Racial/Ethnic Differences in Reproductive Aging and Onset of Cardio-metabolic Risk in the Study of Women's Health Across the Nation (SWAN)

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CAMBRIDGE DIABETES SEMINAR

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SCHOOL OF PUBLIC HEALTH
EPIDEMIOLOGY
UNIVERSITY OF MICHIGAN

MICHIGAN DIABETES RESEARCH CENTER

Racial/Ethnic Differences in Lifespan

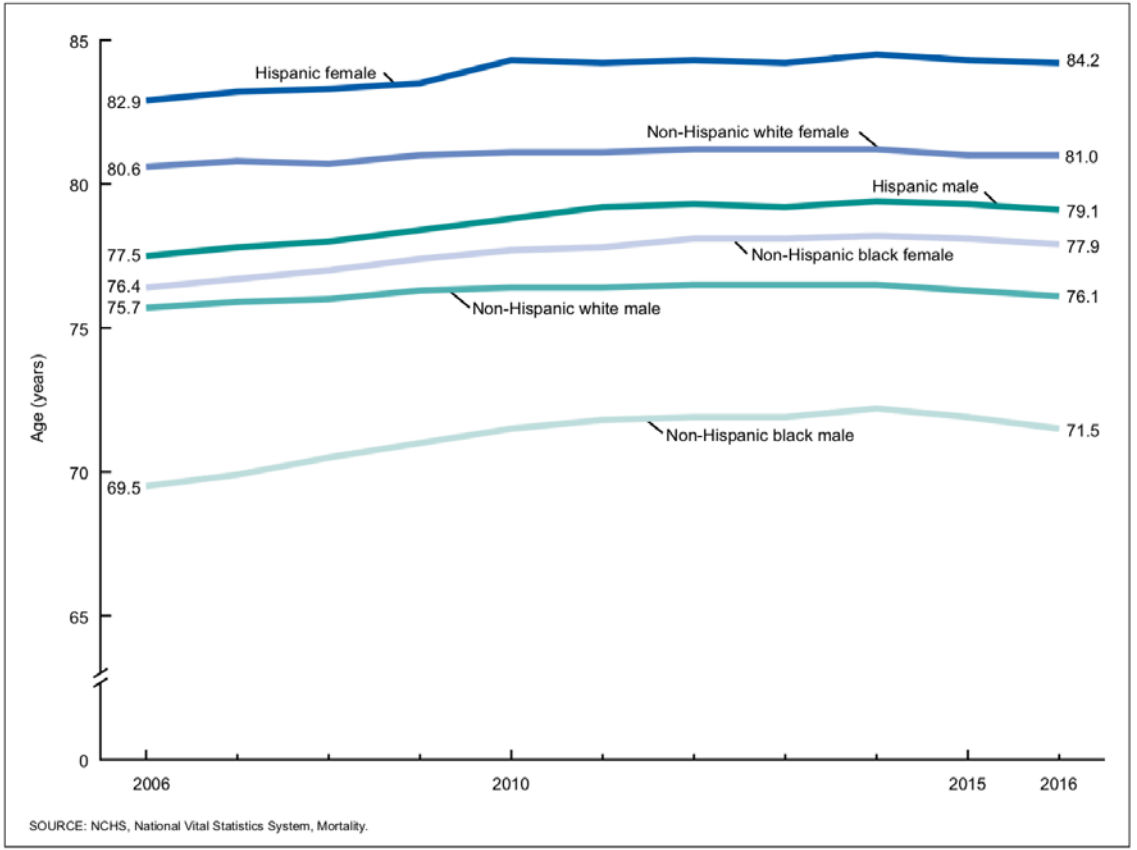

Figure 5. Life expectancy, by race and Hispanic origin and sex: United States, 2006–2016

Xu, Jiaquan, Sherry L Murphy, Kenneth D Kochanek, Brigham Bastian, and Elizabeth Arias. 2018. "National Vital Statistics Reports Volume 67, Number 5 July 26, 2018, Deaths: Final Data for 2016." *National Vital Statistics Reports.* Vol. 67. https://www.cdc.gov/.

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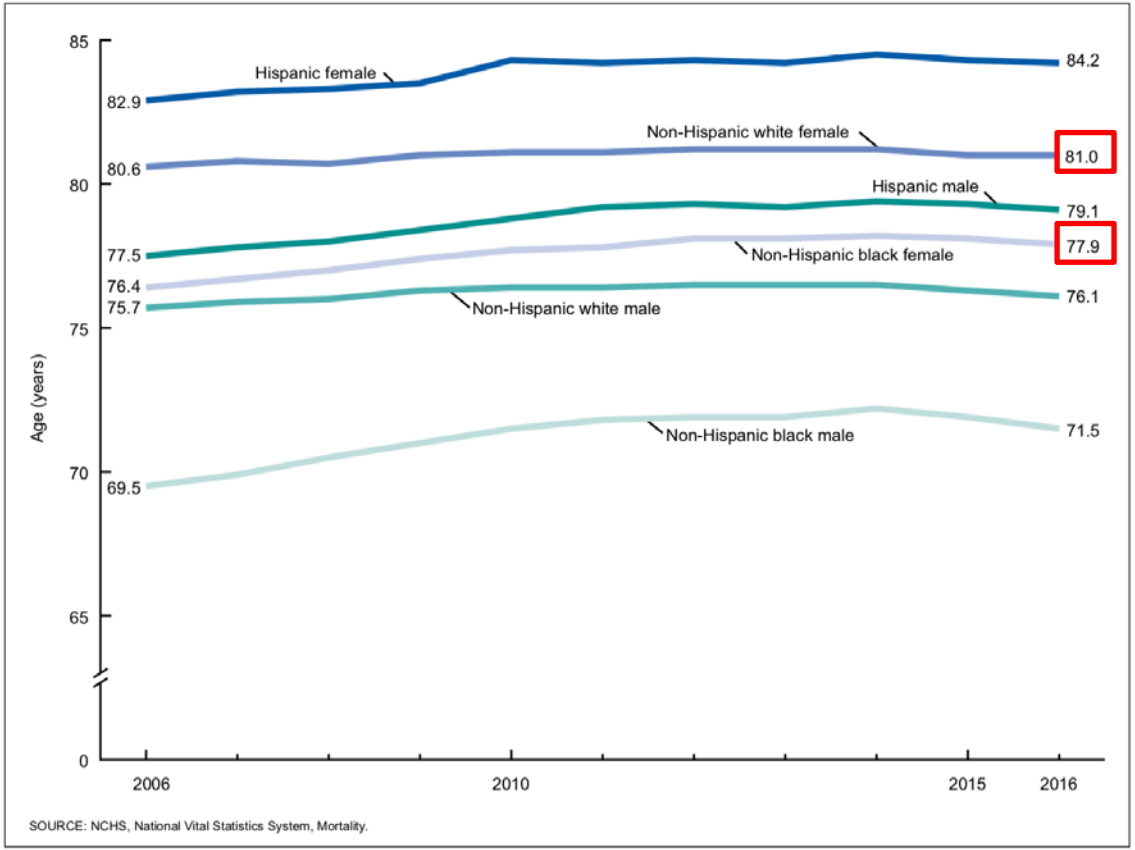

