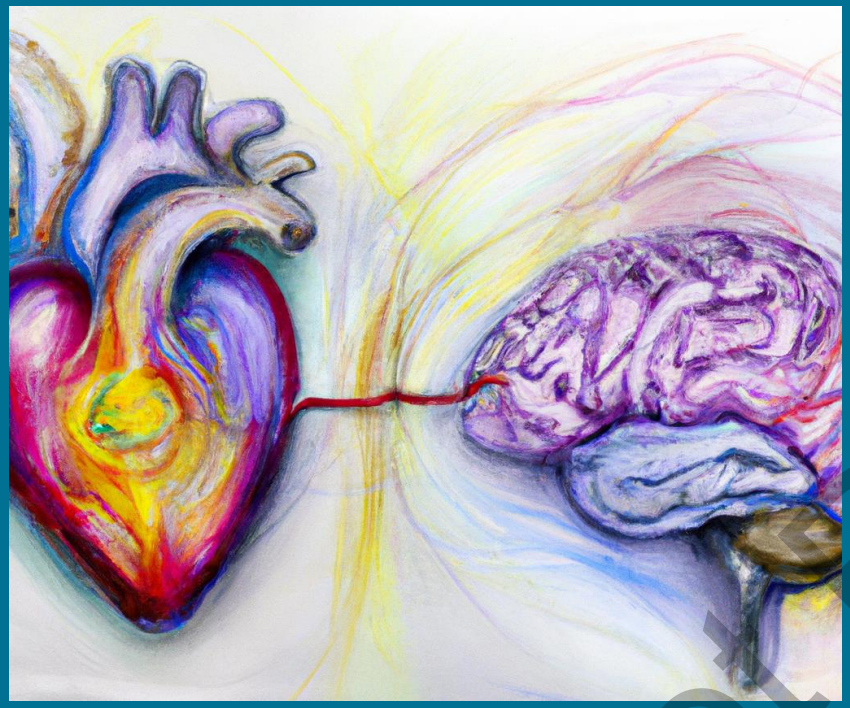

Stress and the Cardiovascular System: Navigating the Intersection

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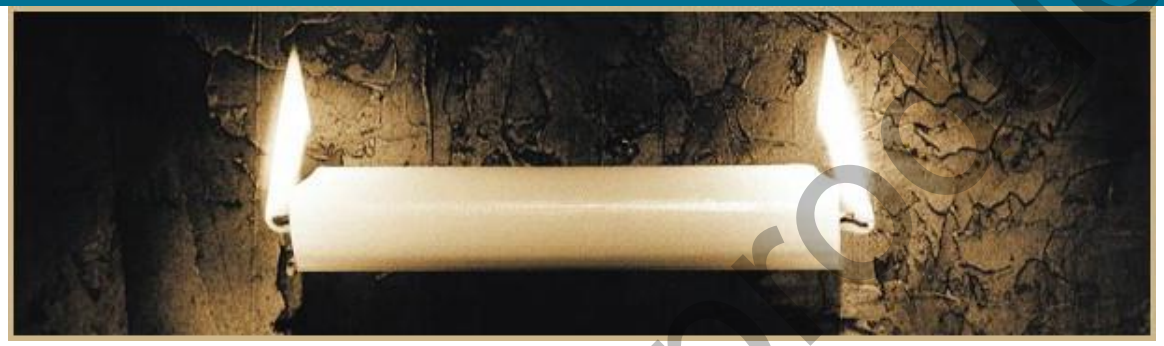
MASSACHUSETTS GENERAL HOSPITAL
CORRIGAN MINEHAN HEART CENTER

Disclosures

- Related to the content of this presentation:
  - None

- Unrelated to the presentation
  - Lung Biotechnology: Research grant
  - Actelion: minor consulting
  - DalCor: minor consulting

Psychosocial stress and Heart Disease

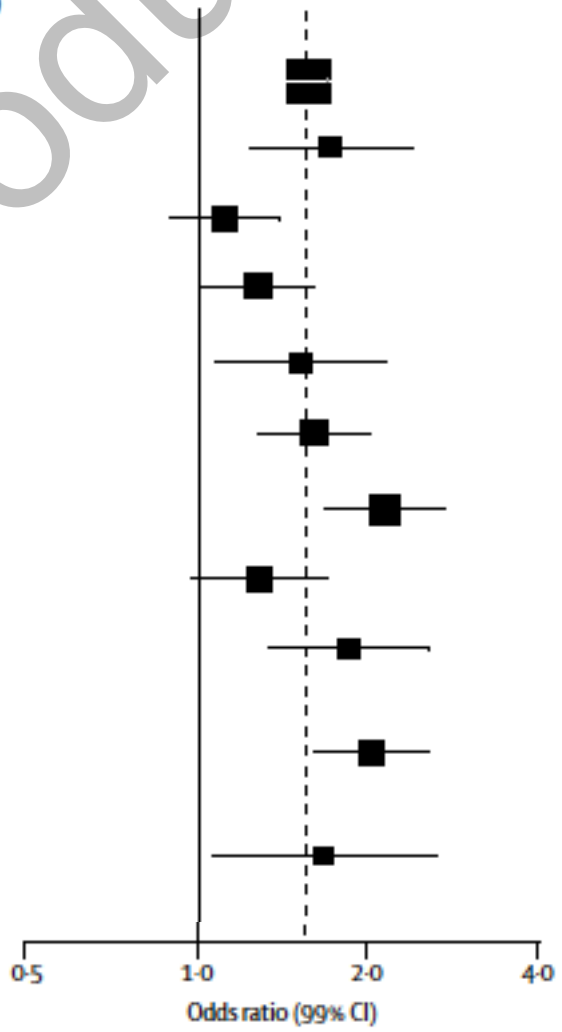


Psychosocial stress:

- Attributable CVD risk is on par with that for smoking, elevated lipids, hypertension, and diabetes.
- Yet relatively little had been known about the mechanisms that translate stress into CVD events.

