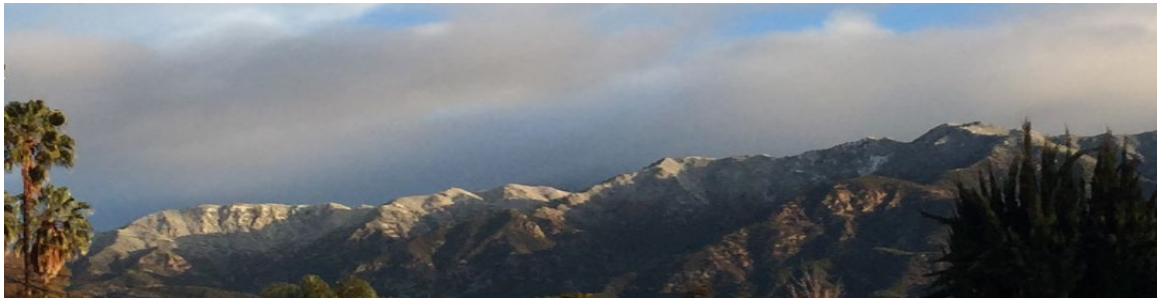
Unequal distribution of wealth and access: measuring the biology of disparities



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Thank you to our Collaborators



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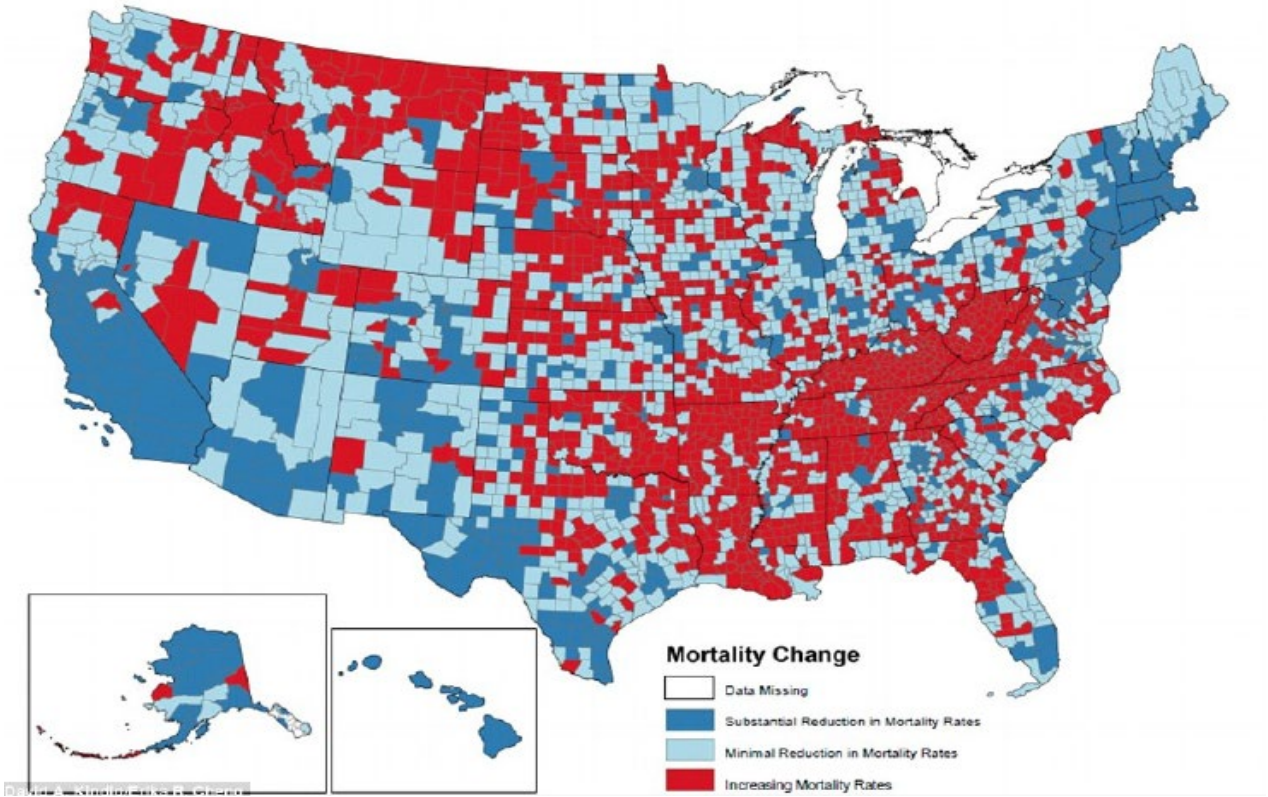
Sheeba Irshad, MD	Kings	Omics, microenvironment
Anita Grigoriadis, PhD	Kings	Microenvironment

Early death in women > 50% US Counties 2006

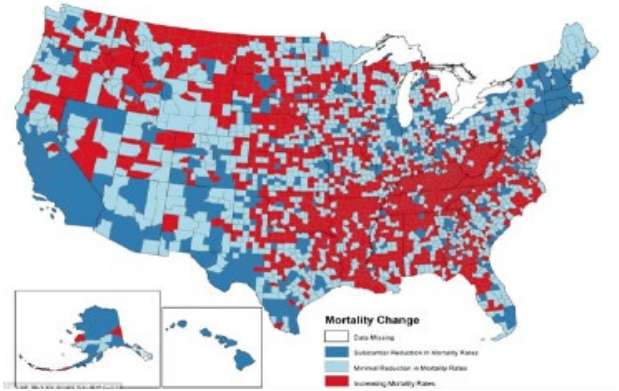
- David Kindig and Erika Cheng, University of Wisconsin
- Chris Murray, University of Washington



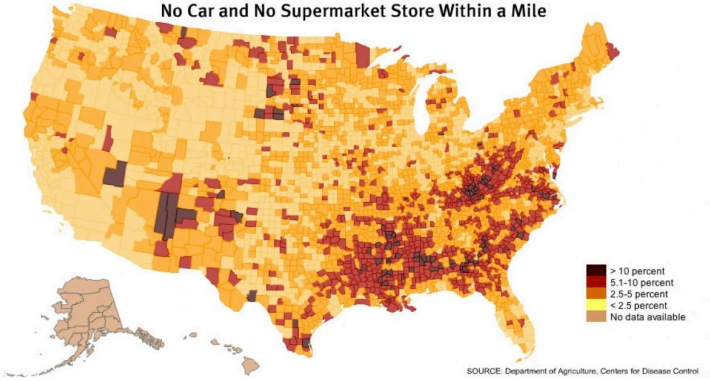
Early death, inactivity, type-2 diabetes

David Kindig and Erika Cheng, University of Wisconsin
Chris Murray, University of Washington