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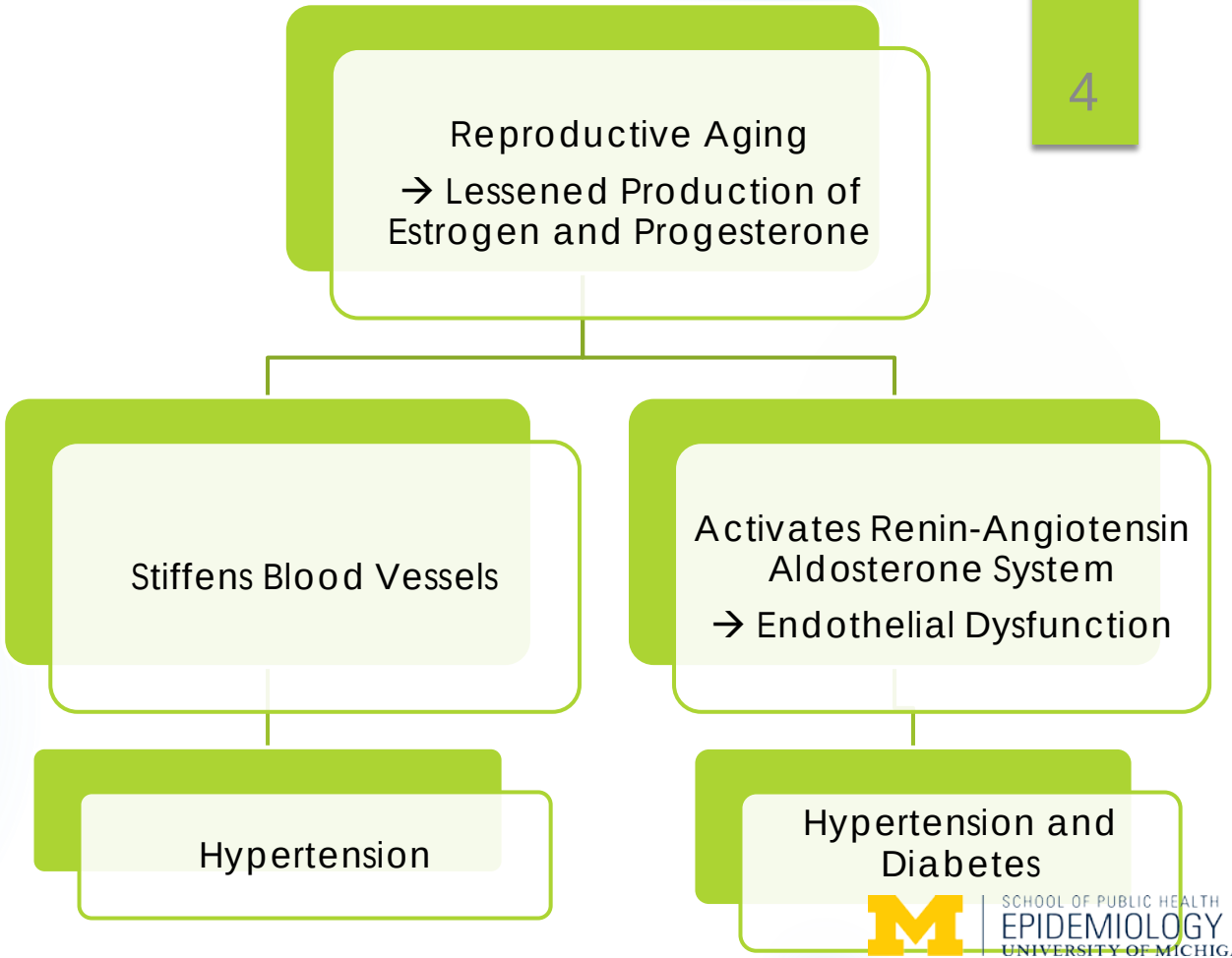
The Role of Reproductive Aging



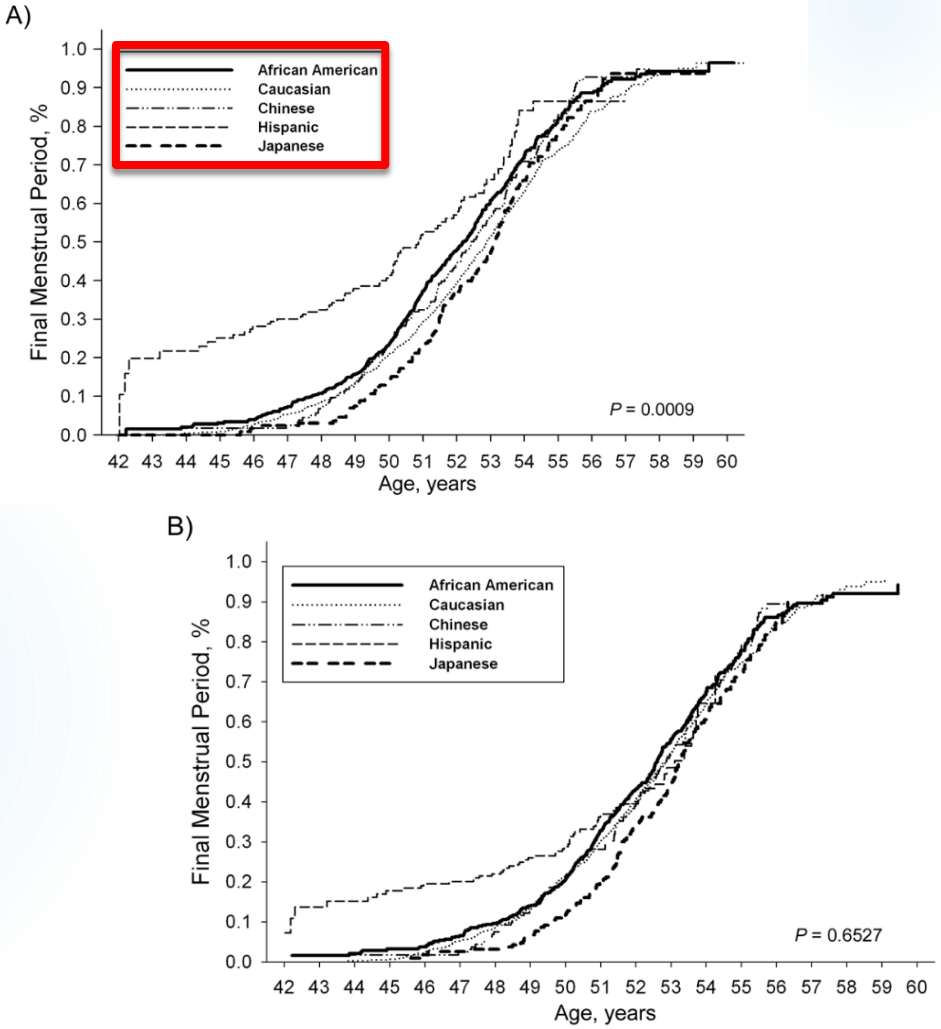
Mendelsohn ME, Karas RH. The Protective Effects of Estrogen on the Cardiovascular System. Epstein FH, ed. *N Engl J Med*. 1999;340(23):1801-1811. doi:10.1056/NEJM199906103402306