The INTERHEART Study

Region	Number	Case (%)	Control (%)	Odds ratio (99% CI)
Overall	24 767	27·3	20·1	1·55 (1·42–1·68)
Western Europe	1375	39·7	29·5	1·70 (1·23–2·34)
Central and eastern Europe	3473	26·6	23·7	1·11 (0·89–1·37)
Middle East	2892	30·2	23·0	1·27 (1·01–1·58)
Africa	1259	29·5	21·7	1·51 (1·07–2·12)
South Asia	3300	25·9	17·4	1·59 (1·28–1·98)
China and Hong Kong	5894	15·6	7·7	2·10 (1·66–2·67)
Southeast Asia	1921	29·8	24·2	1·27 (0·96–1·67)
Australia and New Zealand	1255	42·9	31·3	1·82 (1·32–2·51)
South America and Mexico	2783	40·2	24·6	2·01 (1·6–2·52)
North America	615	43·8	35·3	1·65 (1·05–2·59)



Rosengren et al Lancet 2004

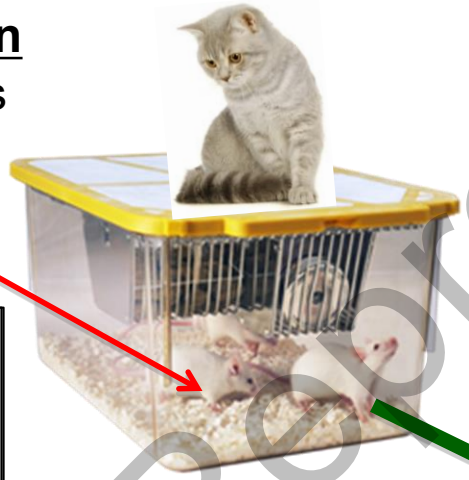
Mechanisms Linking Stress to Heart Disease

- Stress may affect behaviors and factors that increase heart disease risk:
  - Smoking
  - Physical inactivity
  - Overeating
  - HTN
  - Diabetes
  - Adiposity
- These factors do not explain the observed risk

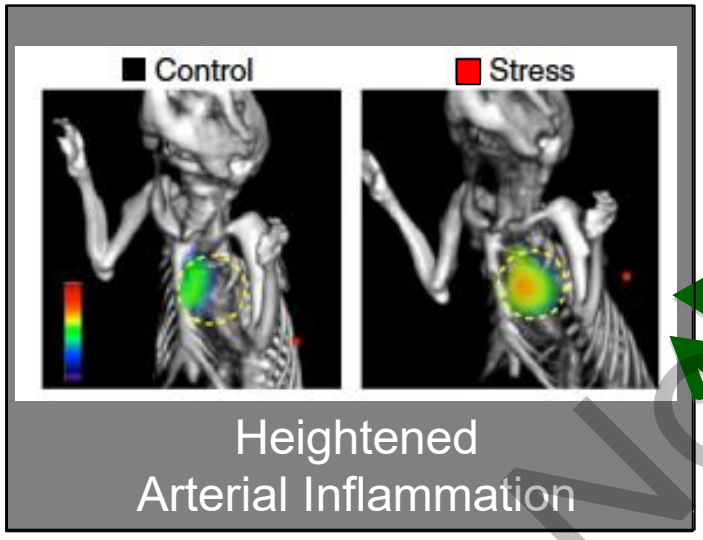
Chronic Stress Promotes Atherosclerotic Inflammation in Mice