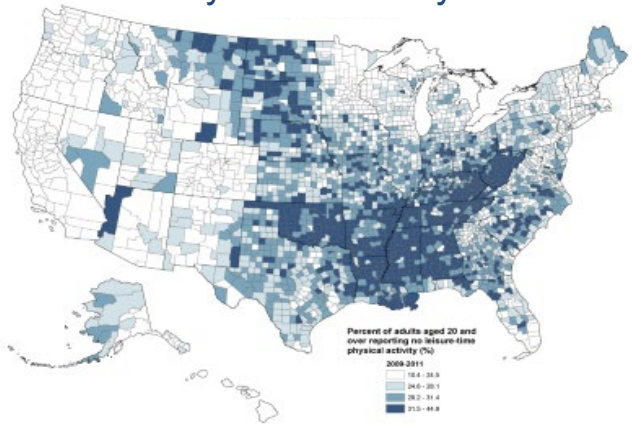
Earlier Age Death Women



Lack of access to healthy food



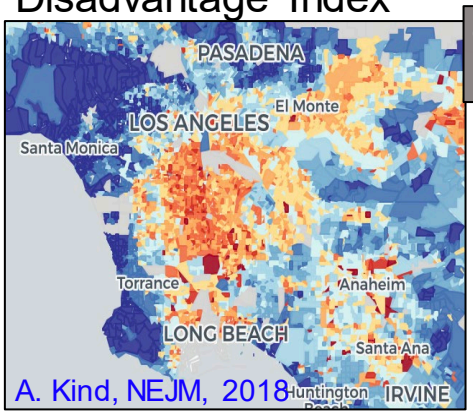
Physical Inactivity

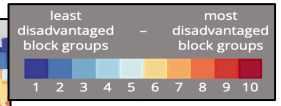


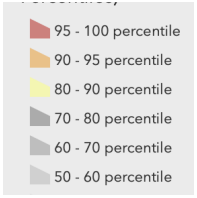
T2 Diabetes

LA as an example: unequal distribution of wealth = shorter lives

Disadvantage Index

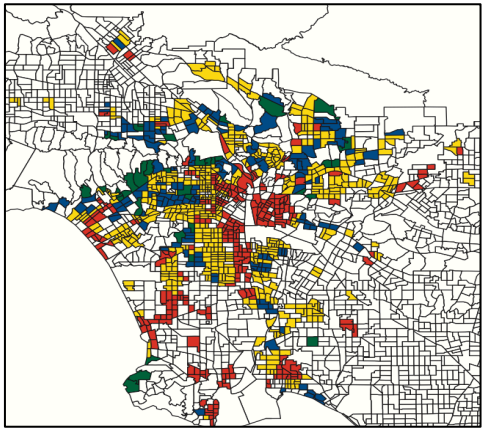


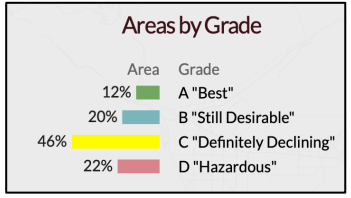




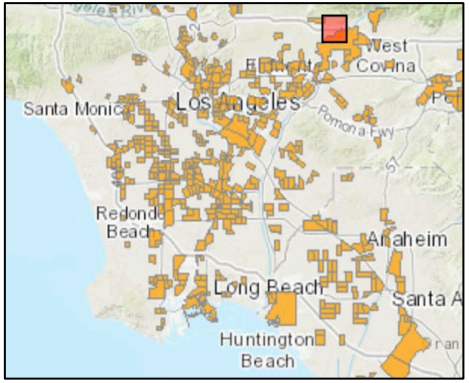
Air Toxics Cancer Risk

Redlining – 1930's



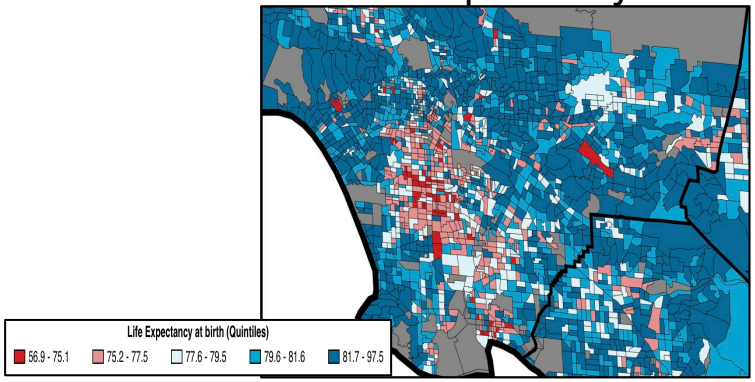


Food Deserts



http://www.ers.usda.gov/data-products/food-access-research-atlas/

CDC Life Expectancy 2023

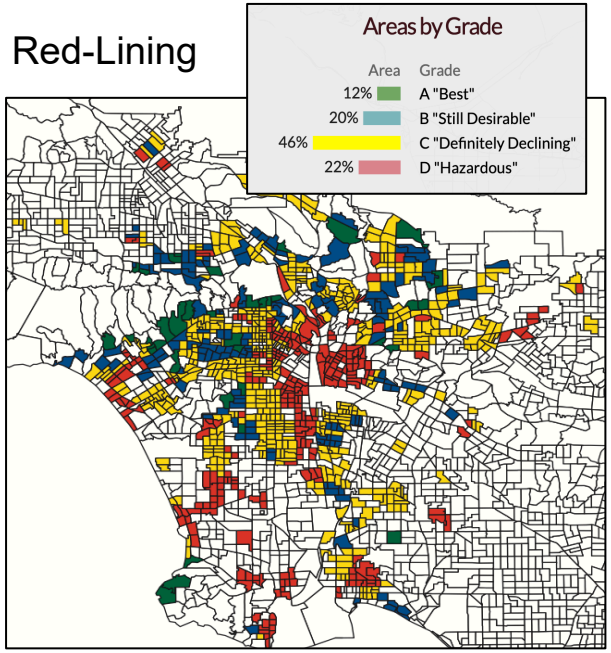


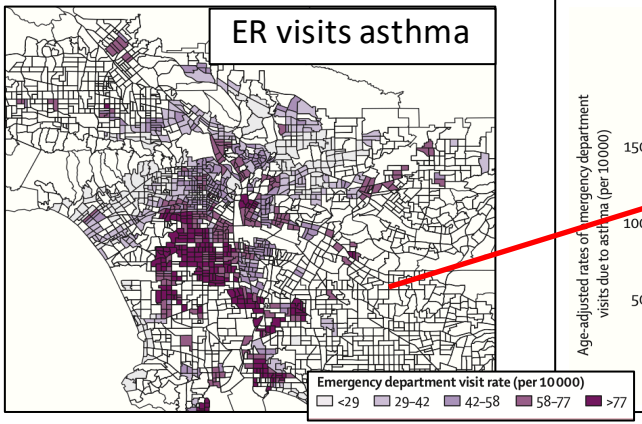
tps://www.cdc.gov/nchs/data-visualization/life-expectancy/index.html

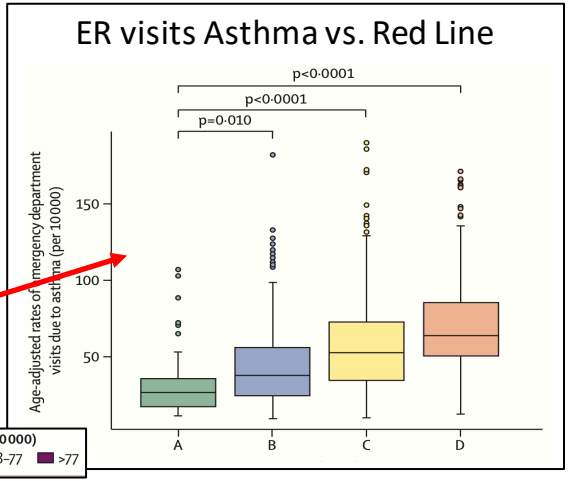
Poor resourced neighborhood links to Redlining – LA

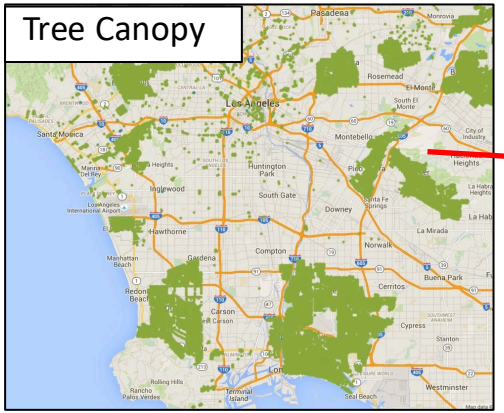
Denial of loans, insurance, health care, supermarkets
Increase ER visits and temperature

