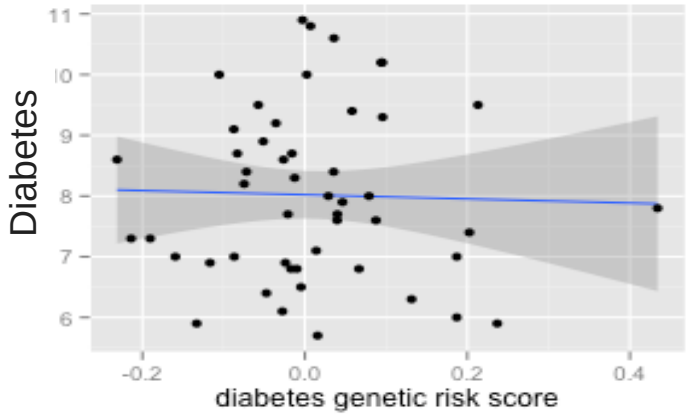

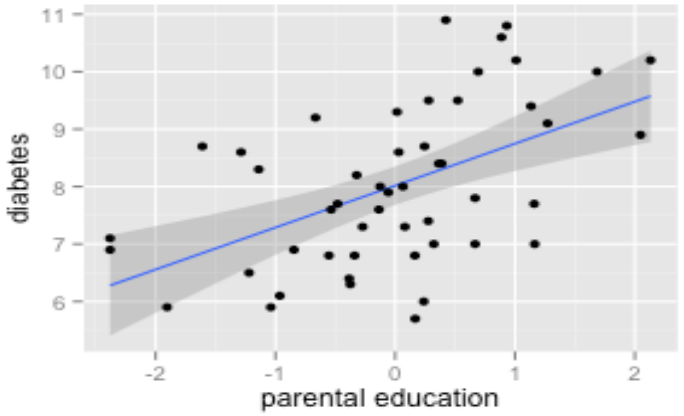

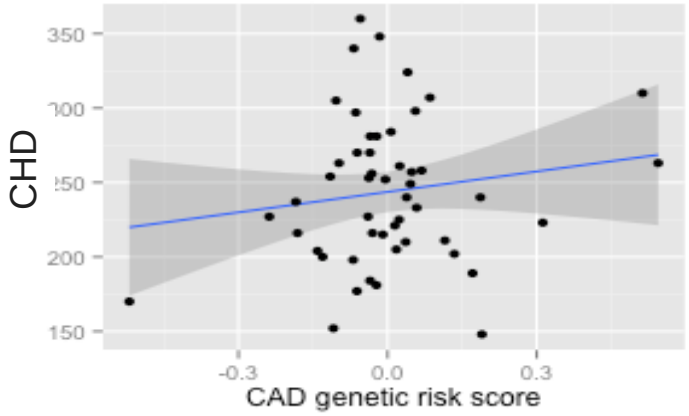

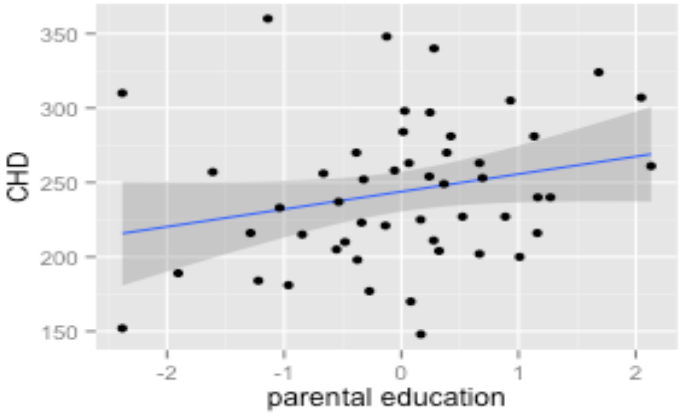

Risk association with genetic & environmental factors for:

- Stroke
- Diabetes
- CHD

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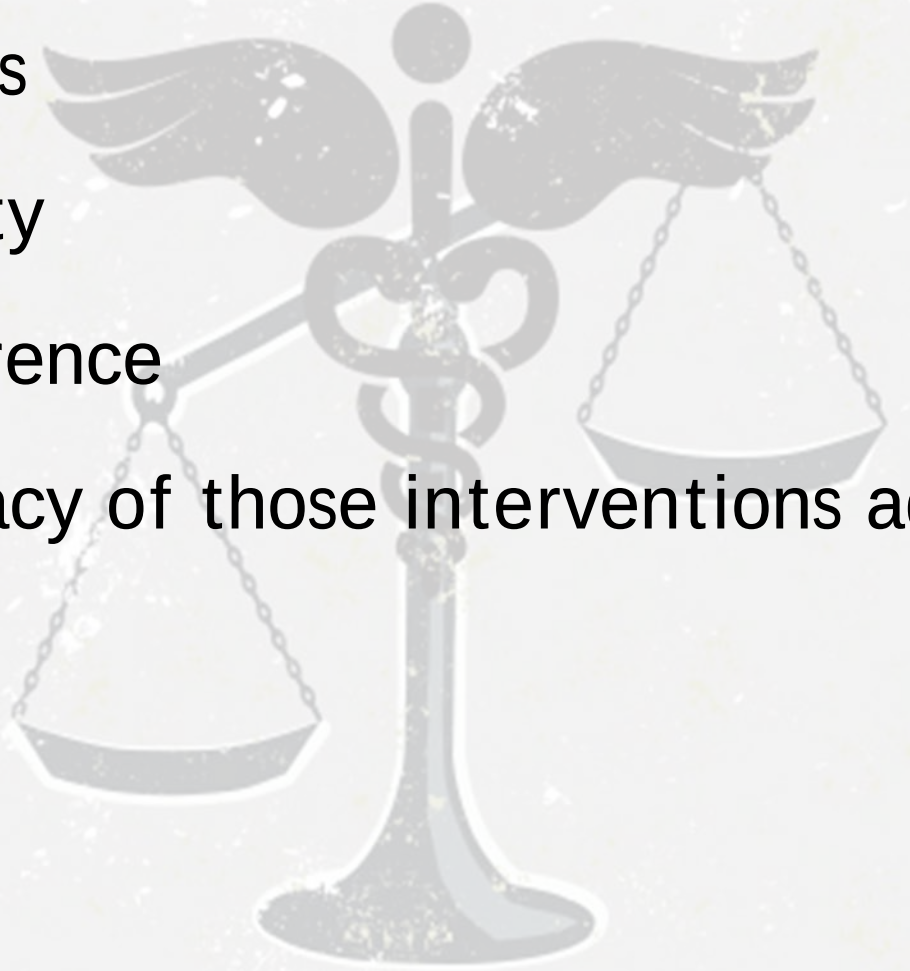
Evidence that healthcare disparities contribute

- Differential access
- Differential quality
- Differential adherence
- Differential efficacy of those interventions adhered to