Stress Induction

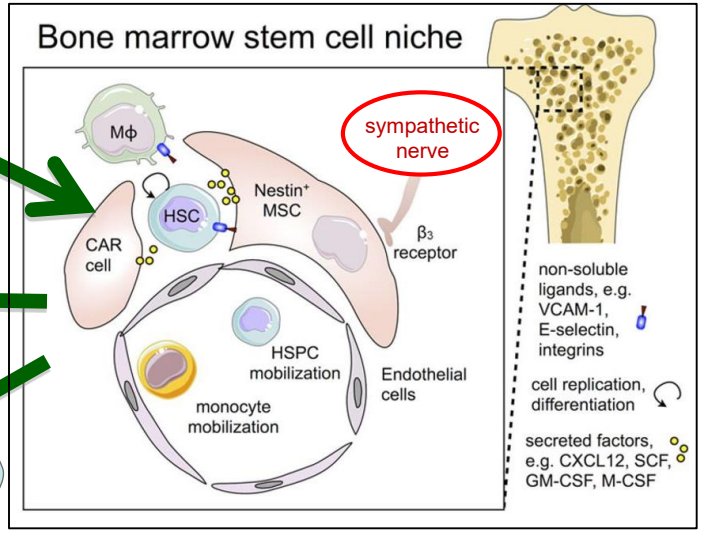
- Shaking cages
- Cat on cage



Worsened Atherosclerosis



Bone Marrow Activation



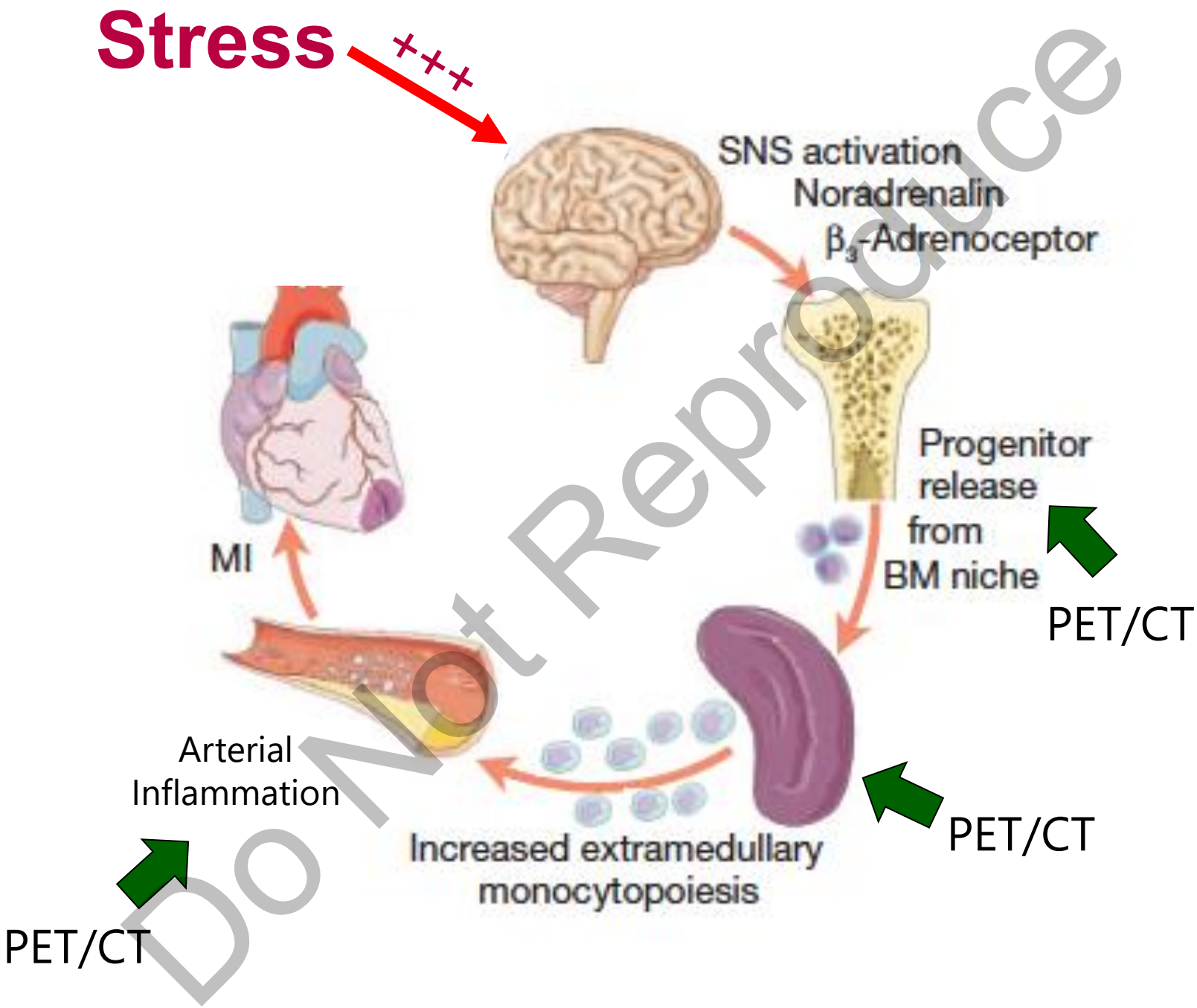
Immune Cell Entry
and Plaque Destabilization