Racial Differences in FMP in SWAN

Gold et al., 2012

Results

- African American = **52.17** (52.59)
- Caucasian = **52.88** (52.85)
- Chinese = **52.41** (52.86)
- Hispanic = **50.86** (53.10)
- Japanese = **53.14** (53.24)



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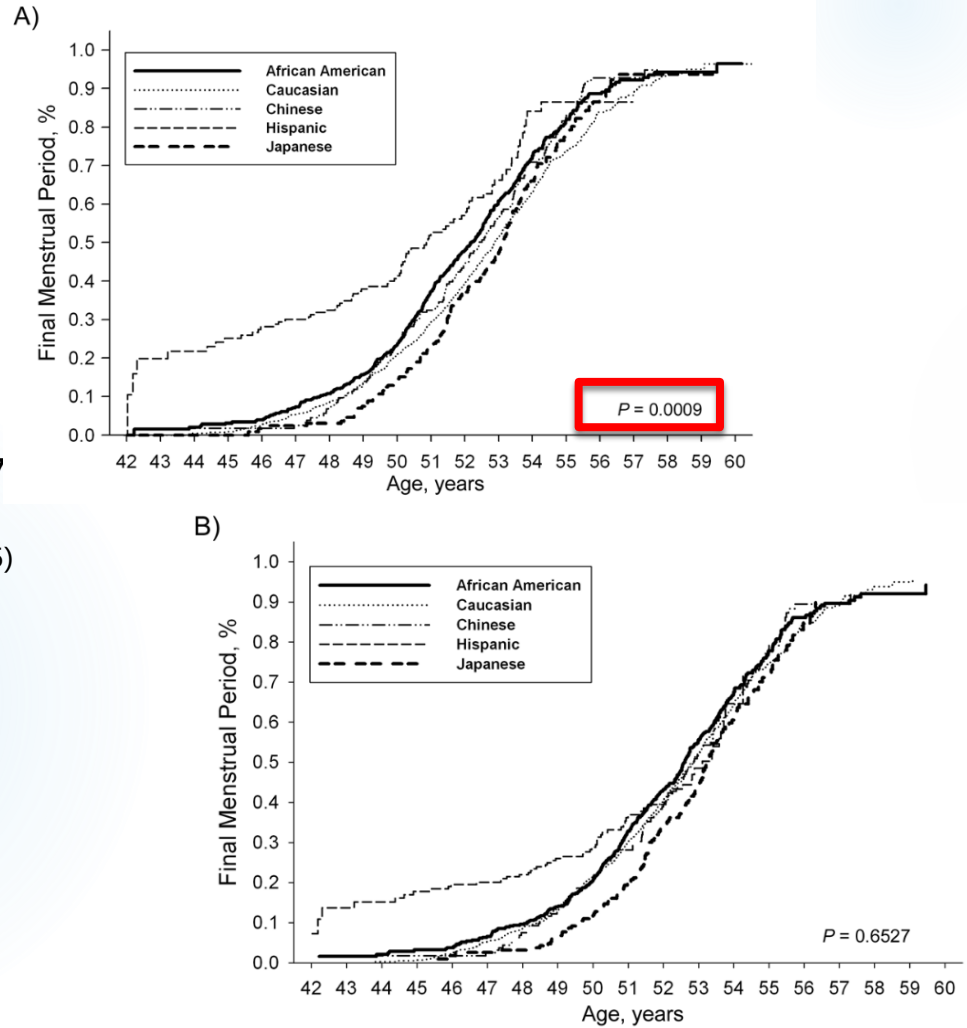

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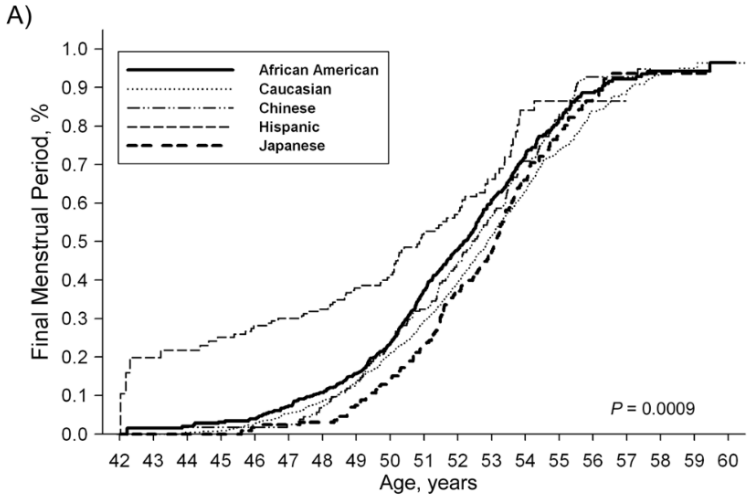

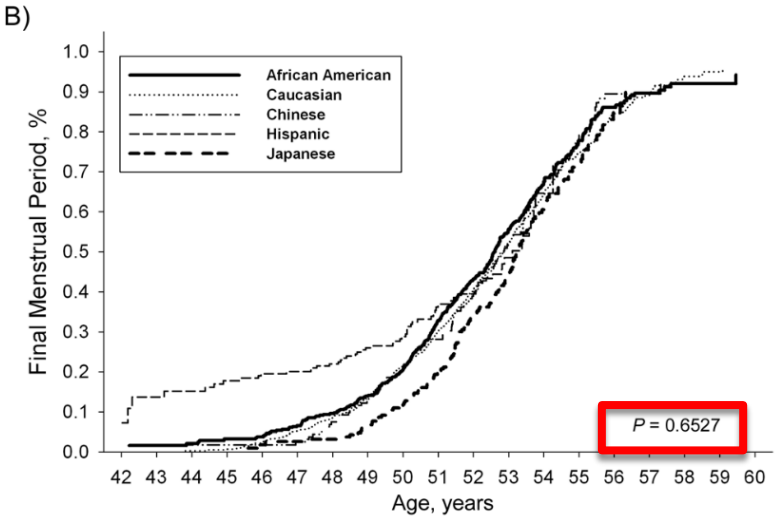

Aim 1

Develop a statistical approach to evaluate the impact of selection bias on race/ethnic specific differences in reproductive aging.