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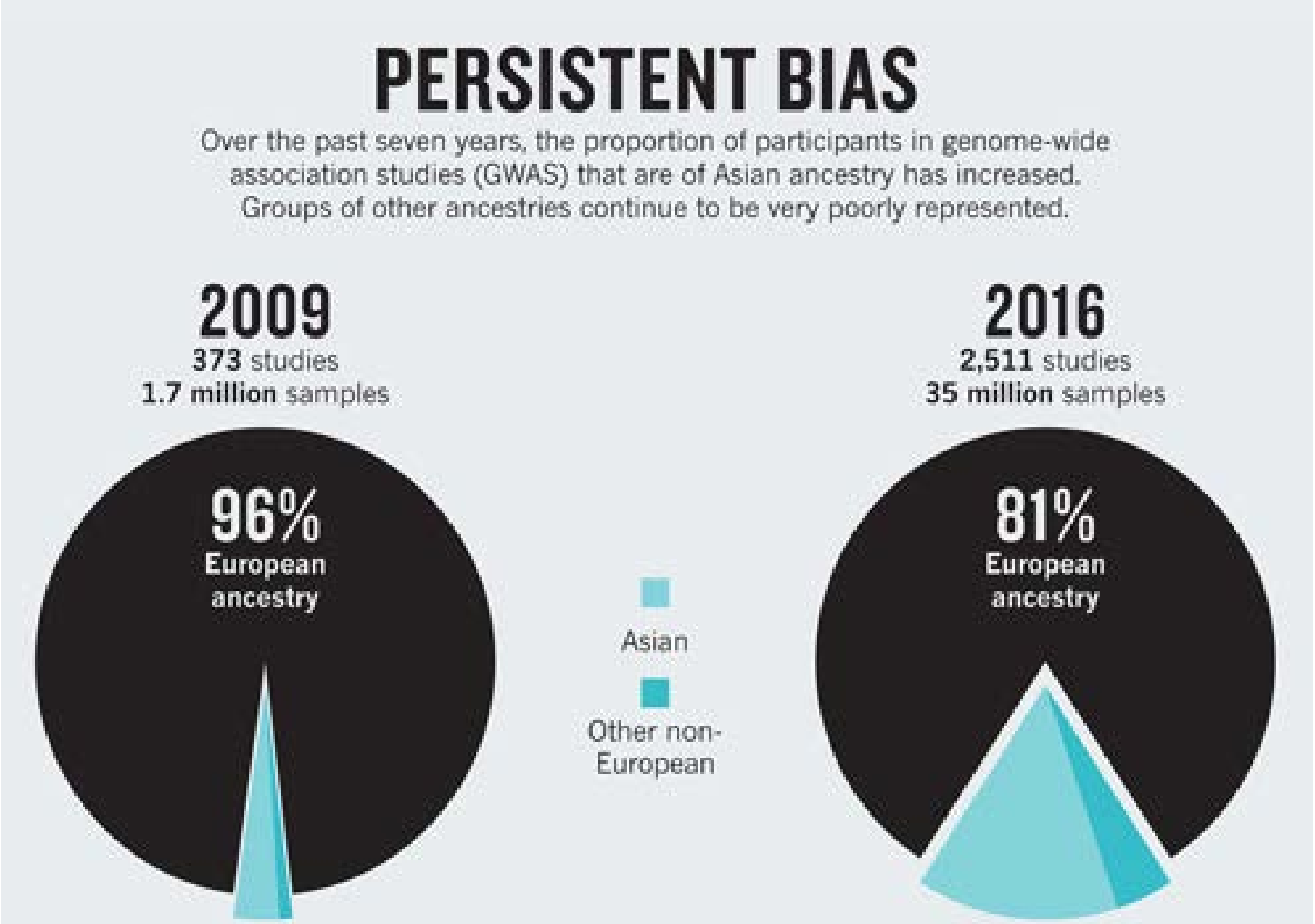
1. First things first
2. **Genome-Wide Association Studies (GWAS) are not too informative for racial minorities.**

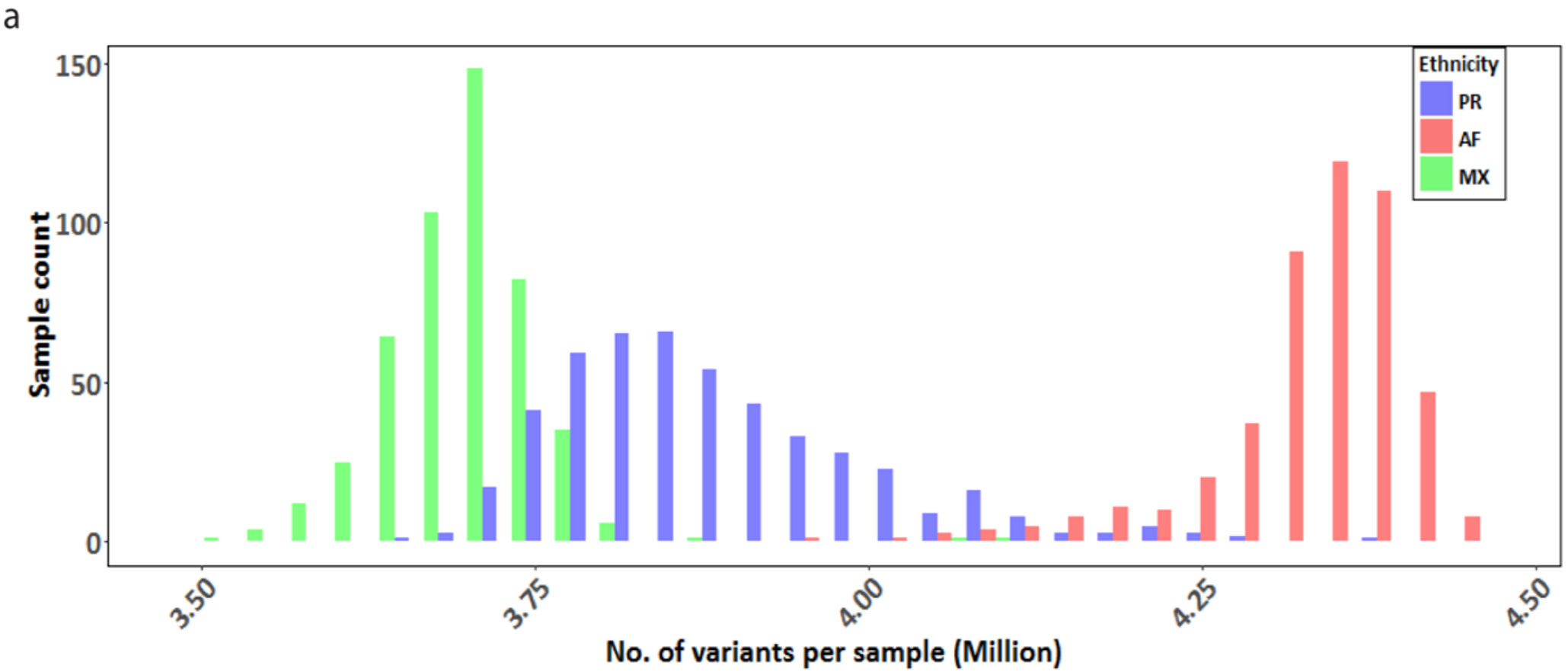
Reasons we shouldn’t go there

Diversity in Biomedical Research: Then and Now



Bustamante, Burchard, De La Vega, *Nature* 2011
Popejoy and Fullerton, *Nature* 2016

Populations Vary by “Variation”



4.1 – 5.3 million variants per sample

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Reasons we shouldn't go there

1. First things first
2. Genome-Wide Association Studies (GWAS) are not very informative, except for Caucasians
3. **Differential access and insurance coverage could result in *widening* of disparities.**