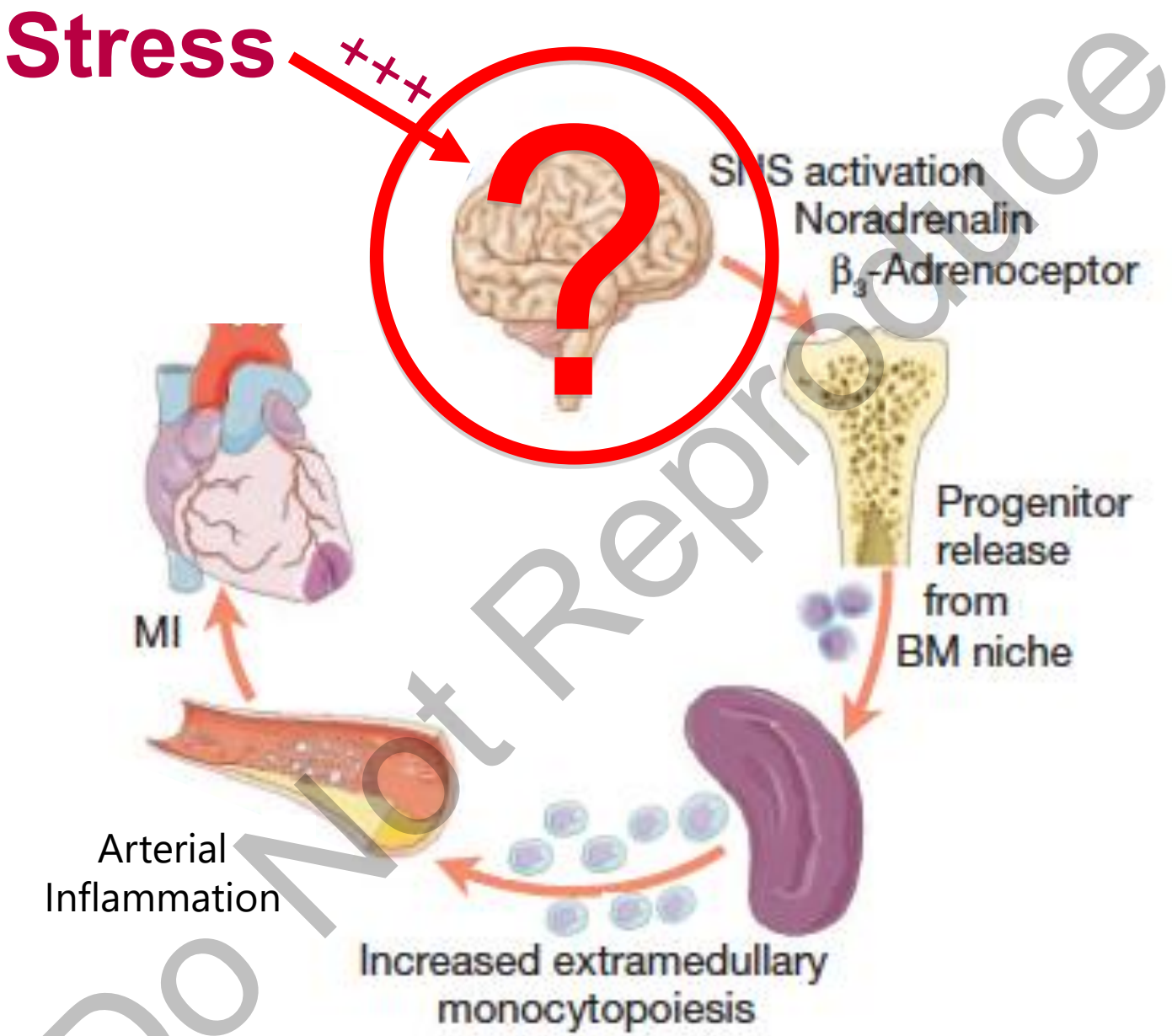
Splenic Activation

Immune Cell Homing and
Further Proliferation

Proliferation and Release
of Immune Progenitor Cells

Dutta et al Nature 2012, Heidt et al Nat Med 2014, Nahrendorf & Swirski, Circ Research 2015