Selection Into the Cohort in 1996:	Total	Black	White	Japanese	Chinese	Hispanic
% Included	57.7	52.6	57.2	70.5	74.2	59.9
% Excluded (Left Truncated)	42.3	47.4	42.8	29.5	25.8	40.1
% Excluded due to -						
Post-Menopausal	14.3	12.7	14.7	10.9	11.7	18.5
Surgical Ammenorhea	20.4	31.3	17.4	9.9	5.8	17.4
Current Hormone Use	7.6	3.4	10.7	8.7	8.3	4.2
Selection Out of the Cohort by 2016:						
% Retained	57.6	52.4	60.1	66.9	72.4	39.2
% Lost to Follow Up (Right Censored)	42.4	47.7	39.9	33.1	27.6	60.8
% Loss to follow up due to -						
Lost contact or Hormone Use	36.7	39.9	34.3	29.5	24.0	57.7
Surgical Ammenorhea	5.7	7.7	5.6	3.6	3.6	3.2

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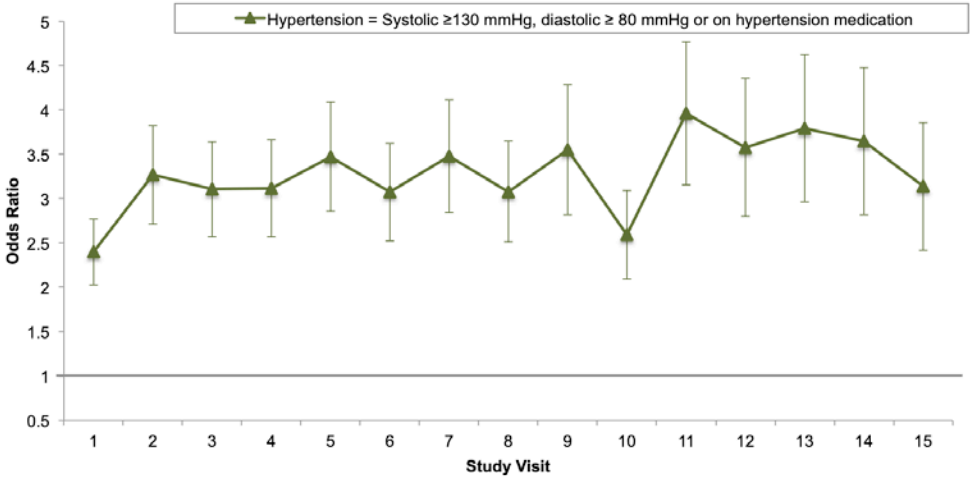
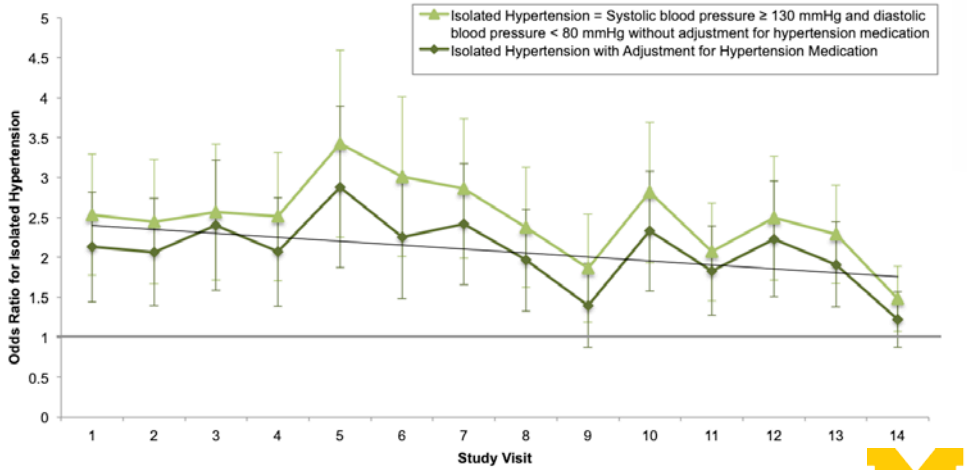
1. Estimate racial/ethnic differences in the timing of onset of cardio-metabolic risk factors (**hypertension, isolated systolic hypertension,** insulin resistance and diabetes)
2. Assess whether racial/ethnic differences in cardio-metabolic risk are more pronounced before or after the FMP





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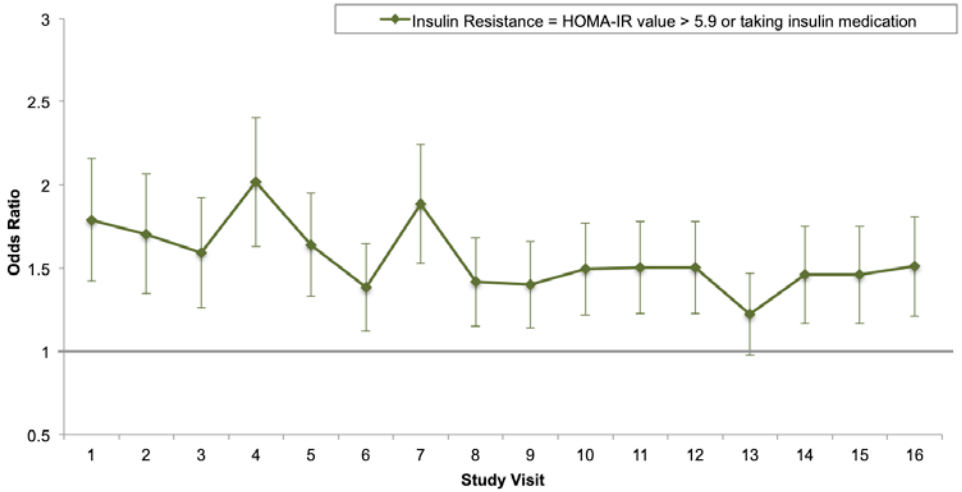

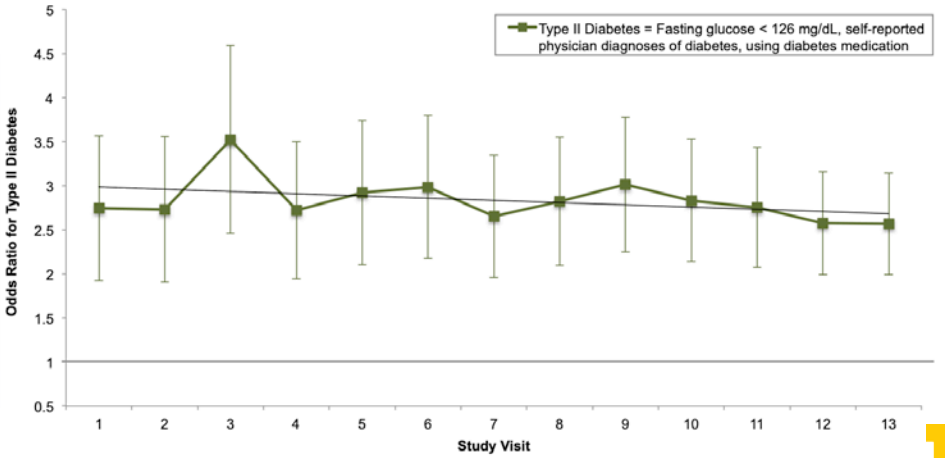

Thank you!