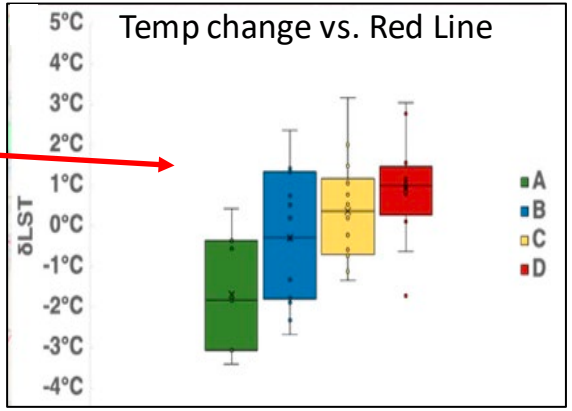
Red-Lining





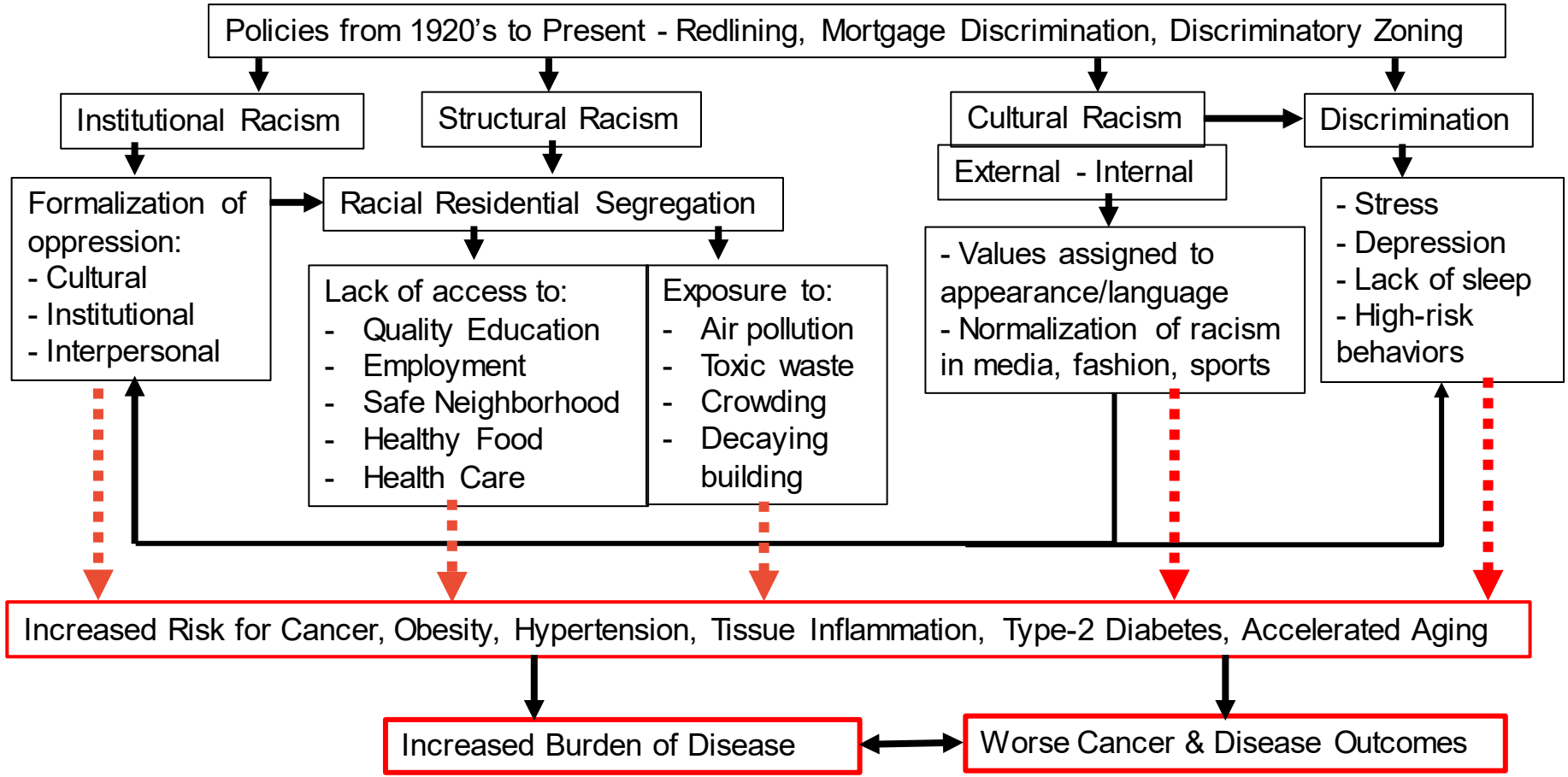






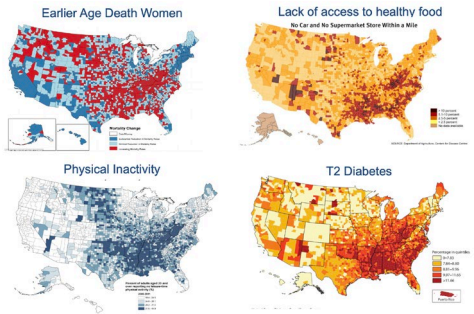
Jeremy Hoffman et al. *Climate*, 2020
Anthony Nardone et al. *Lancet*, 2020

Racism – institutional, structural, cultural - and Discrimination – *need biology*



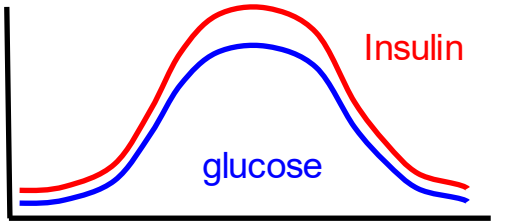
Getting at the biology: nutrition and calories are no longer linked

	Privileged	Disadvantaged
Before 1950's	High calories Good nutrition	Low calories Malnutrition
	↓	↓
	Good health Higher BMI	Poor health – anemia, Scurvy, Rickets, protein/energy malnutrition
Today	Good nutrition Low calories	Poor nutrition High Calories
	↓	↓
	Good health Lower BMI Space to exercise	Obesity, heart disease, HTN, T2DM, cancer No space to exercise



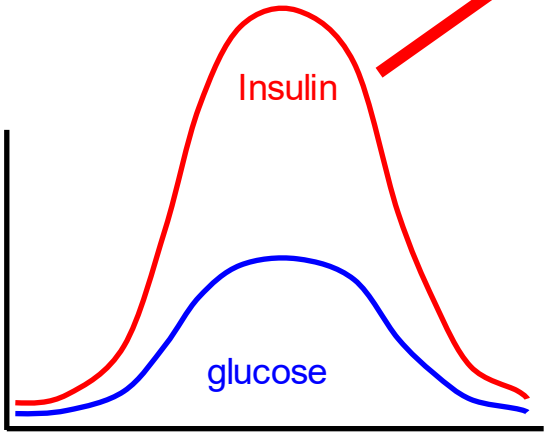
Definitions: T2DM - ***glucose*** ↑; Insulin resistance - ***insulin*** ↑

Difficulty controlling eating is biology not "will-power"

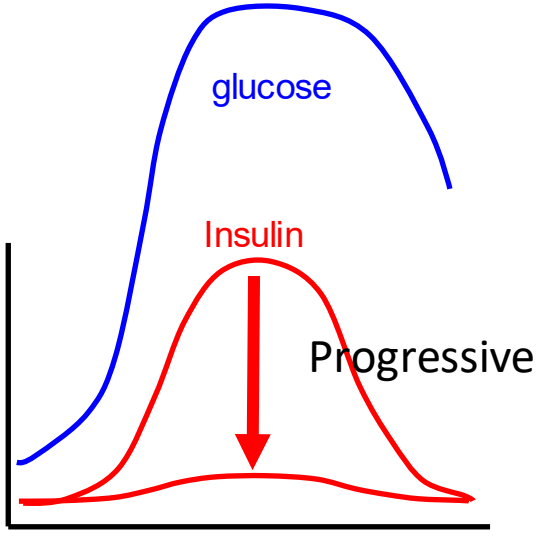


Healthy – HgbA1C = 5.3

- stimulates hunger
- promotes carbohydrate to fat
- prevents fat access (breast feeding)