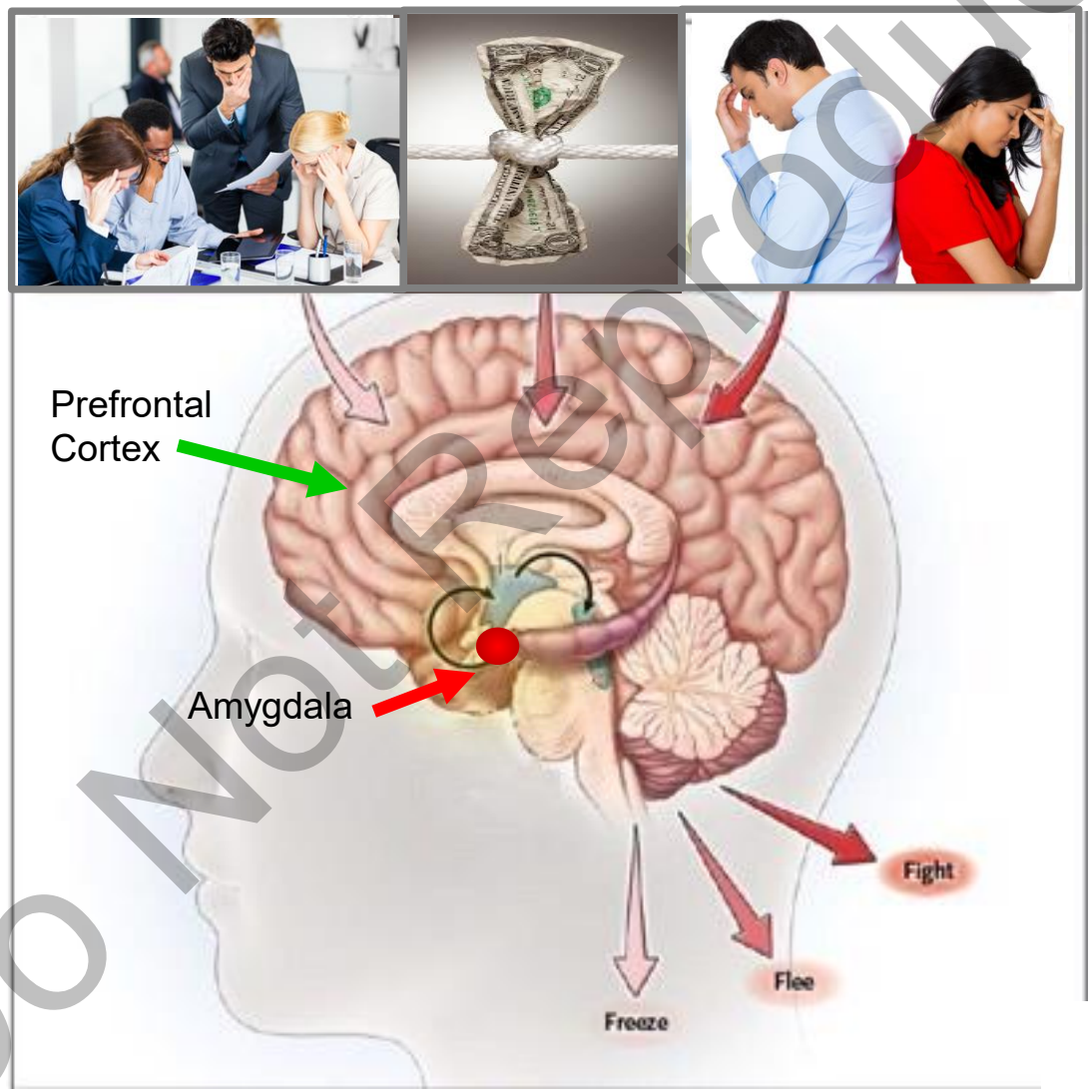




Perceived Stress Scale-10

The questions in this scale ask you about your feelings and thoughts during the last month. In each case, you will be asked to indicate by circling how often you felt or thought a certain way.	Never	Almost Never	Sometimes	Fairly Often	Very Often
1. In the past month, how often have you been upset because of something that happened unexpectedly?	0	1	2	3	4
2. In the past month, how often have you felt unable to control the important things in your life?	0	1	2	3	4
3. In the past month, how often have you felt nervous or stressed?	0	1	2	3	4
4. In the past month, how often have you felt confident about your ability to handle personal problems?	0	1	2	3	4
5. In the past month, how often have you felt that things were going your way?	0	1	2	3	4
6. In the past month, how often have you found that you could not cope with all the things you had to do?	0	1	2	3	4
7. In the past month, how often have you been able to control irritations in your life?	0	1	2	3	4
8. In the past month, how often have you felt that you were on top of things?	0	1	2	3	4
9. In the past month, how often have you been angry because of things that happened that were outside of your control?	0	1	2	3	4
10. In the past month, how often have you felt that difficulties were piling up so high that you could not overcome them?	0	1	2	3	4

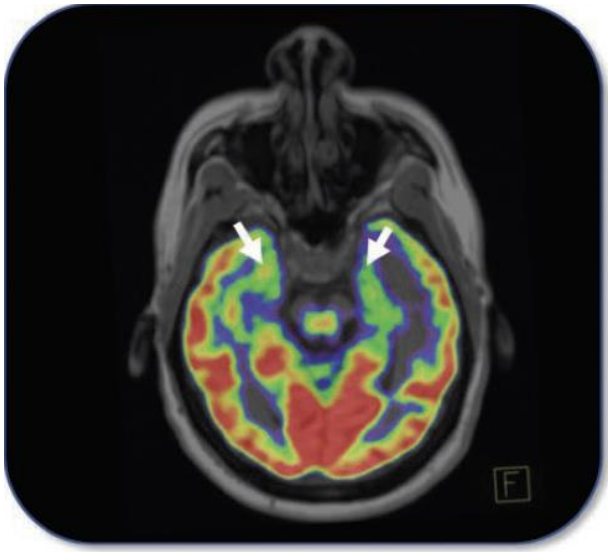
The Brain's Stress-Related Neural Network : Controlling the Physiologic Response to Stressors



Blair et al. NEJM Dec 2014

Imaging the Neurobiology of Stress

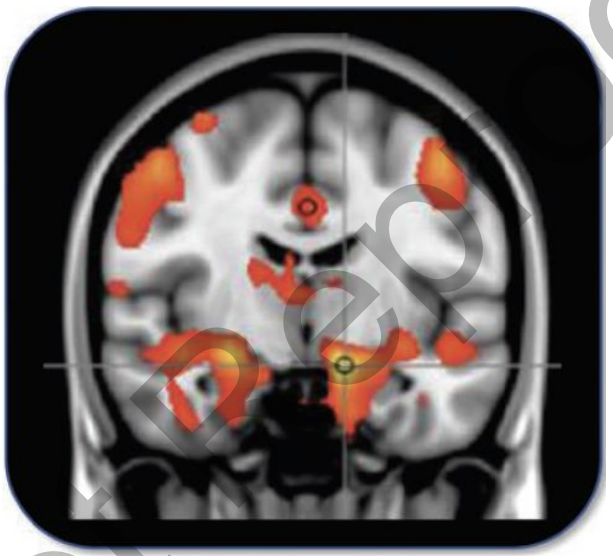
FDG PET



Neural Metabolism

High amygdalar activity (AA_C) relative to counter-regulatory cortical activity

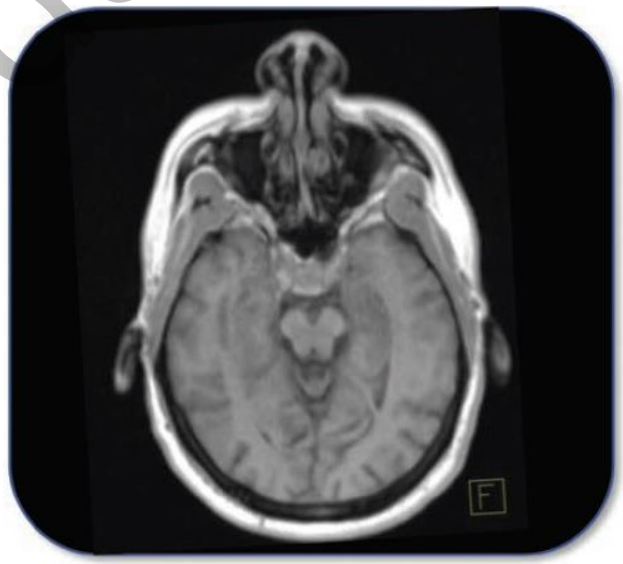
Functional MRI



Neural Activation and Connectivity

- Heightened activation in response to stressful stimuli
- Reduced connectivity to counter-regulatory tissue