My dissertation committee:

- Dr. Sioban Harlow
- Dr. Bill Herman
- Dr. Michael Elliott
- Dr. Carrie Karvonen-Gutierrez
- Dr. Tene Lewis

End.

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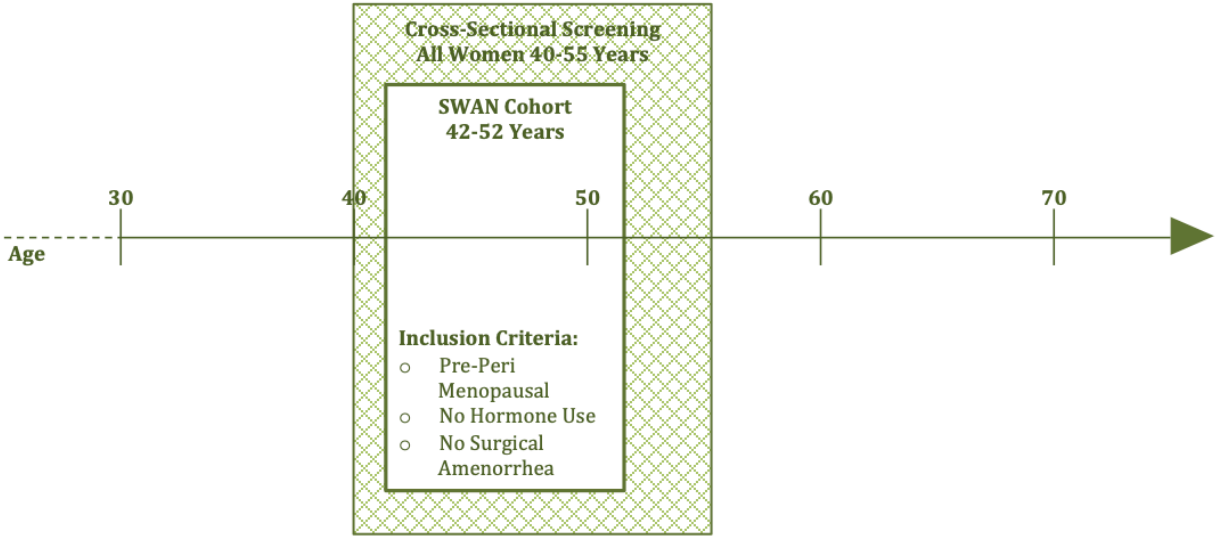
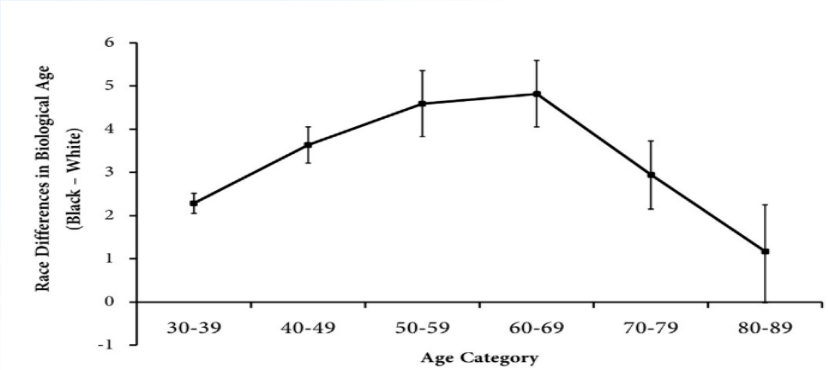
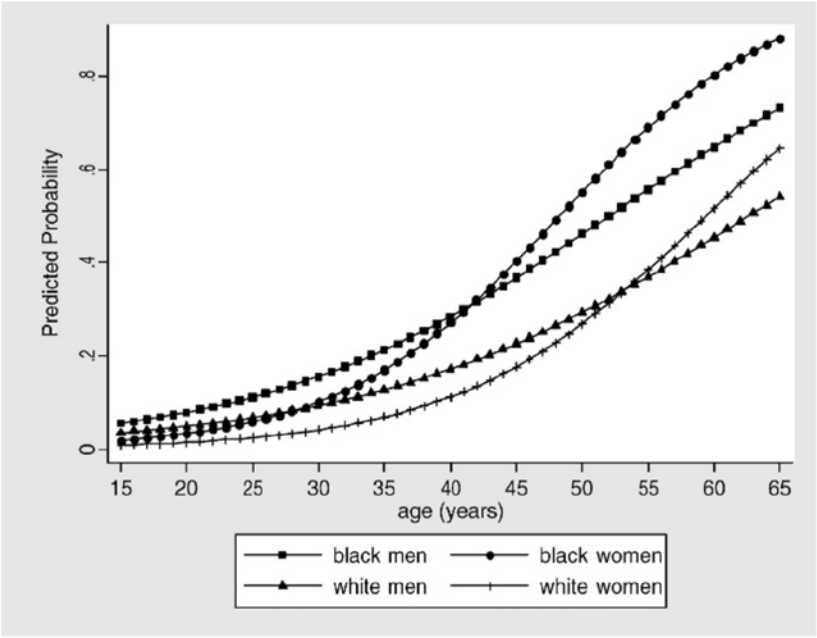


Early Health Deterioration and "Weathering"

- Highest risk of cardio-metabolic disease in mid to late life where racial disparity widens
- Evidence building on racial differences in early biologic dysregulation via allostatic load
- "Weathering" = early health deterioration as a consequence of the cumulative impact of repeated experience with social or economic adversity and political marginalization