Resistant – HgbA1C = 5.7-6.3

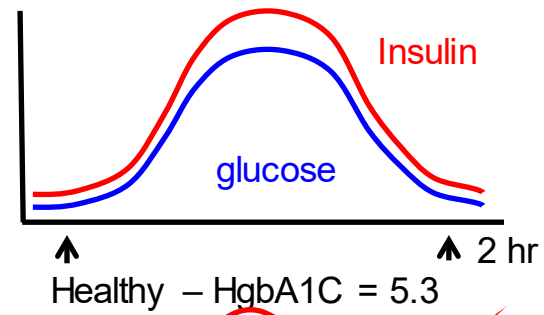


Progressive Pancreas Failure

Diabetes – HgbA1C > 6.3

60% of T2DM can be prevented w/diet, walking, metformin

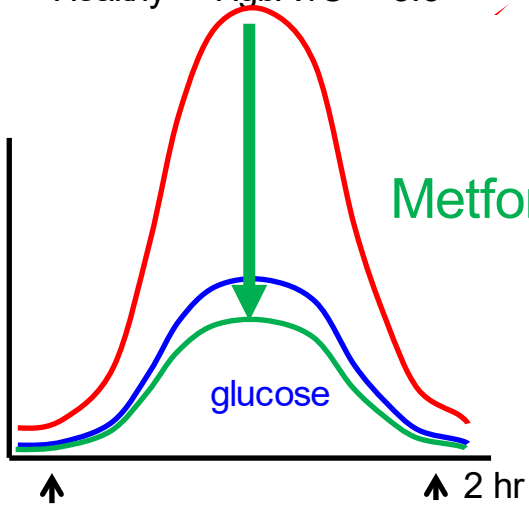
- need for medical education



Healthy – HgbA1C = 5.3

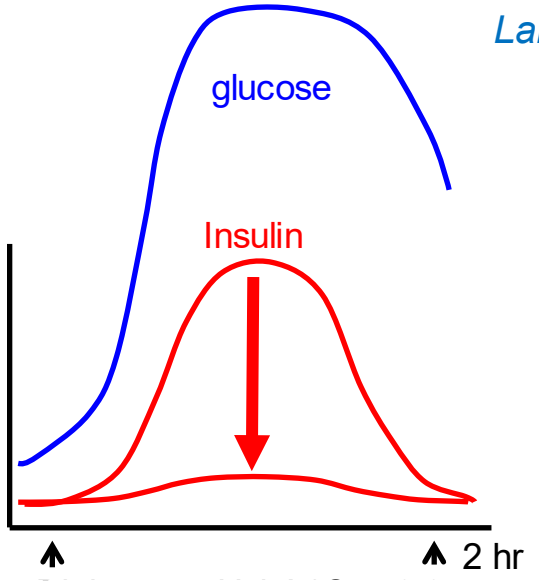
Metformin - decreases serum insulin
- decreases hunger – CNS effects
- increases fat breakdown
- **prevents >60% T2D – DPP & DPPO**

Lancet 374:1677-1686, 2009



Resistant – HgbA1C = 5.7-6.3

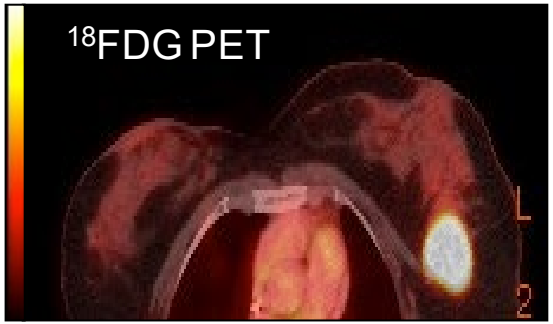
Metformin



Diabetes – HgbA1C > 6.3

Woman: Insulin Resistant

Insulin resistance, produces high insulin



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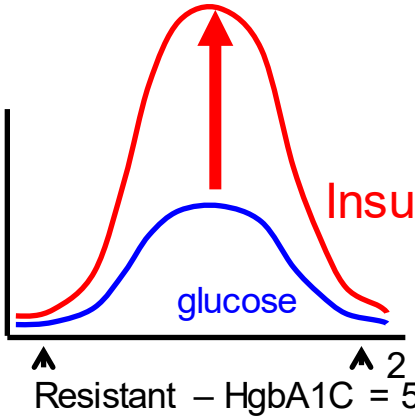
At risk breast tissue

Increased insulin sensitivity



AKT/mTOR/glycolysis

Wnt/beta-catenin

EZH2/Notch/cMyc

IL6/Stat3/NFkB/IRF1

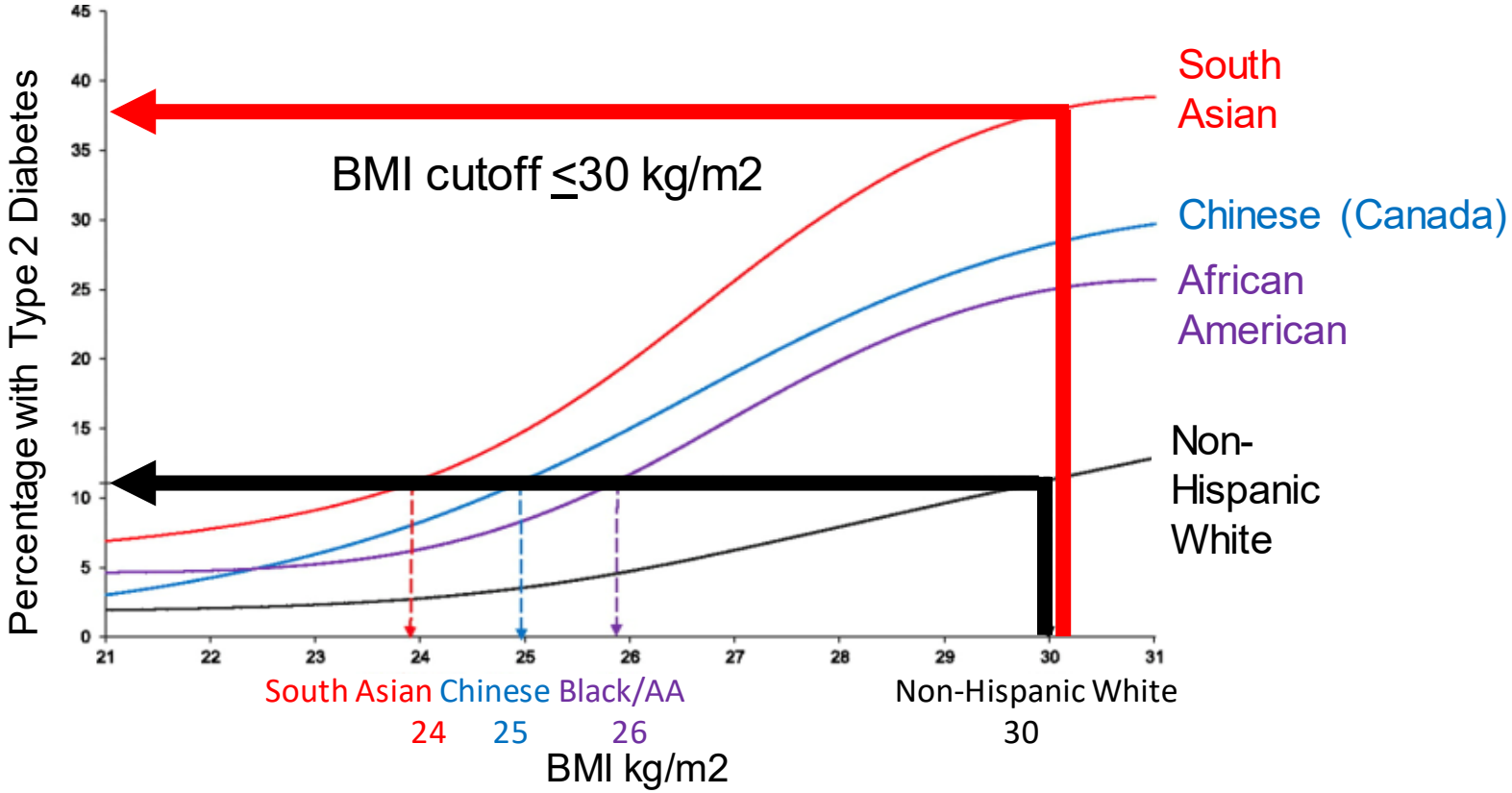
Epi studies are confusing: Obesity does not consistently increase risk of premenopausal TNBC in AA women