Structural MRI



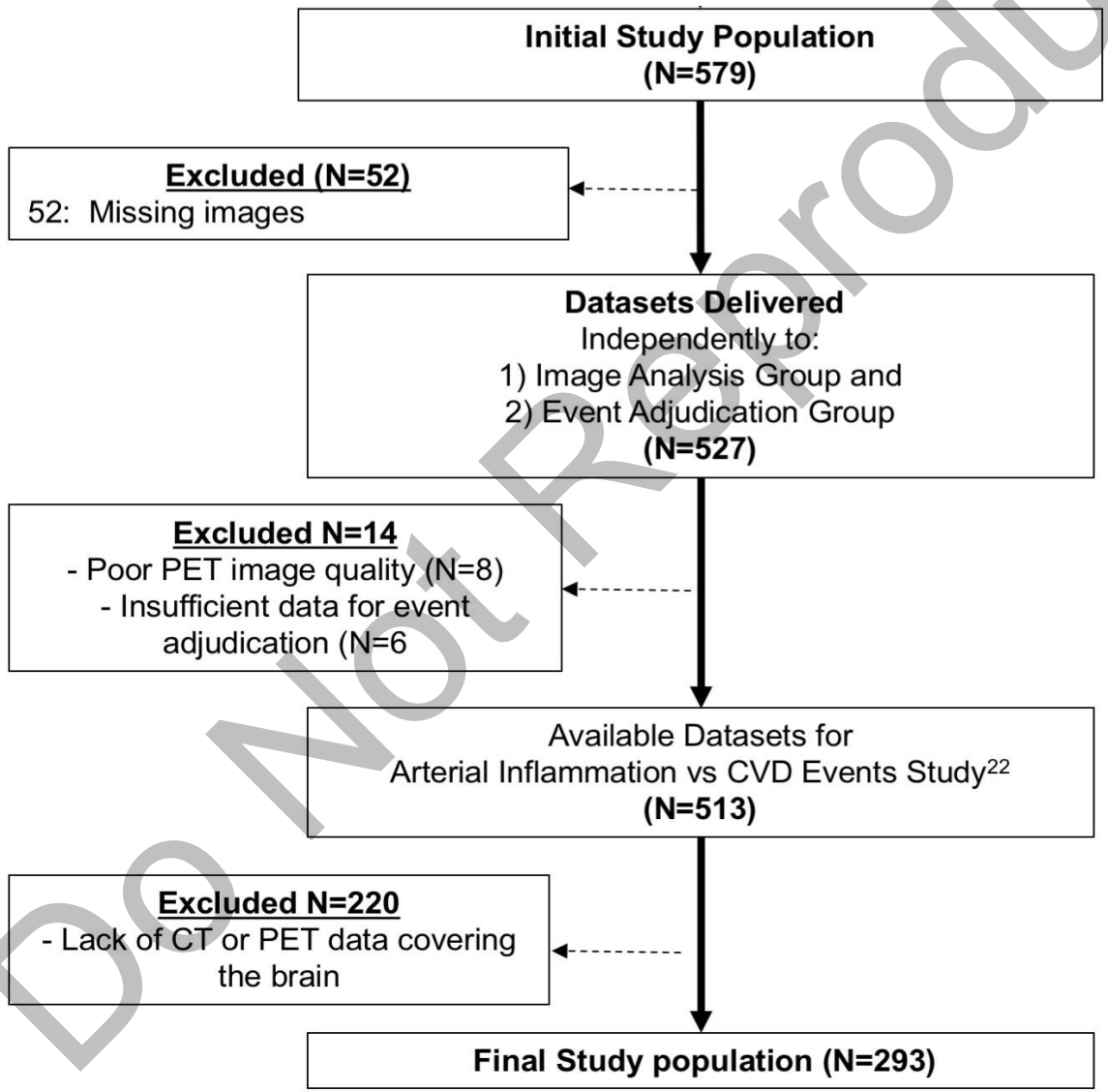
Tissue Volumes

- Amygdalar volume loss
- Due to loss of counterregulatory connections

Study of How Chronic Stress Leads to CVD in Humans

- Sought to test the hypothesis that higher stress neural activity associates with greater risk of CVD
- Employed multi-system imaging w FDG PET/CT and PET/MR to quantify:
  - Amygdalar/Cortical Activity (AA_C)
    - as ratio of amygdalar activity : counter-regulatory cortical activity
  - Leukopoietic Activity
    - bone marrow activity
  - Arterial inflammation
    - Aortic activity
- 5-year follow-up for CVD events (med record rev)