Differential cost and access

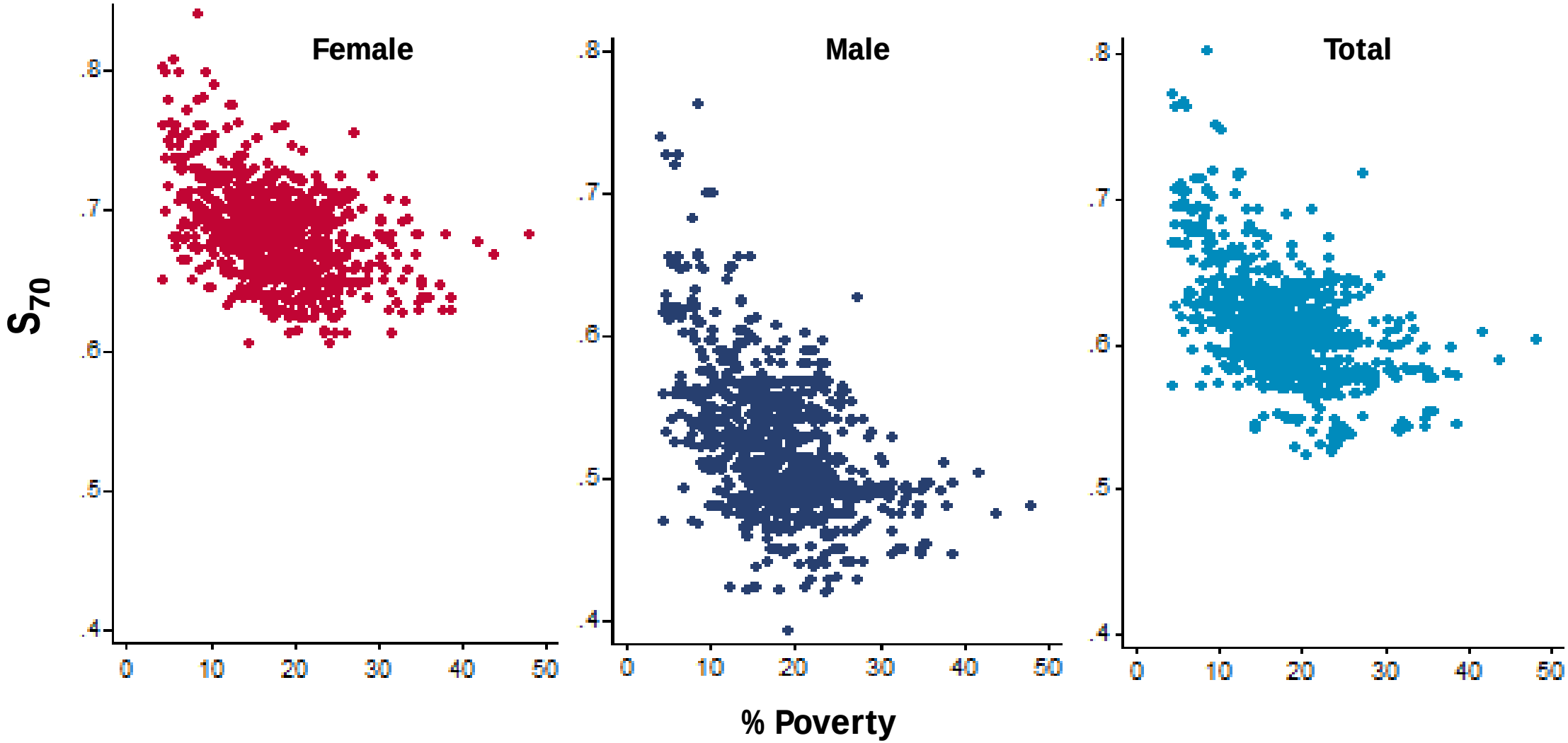
- Benefits of many advances—including those in gene-directed cancer meds—may be inaccessible to many due to cost of care and insurance differences
- There is evidence that many ethnic groups are less willing to accept genetic testing or guidance it confers

Should We Reconsider?

1. **Environmental influences driving disparities might be “gene-modulated”.**

Should We Reconsider?

Male, Female, and Total$_{S70}$ versus % Poverty *(Black Americans)*



2005-2010 CDC condensed mortality tables and US Census for 2005-2010 (American Community Survey) for US counties where black population is at least 5% *(N=833 out of 3,140)*

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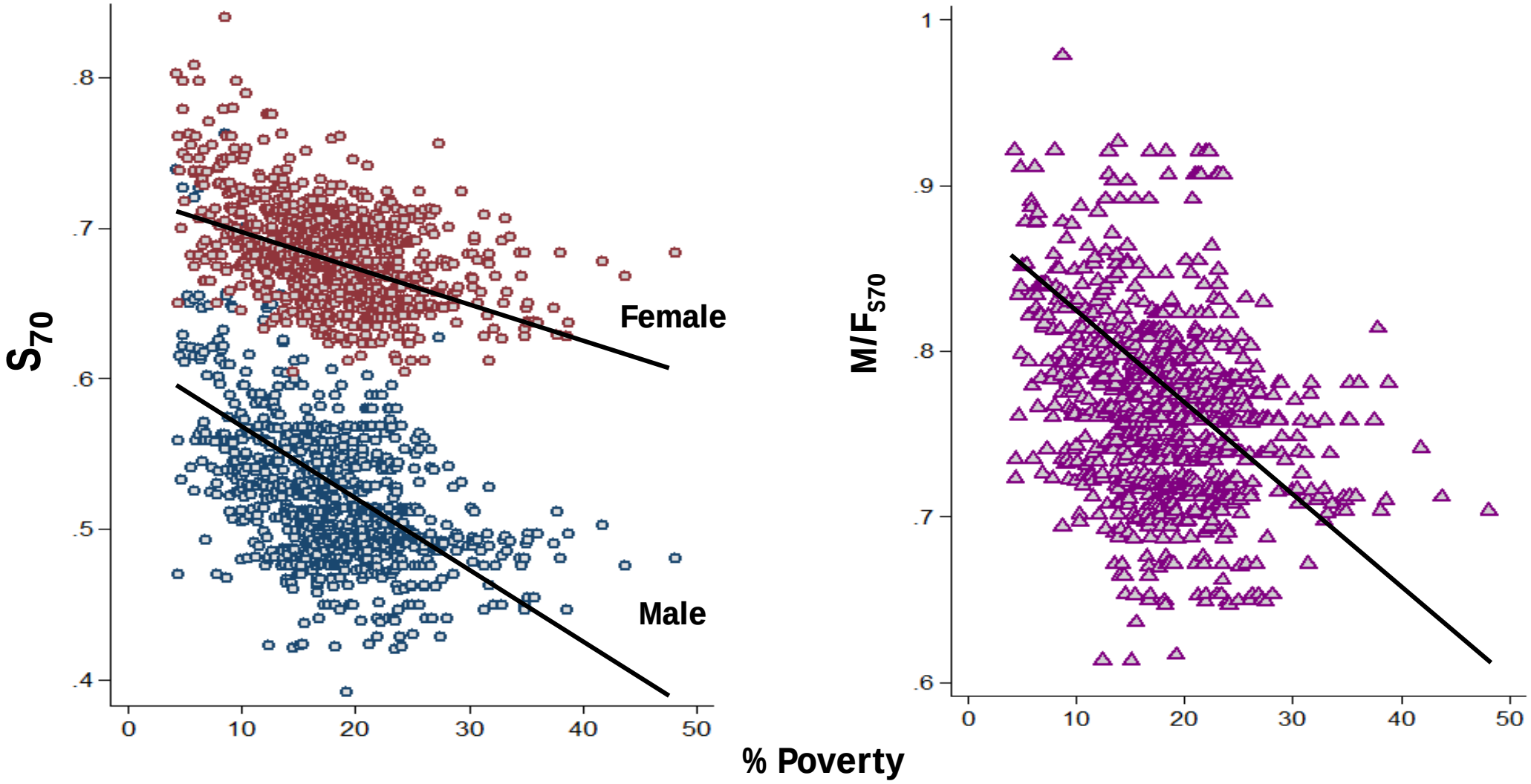
Male, Female, and M/F_{S70} vs % Poverty *(Black Americans)*



2005-2010 CDC condensed mortality tables and US Census for 2005-2010 (American Community Survey)for US counties where black population is at least 5% (N=833 out of 3,140) and linear fit is weighted by square root of county population