- Carolina Breast – Basal type TNBC increased in obese premenopausal Black/African American women (WHR).
- Women's Contraceptive and Reproductive Experience (CARE) (BMI ≥30) – No association
- Black Women's study (BMI) – ***Adams-Campbell*** - inverse association BMI and premenopausal cancer
- AMBER Association – consortium Carolina Breast, Multi-ethnic cohort, Black Women's study ***Adams-Campbell***, Women's Circle of Health - NO association (BMI, WHR)

Biphasic variable - BMI ≥30 YES or NO

Bandera EV, Chandran U, Hong CC, Troester MA, Bethea TN, Adams-Campbell LL, et al. Abrosone C. Obesity, body fat distribution, and risk of breast cancer subtypes in African American women participating in the AMBER Consortium. *Breast cancer research and treatment* (2015)

BMI and metabolic health – one size fits all fails



Chiu M, et al. *Diabetes Care* 2011, 34:1741-8

Significant individual variability in insulin resistance

Carolyn (Sister)
58 years old
6'3" and 243 lbs.
BMI = 31
Diet – carbs, sugar
Smoker, no exercise

HgbA1c = 5.4
Cholesterol (total) = 168
No Asian Ancestry
Lost 40 lbs. on metformin

Vicky (me)
63 years old
5'8" and 128 lbs.
BMI = 19
Diet – low carb, vegetarian, veggies
1 hour swimming & 30 mins running/day

HgbA1c = 6.0 on 2500 mg Metformin
Cholesterol (total) = 190 on Lipitor 40 mg
Asian Ancestry by 23andMe
Off Statin HgbA1c = 5.5

Catchment Area Study – 981 women enrolled

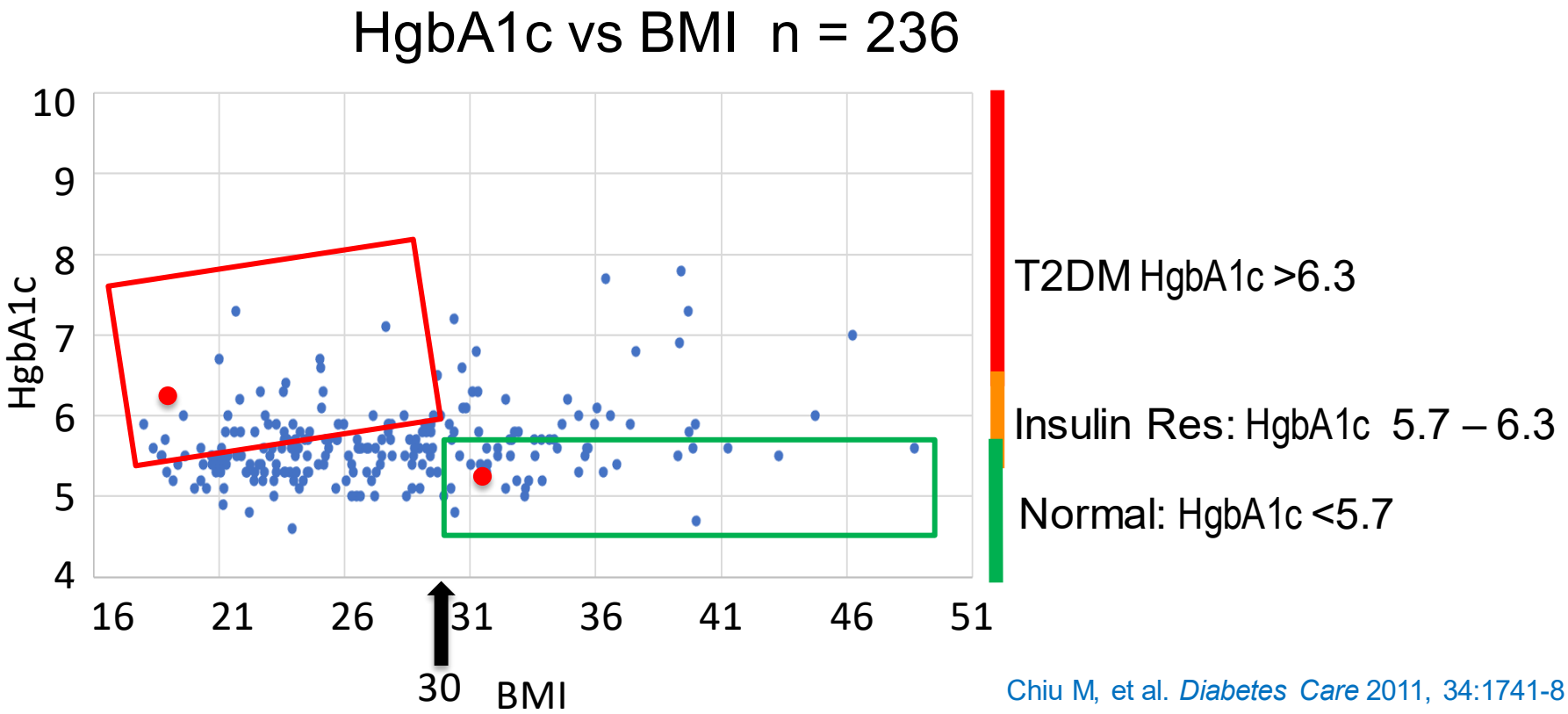
Redcap survey – demographics, zip code, education, employment, nutritional survey, food shopping and access. Mix of neighborhoods.

- Genetic ancestry in progress.

Age	31-61 (mean 43)				
Race/Ethnicity	**NHW**	**HW**	**Black**	**Asian**	**NA**
	288 (35%)	378 (46%)	41 (5%)	116 (14%)	4 (<1%)
Neighborhood Disparity Index	**1-3 (adv)** 312 (38%)	**4-6** 426 (52%)	**7-10** 89 (11%)		
HgbA1C	**≤ 5.6**	**5.7-5.9**	**≥ 6.0**		
236 analyzed	138 (58%)	59 (25%)	39 (17%)		

Neighborhood does not accurately predict disparity

Catchment Area – exclusion known Type-2 DM Metabolically unhealthy low BMI

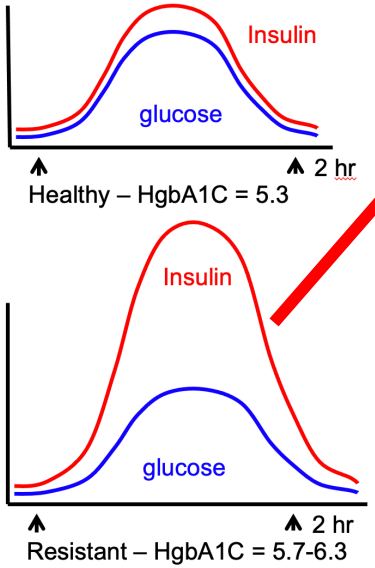


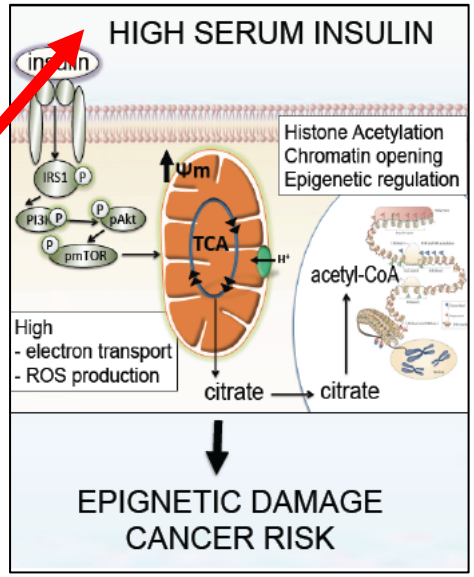
Chiu M, et al. *Diabetes Care* 2011, 34:1741-8

Pre-diabetic/insulin resistance women have chromatin acetylation at H3K9Ac and chromatin opening.