Study Cohort

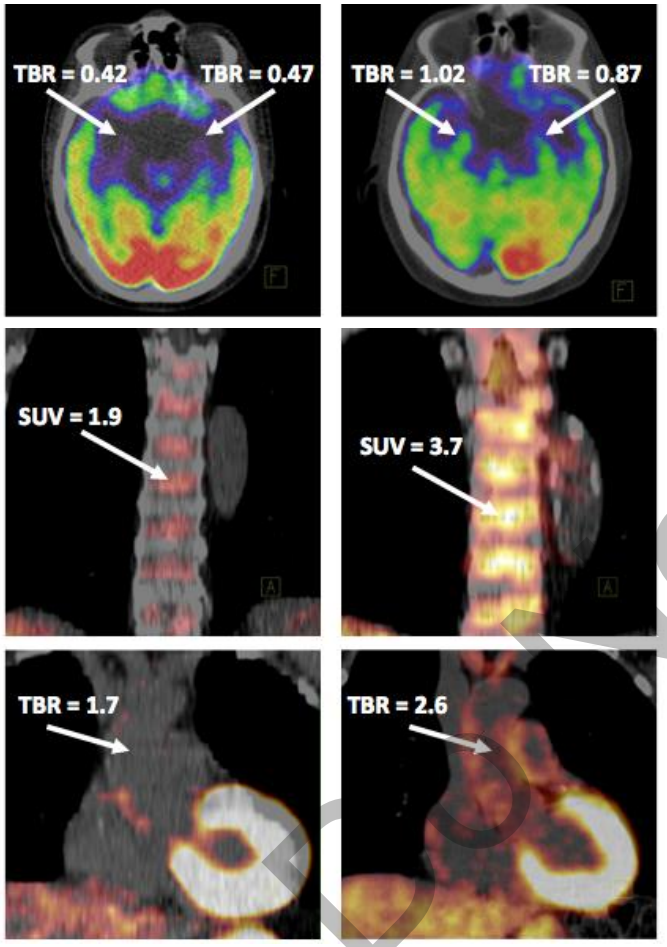


Tawakol et al
Lancet 2017

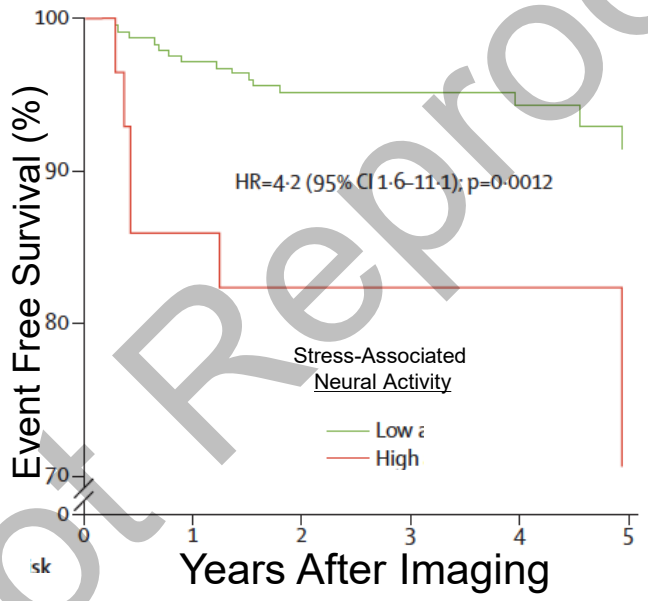
Amygdalar : Cortical Activity (A_cA) vs Subsequent CVD Events

Without Subsequent CVD Event

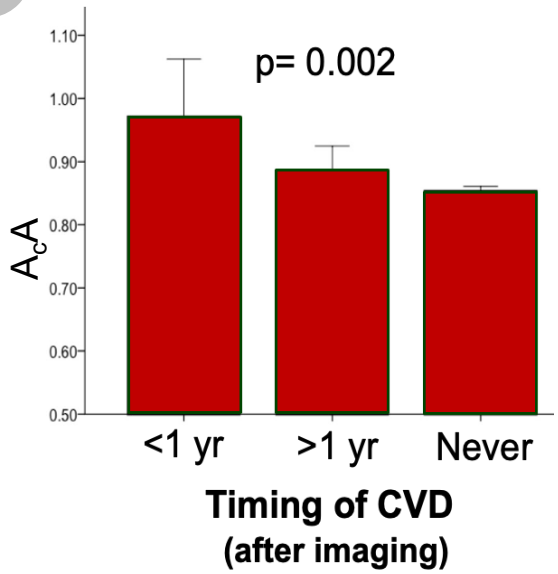
With Subsequent CVD Event

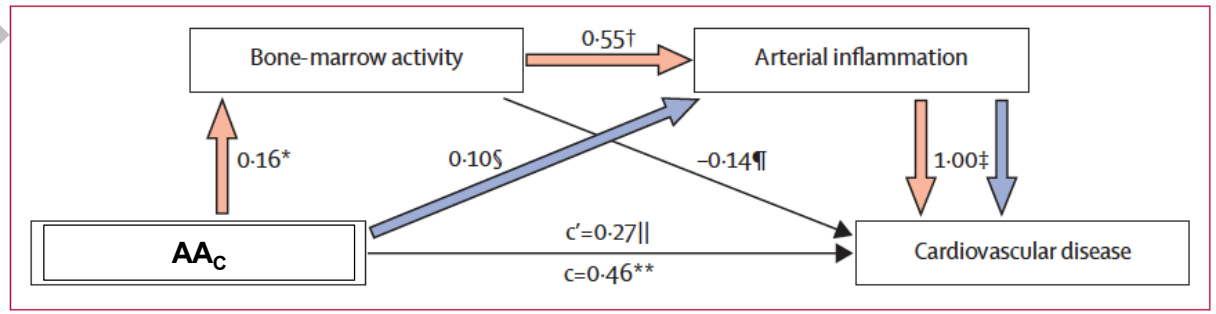


AA_C Vs Event Risk



AA_C Vs Event Timing



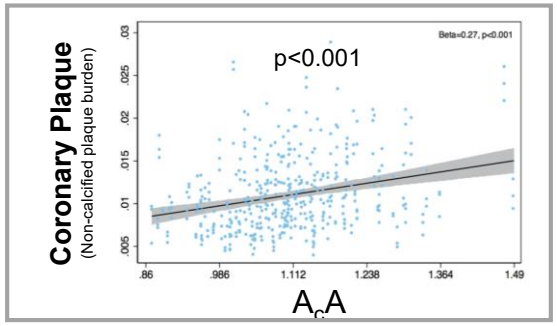


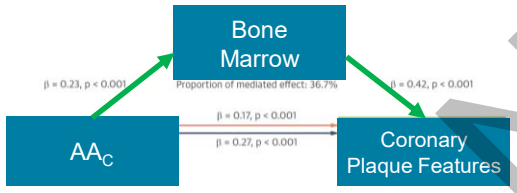
Tawakol et al Lancet 2017

Multi-group support for *neural-immune-arterial* mechanisms of disease

(out of 227 studies mentioning Amygdala and Cardiovascular Disease since January 2017)