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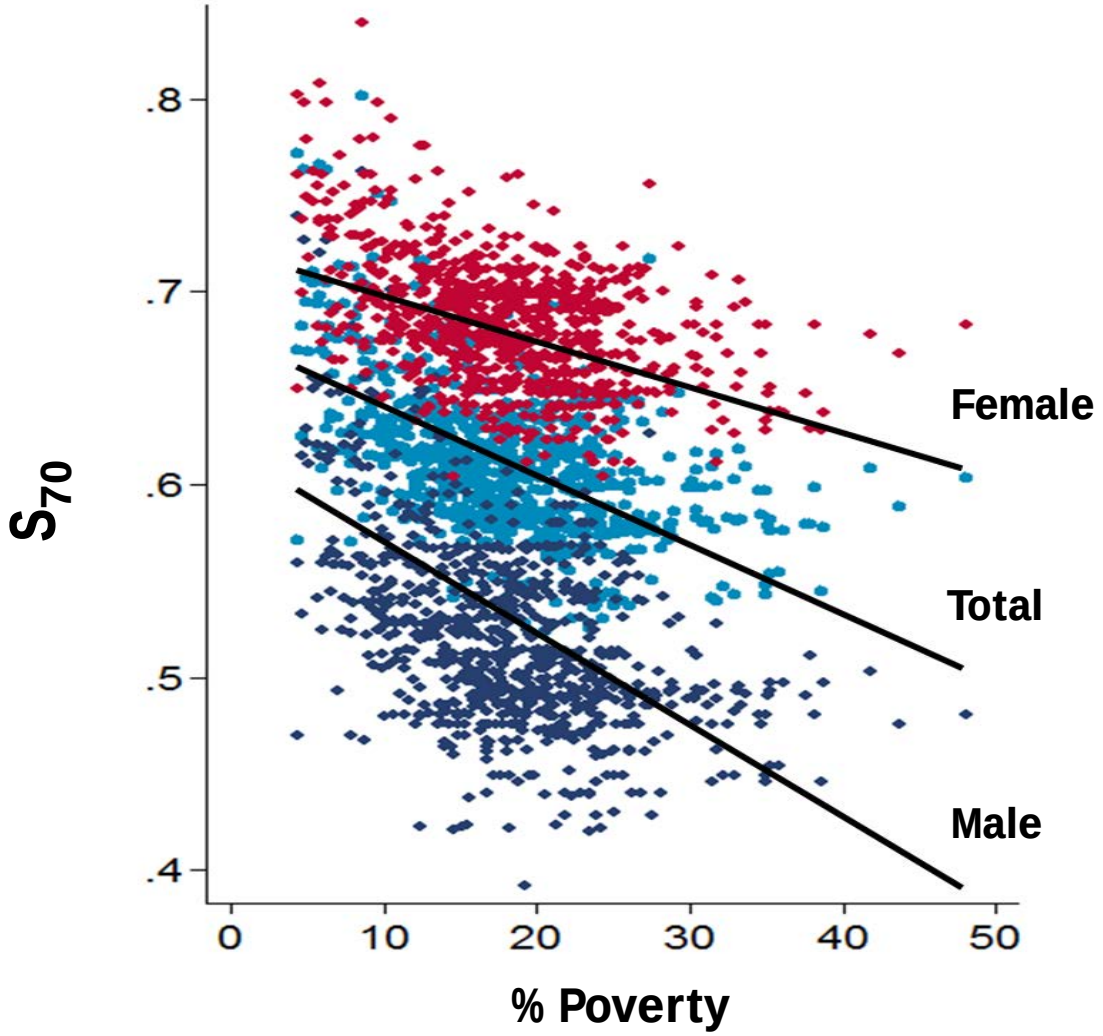
Male, Female, and Total$_{S70}$ versus % Poverty, with Linear Fit *(Black Americans)*



S_{70} Group	Slope for % Poverty *(Univariate Coefficient)*
Female	-0.0021
Male	-0.0040
Total	-0.0032

2005-10 CDC condensed mortality tables and US Census for 2005-10 (American Community Survey) for US counties where black population is at least 5% (N=833 out of 3,140) and linear fit is weighted by square root of county population. Removing county population wts has almost no impact on slopes (<3%).

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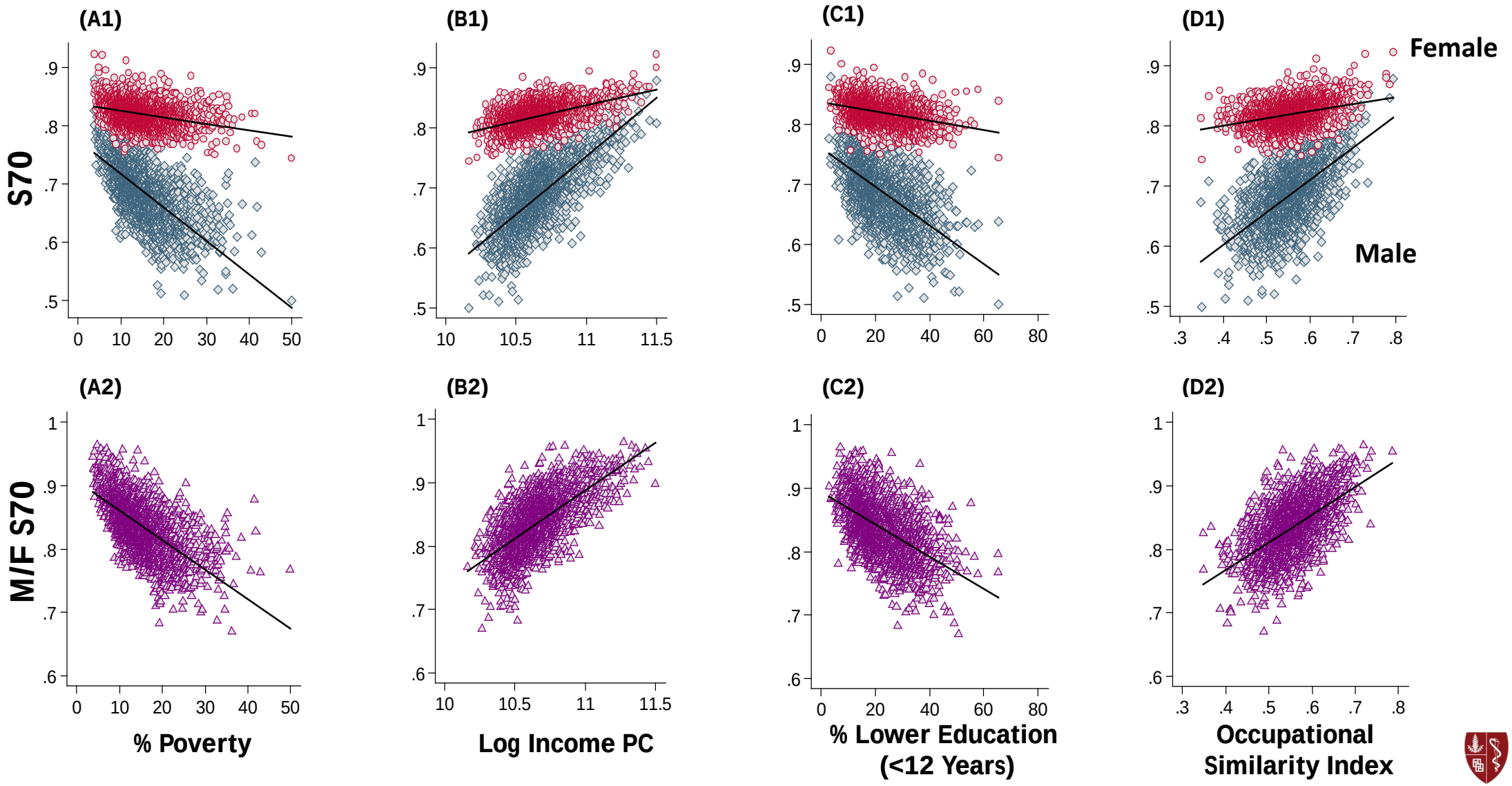
Male, Female, and M/F_{S70} versus Poverty, Log Income, Education, and Occupation