Top hits are promoter regions for genes coding for TNFα and IL6; TNFα/IL6 cytokines are increased.

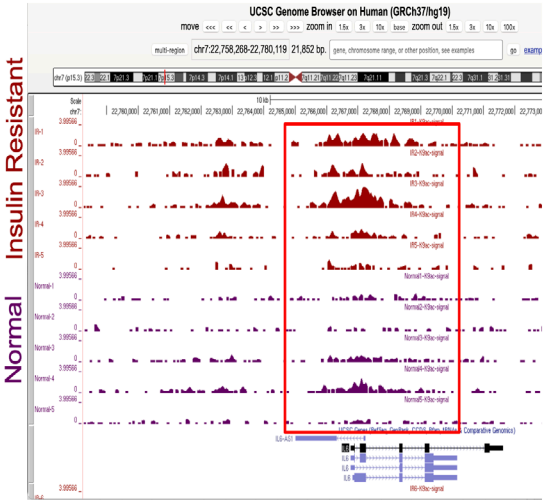
Also increased in racial residential segregation, CVD, cancer.





ChIP-seq - H3K9Ac

n=40: 20 HgbA1c < 5.7 and 20 HgbA1c 6.0-6.3



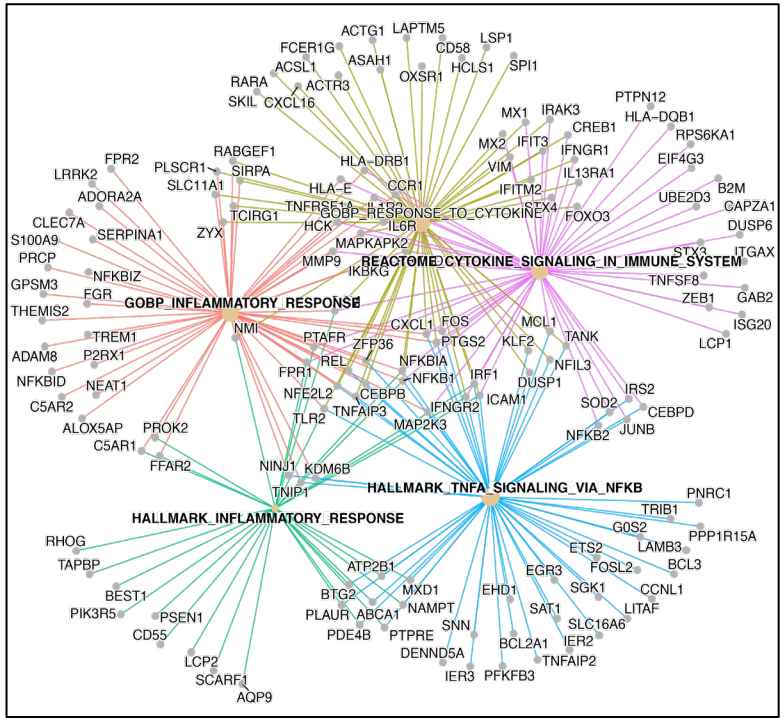
Top Hits:
- TNFα
- IL6

Cytokine n=**245**
correlation HgbA1c
- TNFα p= 0.002
- IL6 p= 0.001

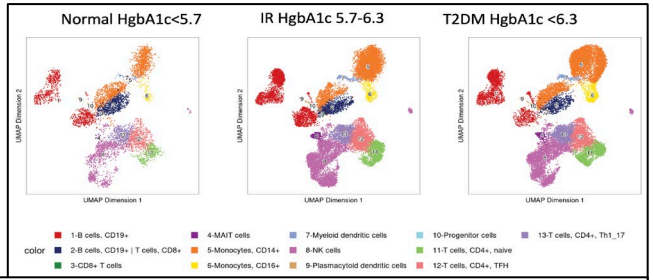
Top Pathways Activated in Insulin-Resistance: NFκB/TNFα-signaling, inflammation, IL6, innate immunity, senescence