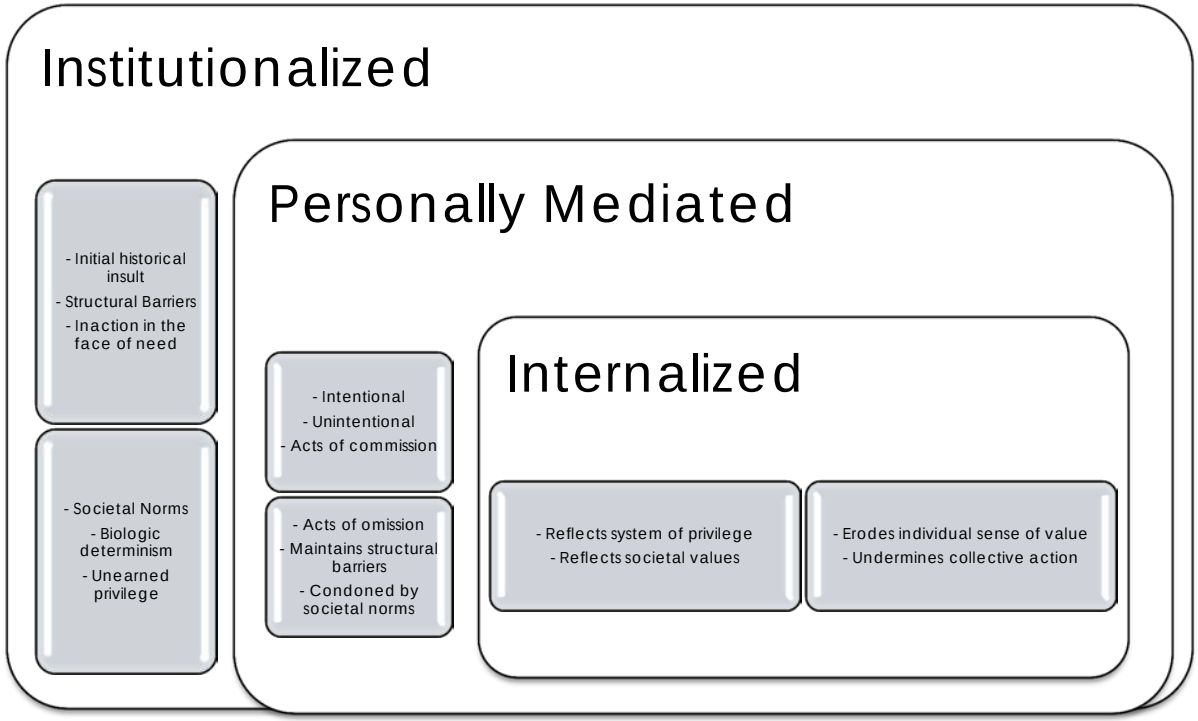




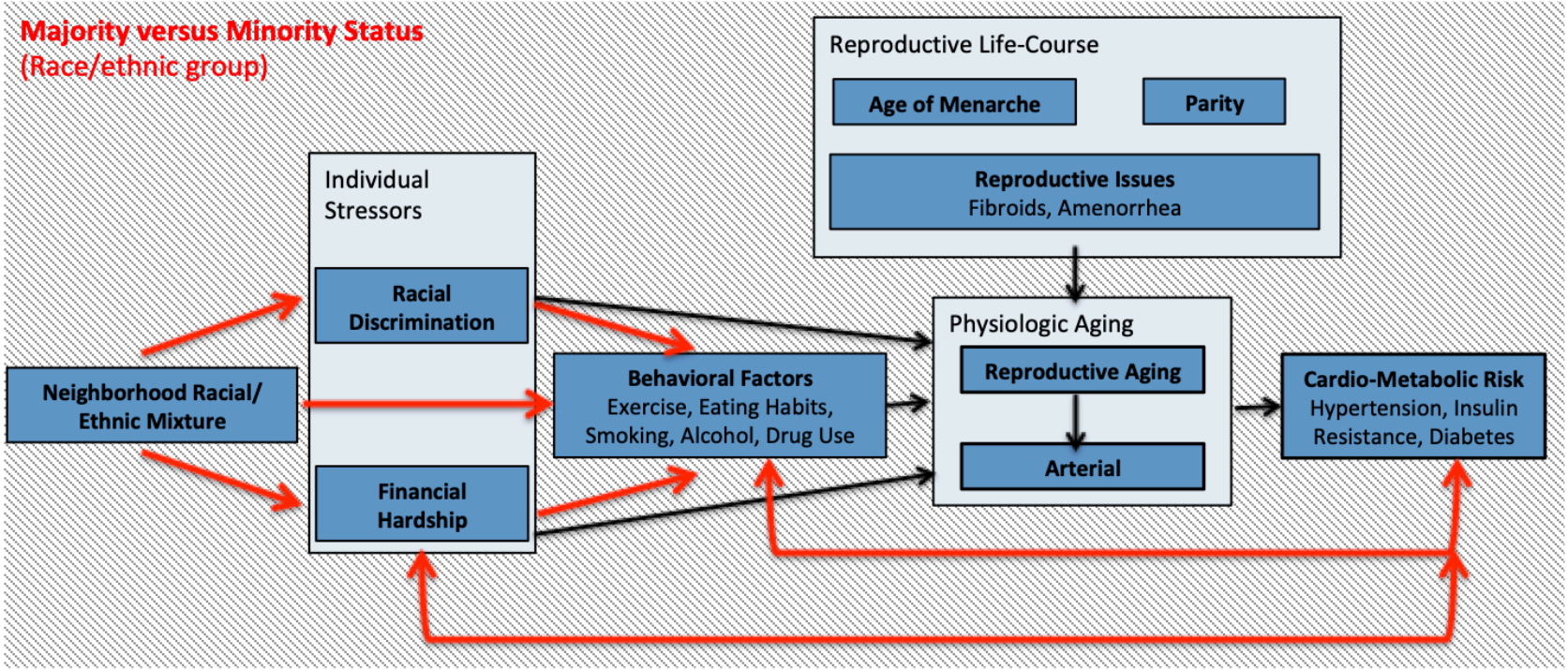
Levine, M.E., and E.M. Crimmins. 2014. "Evidence of Accelerated Aging among African Americans and Its Implications for Mortality." *Social Science & Medicine* 118 (October): 27–32.
Geronimus, Arline T., John Bound, and Cynthia G. Colen. 2011. "Excess Black Mortality in the United States and in Selected Black and White High-Poverty Areas, 1980-2000." *American Journal of Public Health* 101 (4): 720–29. https://doi.org/10.2105/AJPH.2010.195537.