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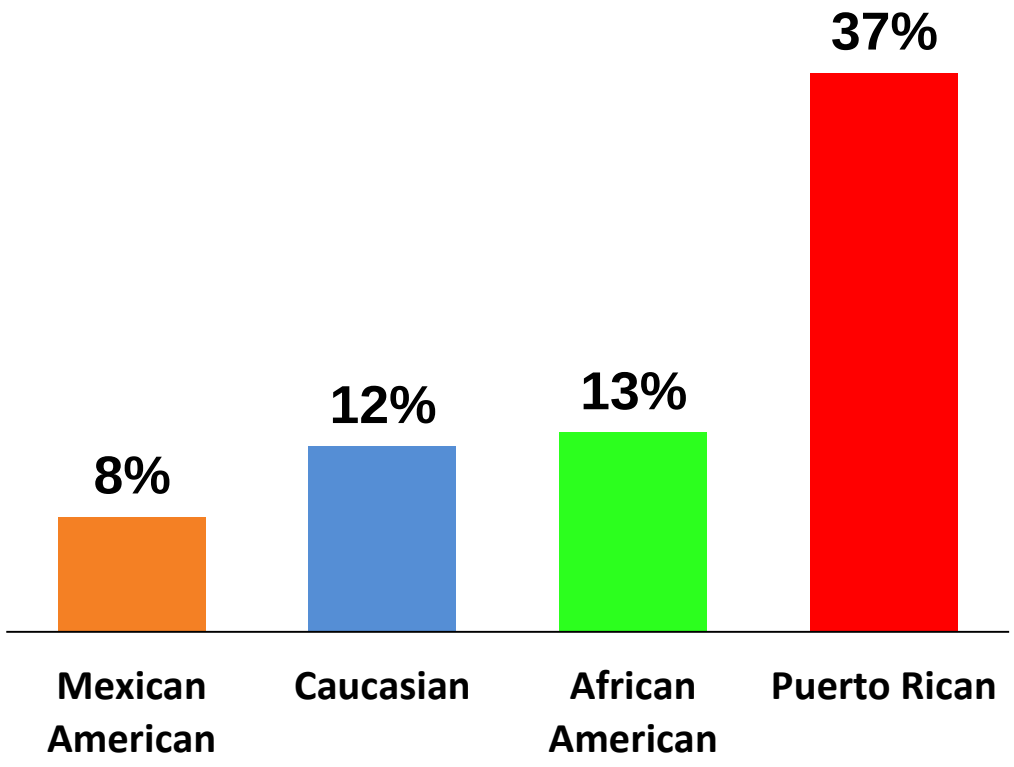
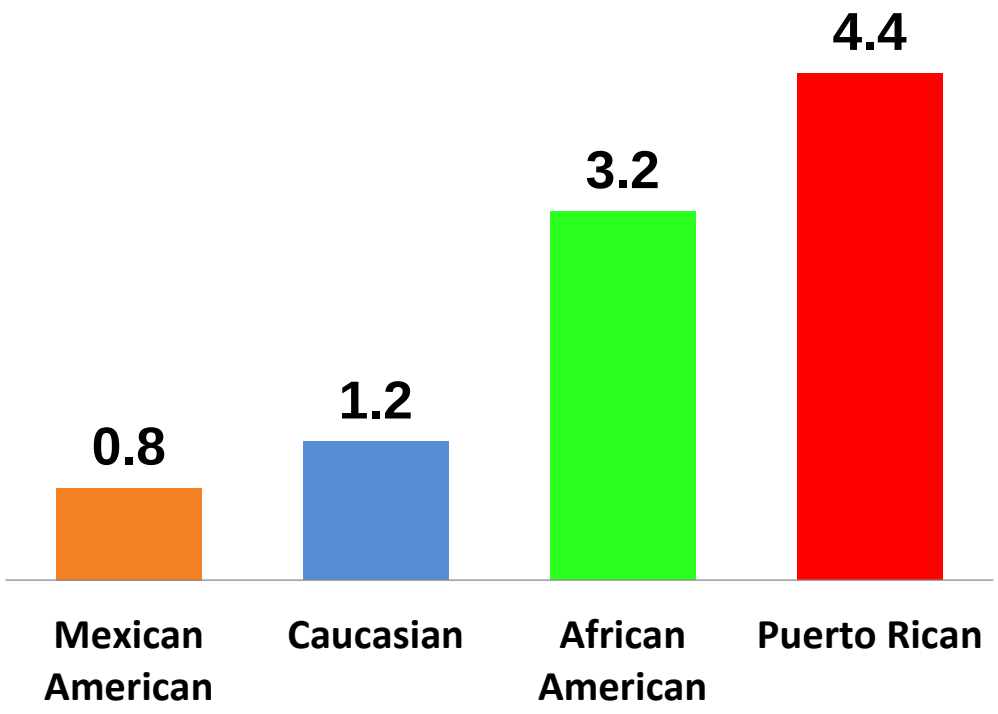
Asthma Health Disparity in the United States

Prevalence of Asthma



Mortality



The Hispanic Community Health Study/Study of Latinos (HCHS/SOL), NHLBI 2014
Barr et al., *AJRCCM* 2016
Akinbami L. CDC/NCHS

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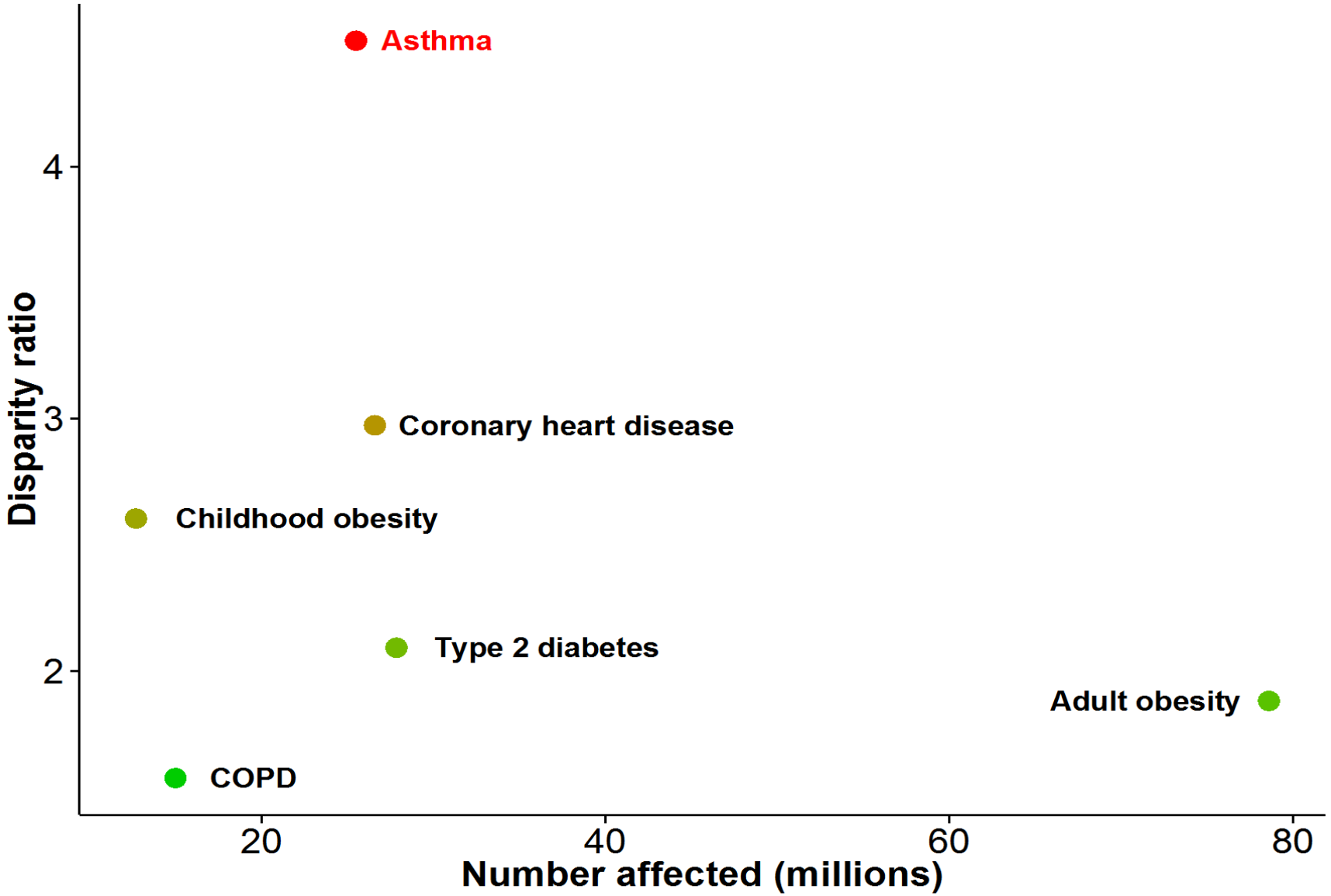

Asthma is the most disparate common disease.