Bulk white blood cells give same results as single cell analysis

Bulk analysis WBC – test n=32; validation 254

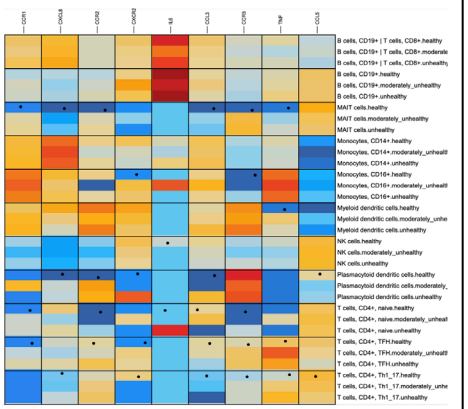


Single cell analysis - 32 URM Latinas

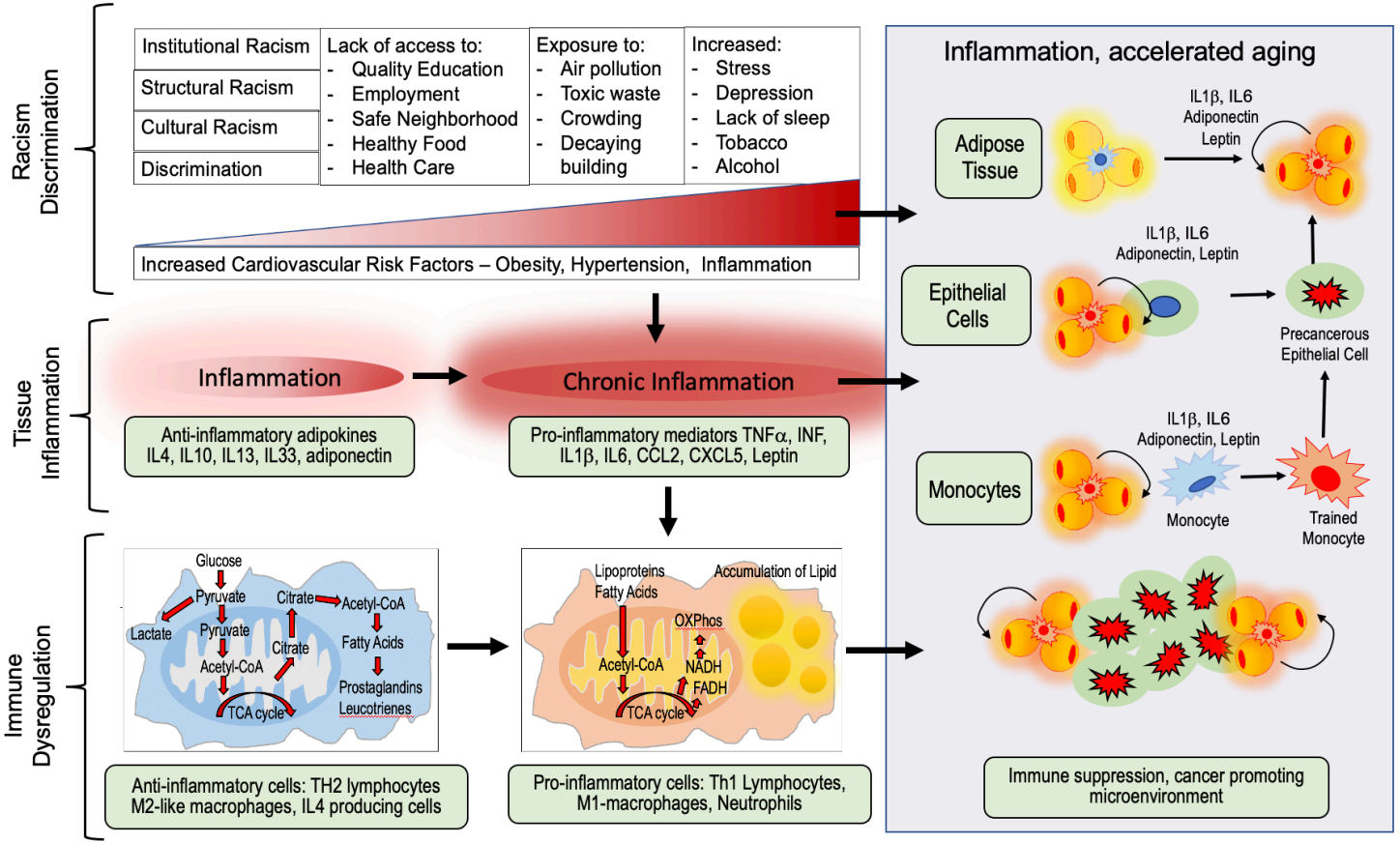


Observations:

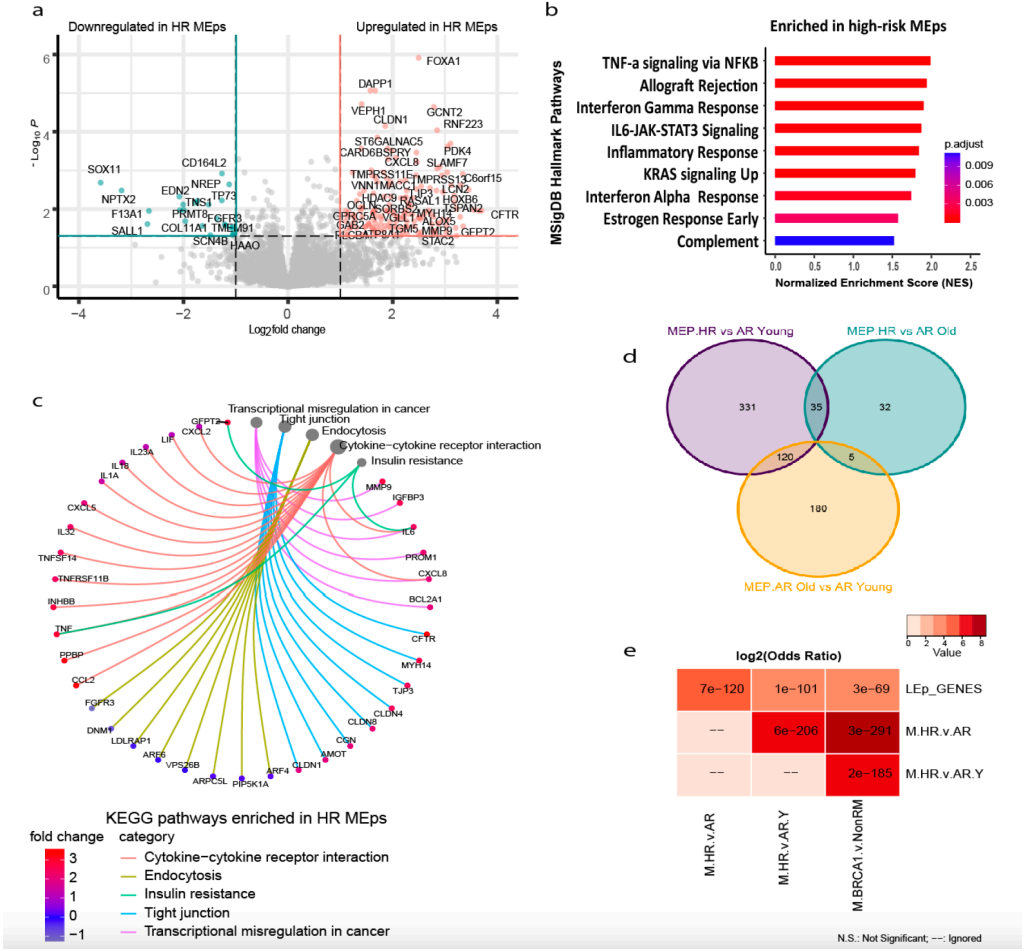
1. MAIT Cells show an increase in all cytokines except in CCL5 which is decreasing.
2. Monocytes CD16+: CCR5, CXCR2
3. Myeloid dendritic cells :TNF
4. Plasmacytoid dendritic cells :CCL3,CXCR2, CXCL8, CCR2, CCL5
5. T cells CD4+, naïve : CCR5, IL6, CCR2, CCR1 CCL3
6. T cells CD4+ TFH: TNF, CCR5, CXCR2, CCR1, CCR2, CCL3
7. T cells, CD4+ TH1_17: TNF, CCR5,CXCL8, CCL5, CCL3, CXCR2



Common Pathways – Racism, lack of access, exposures to toxins, stress, crowding
- Same pathways that drive heart disease, T2 diabetes, kidney disease, cancer



Evidence for accelerated aging in *BRCA1* mt



Sundus Shalabi MD PhD

Upregulated *BRCA1*:
- Wnt/beta-catenin signaling
- EMT
  - → TNFalpha/NFkB
  - → INF-gamma
  - → IL6-JAK-STAT3

Senescence
Accelerated Aging

Shalabi S,…Seewaldt/LaBarge *Nature Aging* 2021

Reversibility: Over 60% of diabetes can be prevented. If insulin-resistant women become metabolically healthy – does the epigenetic/inflammation/aging damage get reversed?

Primary Prevention: ALLIANCE Metformin vs. placebo:

Endpoint: presence/absence mammary atypia; biology "heavy" trial

Inclusion
>20% life-time risk
Cytological breast atypia
BMI ≥25

BMI, WHC
Metabolic markers
- insulin
- HOMA IR
- HgbA1c
- CRP

Plasma
WBC DNA/RNA

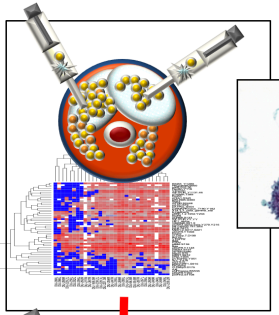
Premenopausal women with mammary atypia

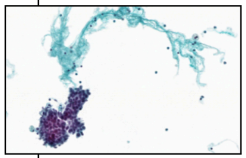
↓

Metformin 850 bid vs. placebo 12 months

↓

RPFNA, RPPM
- 12 mos
- 24 mos





Yes atypia

↓

Yes/no atypia?
- ChIP-seq
- Pathway
- RPPM
- Aging

Public health

Body mass index does not always predict metabolic health.

- Clinicians and research studies need to consider individuals as individuals

Metformin, diet, and exercise can prevent 60% of type-2 diabetes.

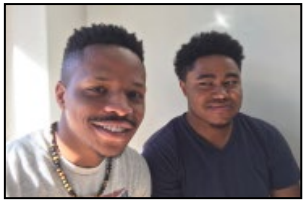
- Trial data exists, guidelines exist, need to include in medical training and Quality Assurance standards.

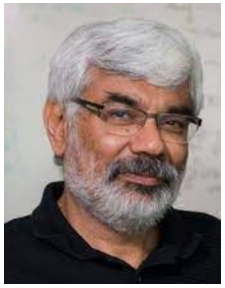
Future Directions

- If insulin-resistance is treated and the person is metabolically health, do the epigenetic and inflammatory changes reverse?
- Early monitoring of HgbA1c and early treatment.