Racial Discrimination as a Fundamental Cause of "Weathering"

- Institutionalized discrimination can lead to segregated neighborhoods
  - Positive and negative impact of segregated versus integrated neighborhoods
- Potentially determines exposure to race related stressors
  - Vigilance
  - Stereotype Threat
  - Internalized Racism
  - Stigma
  - Interpersonal Racial Discrimination



Working Conceptual Framework for the Psychosocial Causes of "Weathering" in Midlife



Selection Bias in Cohort Studies

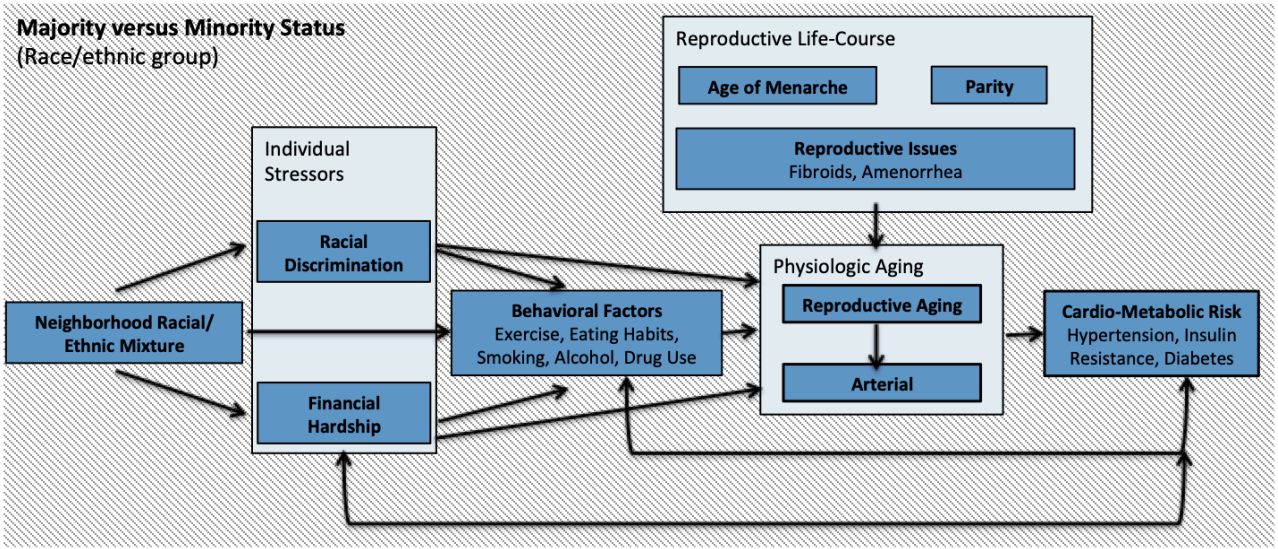
Age: Years from Baseline (BL)	-5	-4	-3	-2	-1	BL	1	2	3	4	5	6	7	8	9	10	11	12	13
Left Truncated Due to:																			
Woman A (Age of FMP)	37	38	39	FMP															
Woman B (Study Timing)	46	47	48	FMP															
Woman C (Selection Criteria)	37	38	Surgery																
Observed	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	FMP	
Right Censored Due to:																			
Woman D (Loss to Follow Up)	40	41	42	43	44	45	46	47	48	49	Dropped Out								
Woman E (Surgical Ammenorhea)	39	40	41	42	43	44	45	46	47	48	49	50	51	52	Surgery				

Note Eligibility criteria: 42-52 years of age, no reproductive surgery, no hormone use and no FMP

- Bias if differential
- May be differential by race –
  - Left Truncation
    - Earlier natural menopause*
    - Surgical amenorrhea**
  - Right Censoring
    - Loss to follow up
    - Surgical amenorrhea

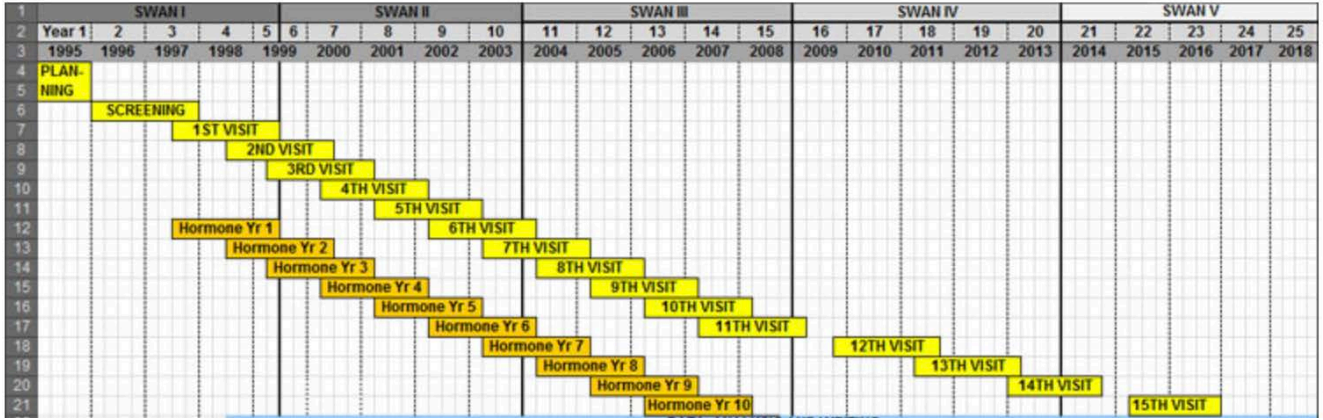
Study Rationale

- Correct for selection bias in a cohort of aging due to left-truncation and right censoring
- Correct estimates of racial/ethnic differences in reproductive aging and cardio-metabolic risk in midlife
- Determine the impact of mid-life race related contextual and interpersonal stress or



Methods

The SWAN Study



- Multi-ethnic, multi-site, 20 year longitudinal cohort of 3,302 women ages 42-52 years old
- 7 sites total (Chicago, Detroit, Boston, Pittsburgh, Oakland, New Jersey, Los Angeles)
- Annual follow up visits
- Selection from cross-sectional screening study

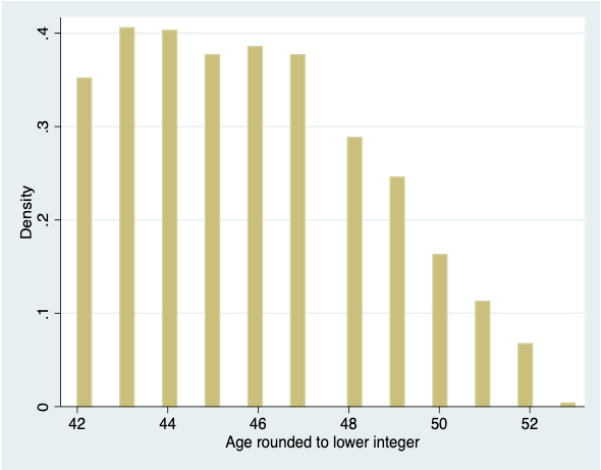
Measures

- Racial/Ethnic Group
- Final Menstrual Period
- Cardio-metabolic Risk Factors
  - Hypertension
  - Isolated Systolic Hypertension
  - Insulin Resistance (HOMA-IR)
  - Diabetes
- Neighborhood Racial Composition
- Discrimination (Racial Discrimination)
- Financial Stress/Hardship
- Covariates
  - Reproductive Hormone Use
  - Reproductive History (age of menarche, parity, fibroids, reproductive surgeries)
  - Socioeconomic Status
  - Health Behaviors (Smoking, Alcohol and Drug Use)
  - Medical History