Oh *et al*. Making Precision Medicine Socially Precise *AJRCCM* 2016

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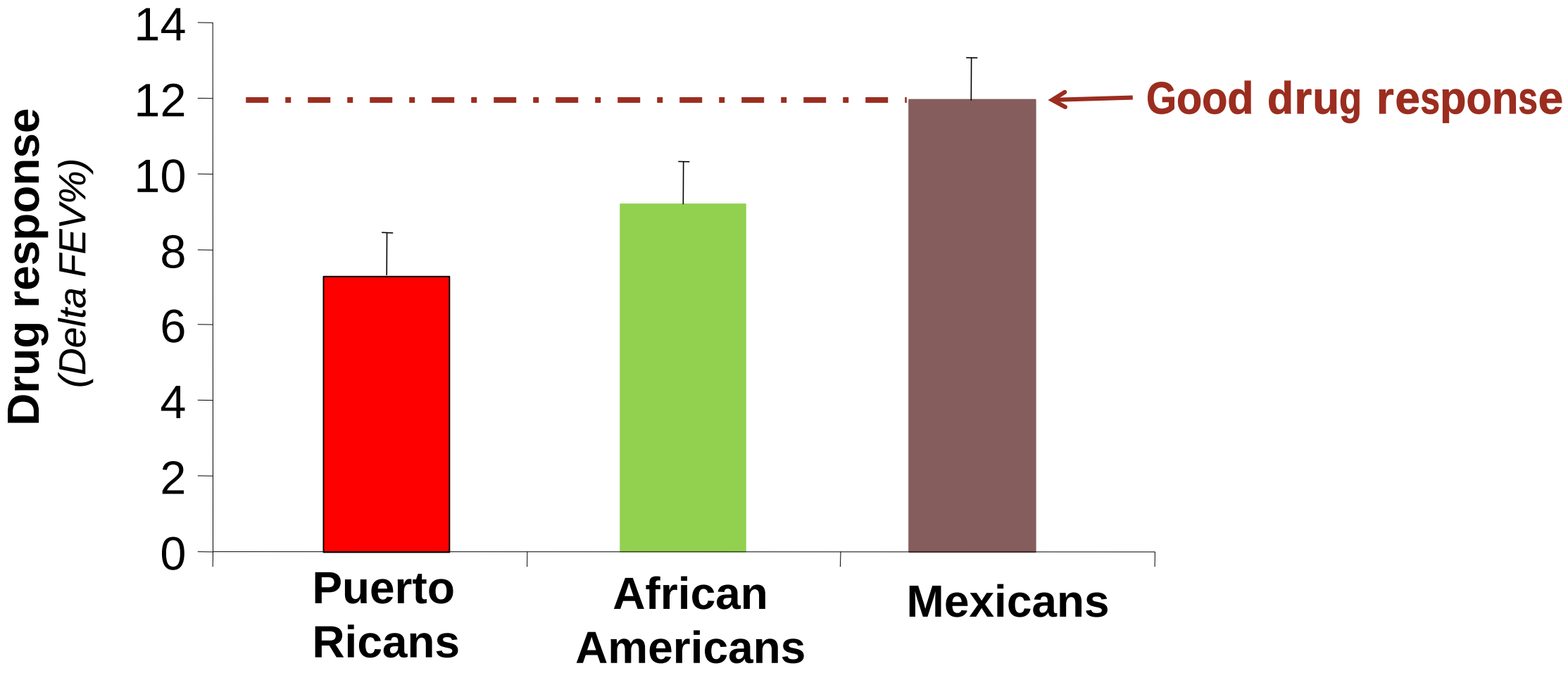
1. Environmental influences driving disparities might be “gene-modulated”.
2. **Pharmaco-genomic evidence suggests treatments should be tailored to race/gene interactions.**

Should We Reconsider?

Variation in ***drug response*** may contribute to disparities



Naqvi *et al.* (2007) *J. of Asthma*

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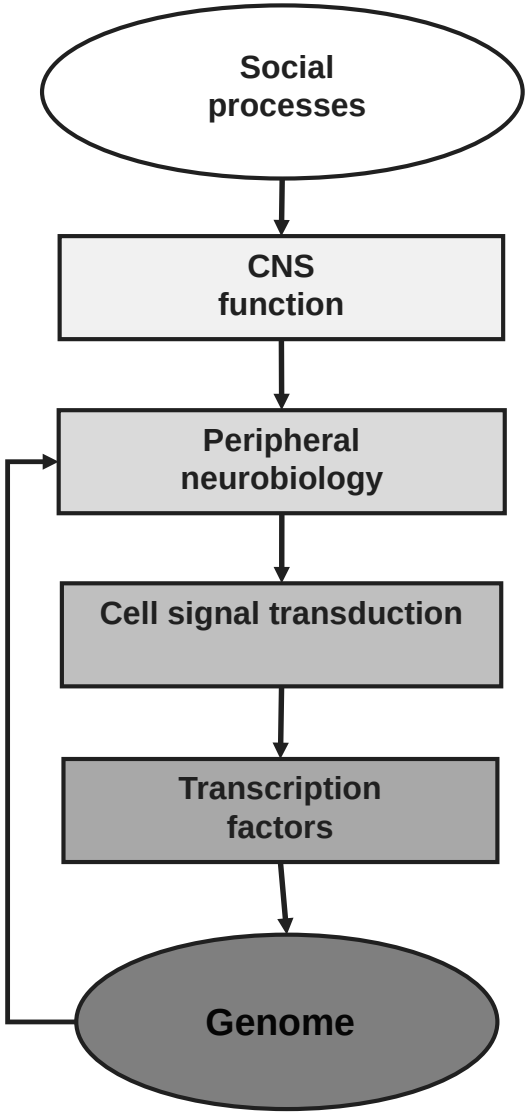
1. Environmental influences driving disparities might be “gene-modulated”.
2. Pharmaco-genomic evidence suggests treatments should be tailored to race/gene interactions.
3. **“Omics” studies may reveal pathways of therapeutic opportunity.**

Should We Reconsider?

Social signal transduction



Simple questions

1. Which gene modules are sensitive to social processes?
2. Which transcription control pathways mediate those effects?

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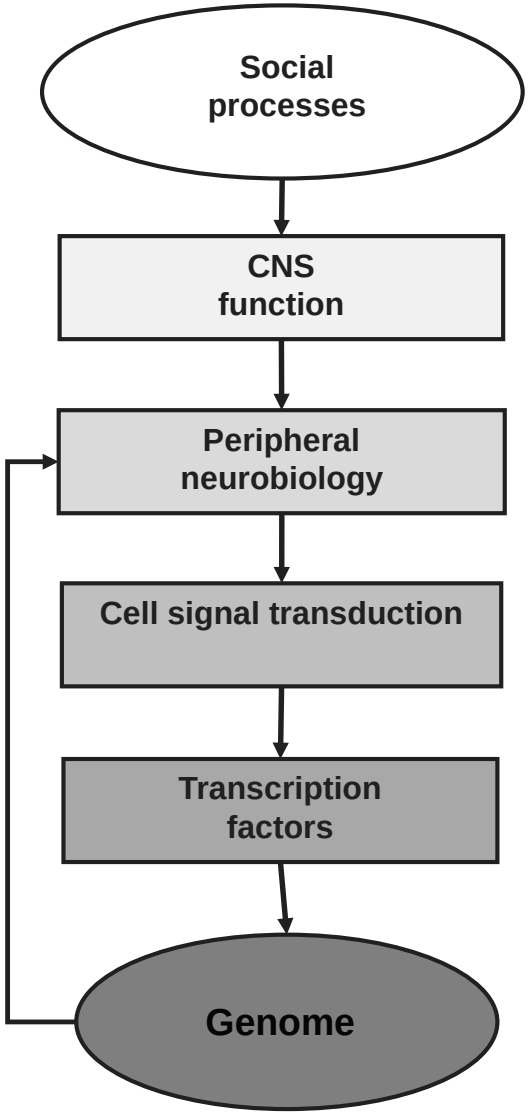
Social signal transduction