Angie Sanchez, Nancy Sanchez, Myriam Robles, Allen Nunez, Angela Wong, Tanya Chavez, Christina Tsai, Omi Idassi, Kendal Kennedy

leap





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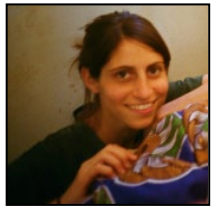
UCSD

Faye Burt



Terry Hyslop PhD
Duke

Christina Vidal PhD Parajat Senapati PhD



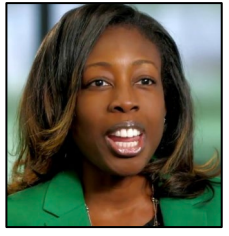


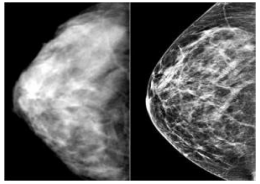








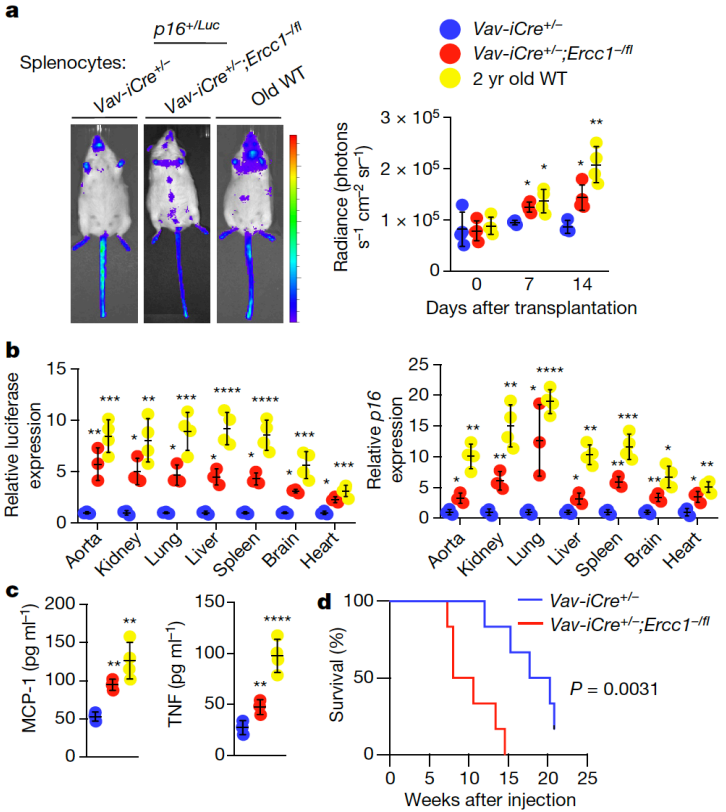





DUKE NAVIGATOR PROGRAM


Senescence of heart, pancreas, brain, lung can be driven by immune system. Can be transplanted.

Adoptive transfer of splenocytes from 10 mos old Ercc1 – deficient mice – aging of recipient mice



Article

An aged immune system drives senescence and ageing of solid organs

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Check for updates

Matthew J. Yousefzadeh[1,2,14], Rafael R. Flores[1,2,14], Yi Zhu[3], Zoe C. Schmiechen[4], Robert W. Brooks[5], Christy E. Trussoni[6], Yuxiang Cui[7], Luise Angelini[1,2], Kyoo-A Lee[1,2], Sara J. McGowan[1,2], Adam L. Burrack[4], Dong Wang[8], Qing Dong[8], Aiping Lu[9], Tokio Sano[5], Ryan D. O'Kelly[1,2], Collin A. McGuckian[1,2], Jonathan I. Kato[5], Michael P. Bank[5], Erin A. Wade[5], Smitha P. S. Pillai[10], Jenna Klug[11], Warren C. Ladiges[11], Christin E. Burd[12], Sara E. Lewis[13], Nicholas F. LaRusso[6], Nam V. Vo[9], Yinsheng Wang[7], Eric E. Kelley[13], Johnny Huard[9], Ingunn M. Stromnes[4], Paul D. Robbins[1,2]✉ & Laura J. Niedernhofer[1,2]✉

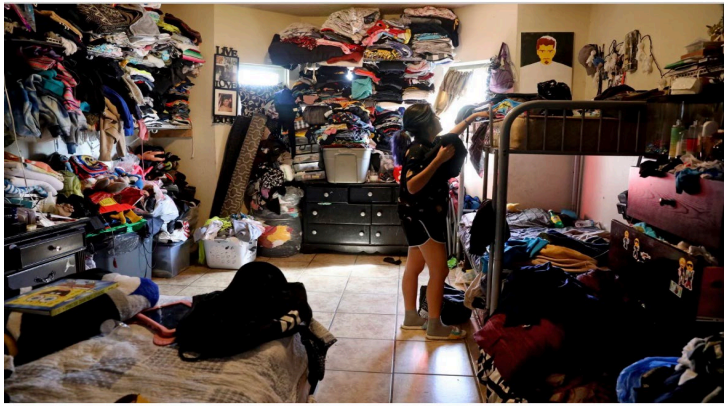
Nature Vol 594 3 June 2021 - Niedernhofer

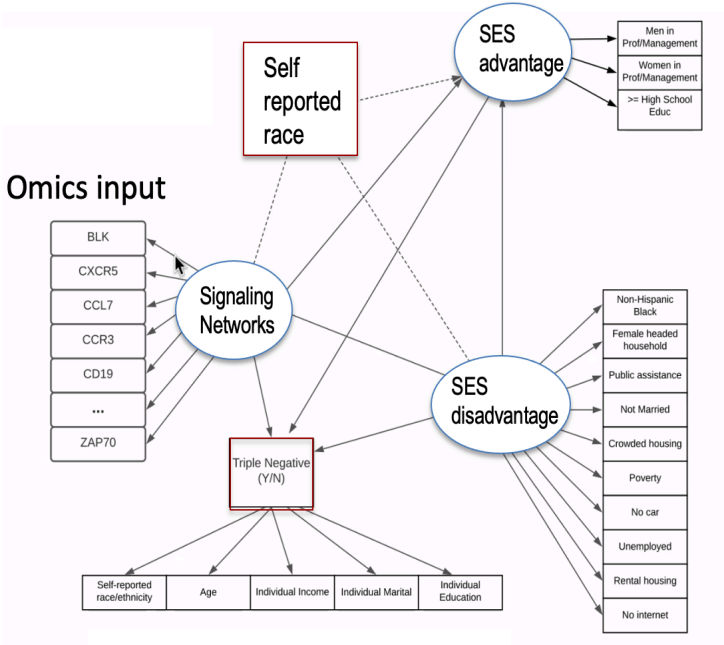
Modeling disparities - integration with biology

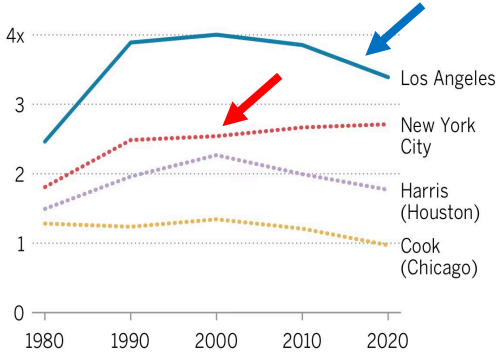
Terry Hyslop PhD

Modeling
Data input

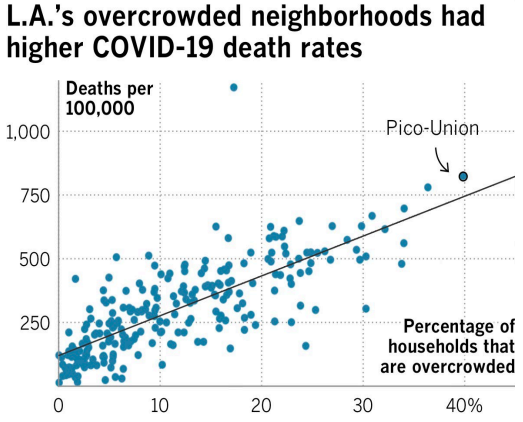
Fixed
variables







U.S. Census Bureau



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