Aim 1 Statistical Analyses

"Selection Bias and Racial/Ethnic Differences in FMP"

- For right censoring → Multiple imputation
- For left truncation → Inverse Probability Weighting
  - 1. For the study design



  - 2. For selection into the cohort from the cross sectional study

$$\text{Logit(inclusion into cohort from screening)} = \beta 0 + \beta 1*\text{RacialGroup} + \beta 2*\text{SocioeconomicStatus} + \beta 3*\text{FibroidHistory} + \beta 4*\text{ChronicStress} + \beta 5*\text{Medications} + \beta 6*\text{HistoryofCardiovascularDisease} + \beta 7*\text{HistoryofDiabetes} + \beta 8*\text{Behaviors} + \beta 9*\text{Weight}$$

- Baseline differences
  - χ^2 statistics for categorical
  - Kurskal-Wallis tests for continuous variables

- Follow the Cox models with age as the timescale from Gold et al.'s 2011 paper to assess the differences and impact of potential selection bias
  - Covariates: time-varying smoking, self-reported health at baseline, educational level at baseline, baseline use of oral contraceptives, time varying alcohol use, time-varying employment, time-varying physical activity score and weight.

- Race/Ethnic Specific Estimates of FMP will be compared across datasets:
  - Original Data (Gold analysis: n = 1,483)
  - Imputed data only → Loss to follow up (n = 3,302)
  - IPW weight 1 → Study design (n = 1,483)
  - IPW weight 2 → Selection from cross sectional screening (n = 1,483)
  - Product of IPW weights and Imputed Data → All (n = 3,302)

Limitations and Alternative Strategies for Aim 1

- Un-stabilized versus Stabilized Weights
- Potential for Differential Right Censoring
  - Surgical amenorrhea – MI and stratify by amenorrhea
  - Death before FMP – competing risks
  - Loss to Follow up before FMP – IPW weight for left censoring
- Site versus Race Differences
  - African-Americans = Chicago, Detroit, Boston, Pittsburgh
  - White = Chicago, Detroit, Boston, Pittsburgh, Oakland, New Jersey, Los Angeles
  - Hispanic = New Jersey
  - Chinese = Oakland
  - Japanese = Los Angeles

Aim 2 Statistical Analysis

"Racial/Ethnic Differences in Cardio-Metabolic Risk and the Role of FMP"

- Use fully imputed and weighted dataset
- Baseline differences
  - χ^2 statistics for categorical
  - Kurskal-Wallis tests for continuous variables
- *1. Are there racial/ethnic differences in cardio-metabolic risk onset?*
  - Accelerated Failure Time Model with Age as the Timescale
  - **log(age of onset of cardio-metabolic risk) = β0 + β1* RacialGroup + β2*Covariates**

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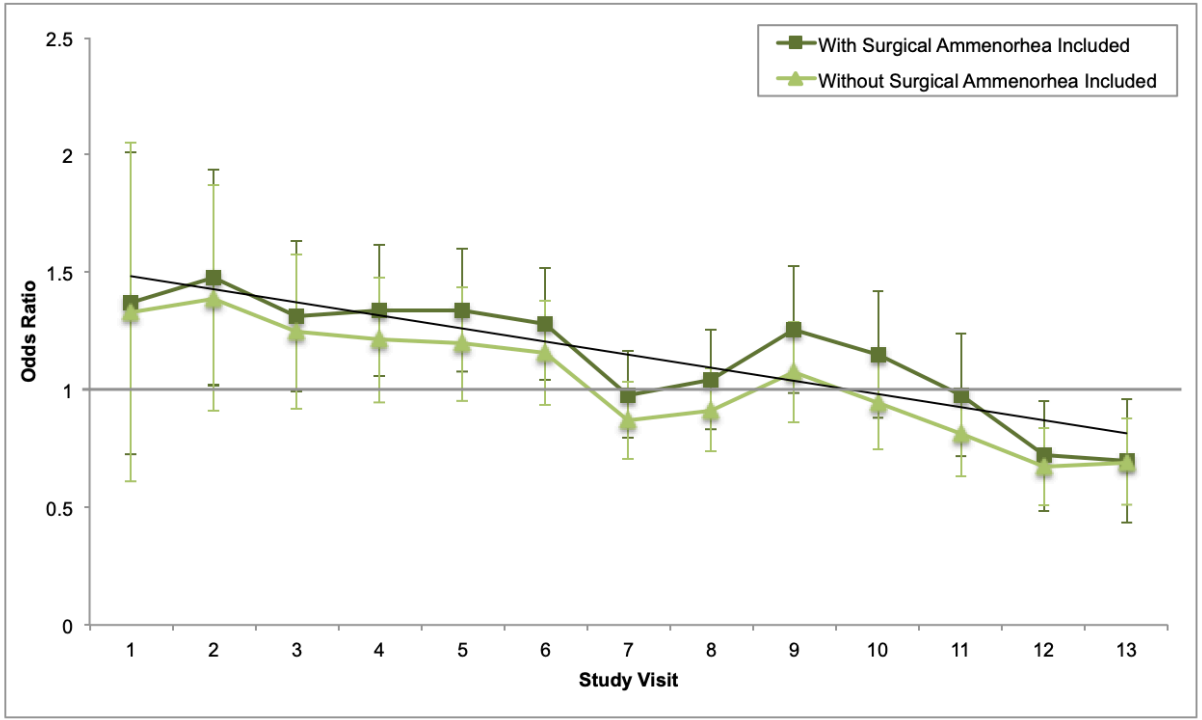
- *2. Are the racial/ethnic differences in cardio-metabolic risk onset moderated by age of FMP?*
  - *Multinomial logistic model*
  - **log(onset of cardio-metabolic risk factor before FMP) = β0 + β1* RacialGroup + β2*Covariates**
  - **log(onset of cardio-metabolic risk factor after FMP) = β0 + β1* RacialGroup + β2*Covariates**
  - **log(no onset of cardio-metabolic risk factor) = β0 + β1* RacialGroup + β2*Covariates**

Limitations and Alternative Strategies for Aim 2

- Right censoring for cardio-metabolic factors
- Cut points for some cardio-metabolic factors
  - Hypertension (130/80 mmHg versus 140/90 mmHg)
  - Insulin resistance
- Race versus site differences

Aim 1

"Selection Bias and Racial/Ethnic Differences in FMP"



Significance

- Handling selection bias is important in all cohorts of aging
- Potentially underestimating racial/ethnic disparities in aging
- Racial/ethnic disparities in reproductive aging unclear as well as its potential association with cardio-metabolic risk
- Findings on the contribution structural differences to psychosocial stress and disparities can guide future public health policy