Simple questions

1. Which gene modules are sensitive to social processes?
2. Which transcription control pathways mediate those effects?

Not-so-simple questions

1. **Recursive persistence**
2. **Environmental embedding**

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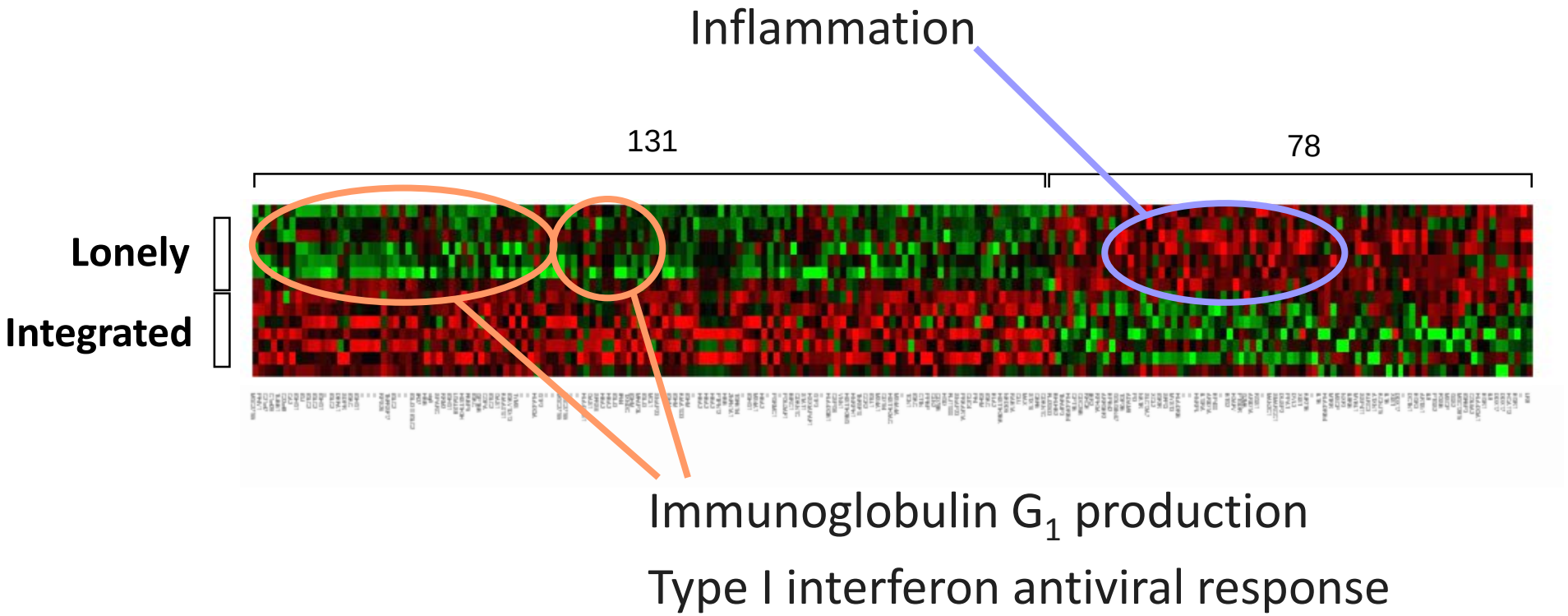
Example: **Impact of Social Isolation**



Cole et al. Social regulation of gene expression in human leukocytes, Genome Biology 2007

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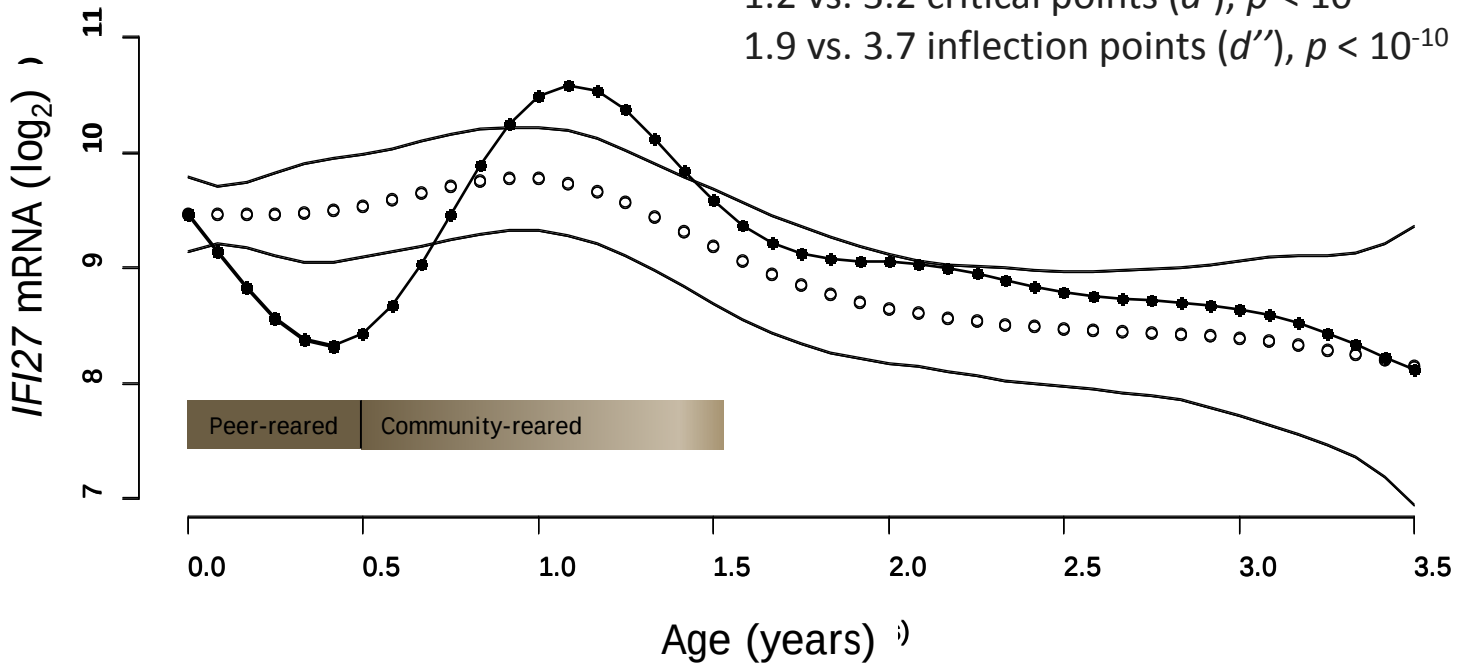
Instability/sensitivity:
1.2 vs. 3.2 critical points (*d'*), $p < 10^{-10}$
1.9 vs. 3.7 inflection points (*d''*), $p < 10^{-10}$



650 Recovered – 95%
31 Embedded – 5%

681 Diverged by mo. 6

Example: Genomic resilience to early adversity?

Suomi et al. unpublished 2016

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Stanford Precision Health for Ethnic and Racial Equity

Projects Exploring Opportunity in Omics Profiles

Mark Cullen, MD
Yvonne Maldonado, MD

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Bio-Repository for American Indian Capacity, Education, Law, Economics and Technology (**BRAICELET**)

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Project 1: BRAICELET Aims

1. Establish an **American Indian Biobank** with BRAICELET (Bio-Repository for American Indian Capacity, Education, Law, Economics and Technology).
    - Create a Lakota Health Community Advisory Group that will optimize educational methods and promote cultural exchange
    - Establish Lakota Biobank infrastructure and engage, educate and train tribal community members as biobank personnel
    - Endorse longterm sustainability through strategic and business management and early pursuit of diverse funding approaches.

2. Establish a **pilot for first set of biobank material** through the collection of 200 additional participants for SAIL (Studies of AutoImmune Illnesses with the Lakota).

3. Develop, implement and evaluate **Science Health Education and Literacy** among Lakota as part of BRAICELET.

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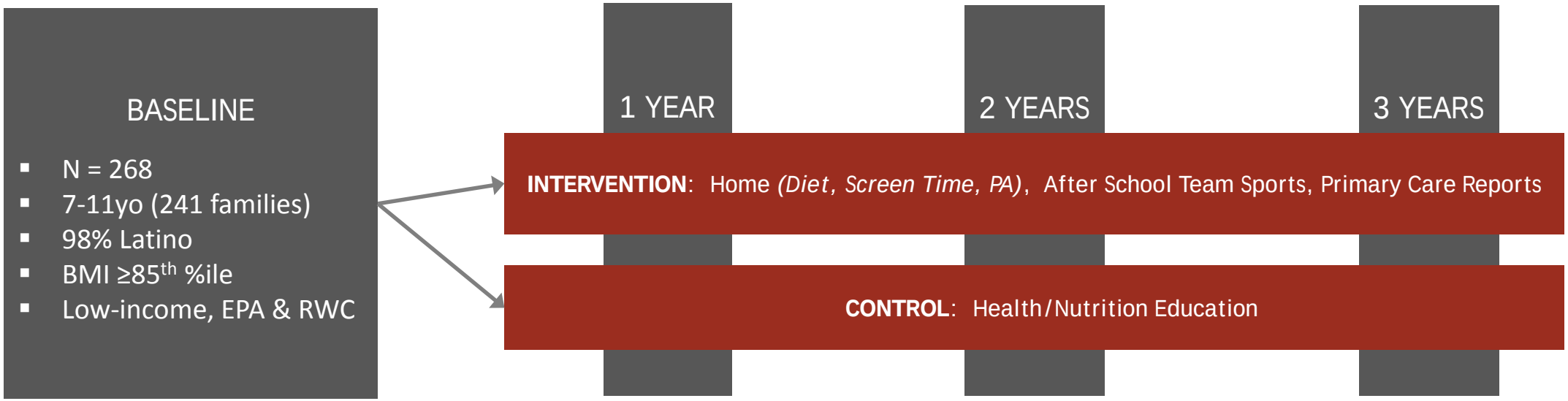
Project 2: **Why do Some Obese Latino Adolescents Respond?**



Primary outcome: BMI trajectory over 3 years.

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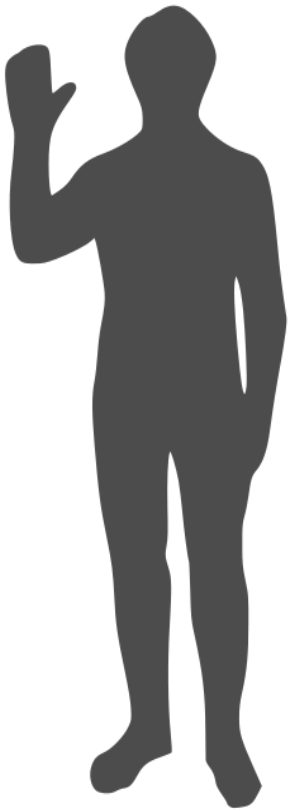

Omics Measurements

Biosensors

- Genome
- Epigenome
- Transcriptome
- Proteome
- Cytokines
- Metabolome
- Lipidomics
- Autoantibody-ome
- Microbiome *(Gut, Urine, Nasal, Tongue, Skin)*
- Medical Tests and Questionnaires

Billions of Measurements!

Personal Omics Profiling

Year 1 — *Viral infection* — Year 2

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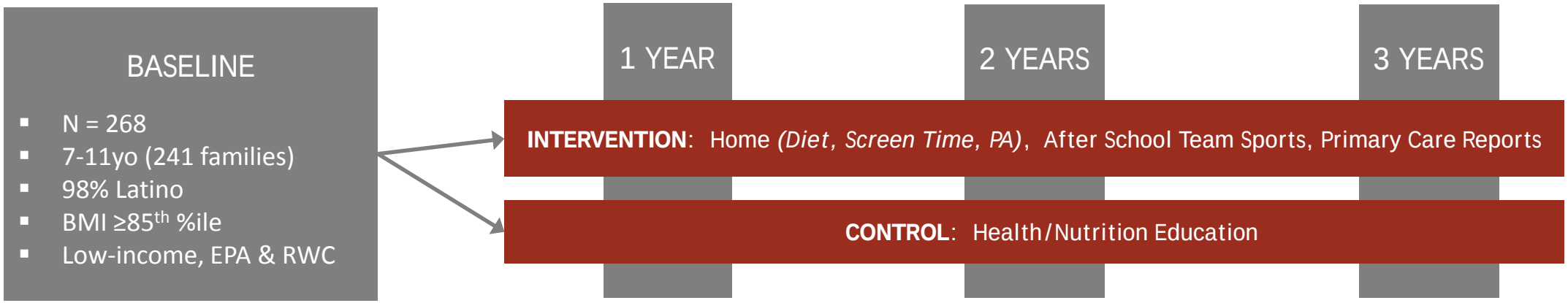
Project 2: **Why do Some Obese Latino Adolescents Respond?**



Anthropometrics/ Physical	Accelerometry	Self-Reported Behavioral	Self-Reported Demographic & Psychosocial	Biological Measures	Multi-Omics
Height, Weight, BMI Waist circumference Triceps skinfold BP Resting HR Parent Ht, Wt, WC	Actigraph GT3X+ (triaxial) Waist 24h/d x 4-7+ days (min. 3 week days + 1 weekend day) Recorded @ 40Hz	3 x 24-hour dietary recalls Screen time; other sedentary behaviors Sleep times & symptoms Parent behaviors	Demographics, Household income, Parental Education, Acculturation, etc. Sexual maturation Weight concerns Depressive Sxs	Fasting Total Cholesterol, HDL-C, TG, LDL-C Fasting Glucose, Insulin, HgA1c hsCRP ALT	Genomics Transcriptomics Epigenomics Metabolomics Lipidomics Oral Microbiomics

Primary outcome: BMI trajectory over 3 years.

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Project 2: Integrated Personal Omics Profile (iPOP) Aims

1. Assess **associations of iPOP markers with measures of adiposity and diabetes risk** at baseline.

2. Assess the associations of **baseline and 3-year longitudinal** iPOP markers with changes in measures of adiposity and diabetes risk.

3. Test the additional **predictive value of iPOP signatures** for changes in adiposity and diabetes risk over 3-years when combined with cognitive, behavioral, socio-demographic and environmental measures, across all participants and as possible **moderators and mediators of intervention effects**.

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Project 3: Communicating Genetics Information Aims

1. Assess **confidence of clinicians communicating** genetic test results and genetic risk information on breast cancer to diverse patients.
2. Audiotape the information that clinicians communicate during the clinical encounter in delivering genetic test results and assess whether the information provided to patients **differs by patient ethnicity, health literacy, and study site**.
3. Assess the correspondence between the **recommendations** of doctors and the **subsequent actions** of patients over and whether this correspondence differs by ethnicity, health literacy, and study sites.
4. Identify if/when patients **share their personal genetic risk information** with family member(s) and to what extent this process is influenced by ethnicity, health literacy, and study sites.

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Thank you!

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