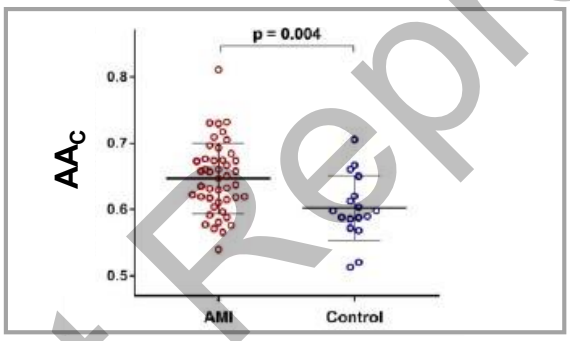
AA_C associates with higher-risk coronary plaque

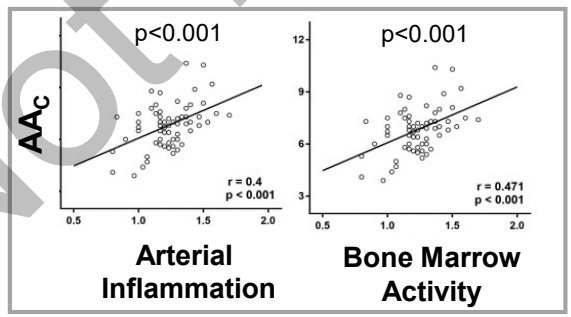




Goyal et al JACC CV Imaging 2020

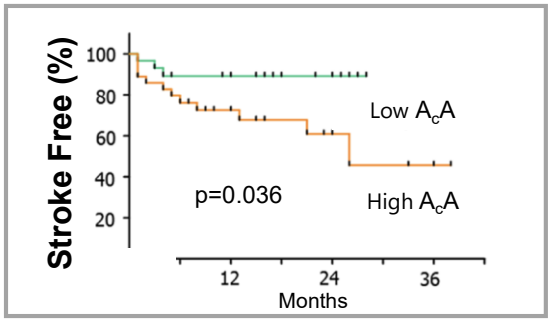
AA_C increased in acute MI

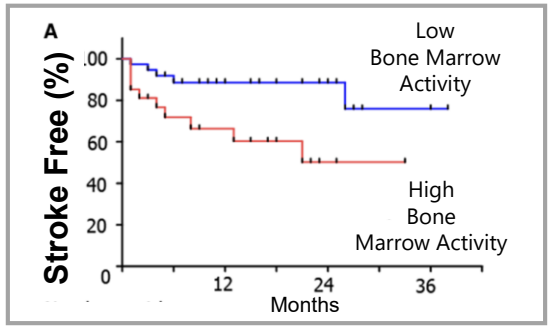




Kang et al EHJ 2021

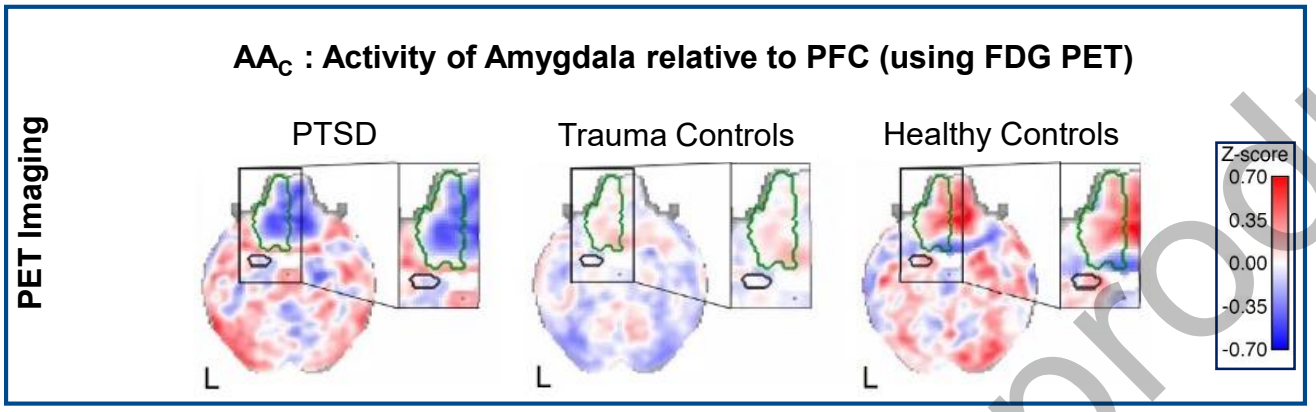
AA_C predicts recurrent events

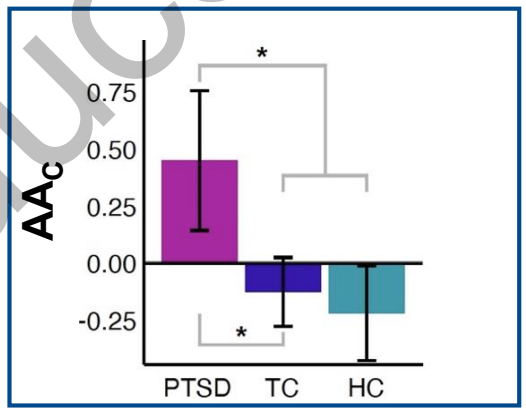


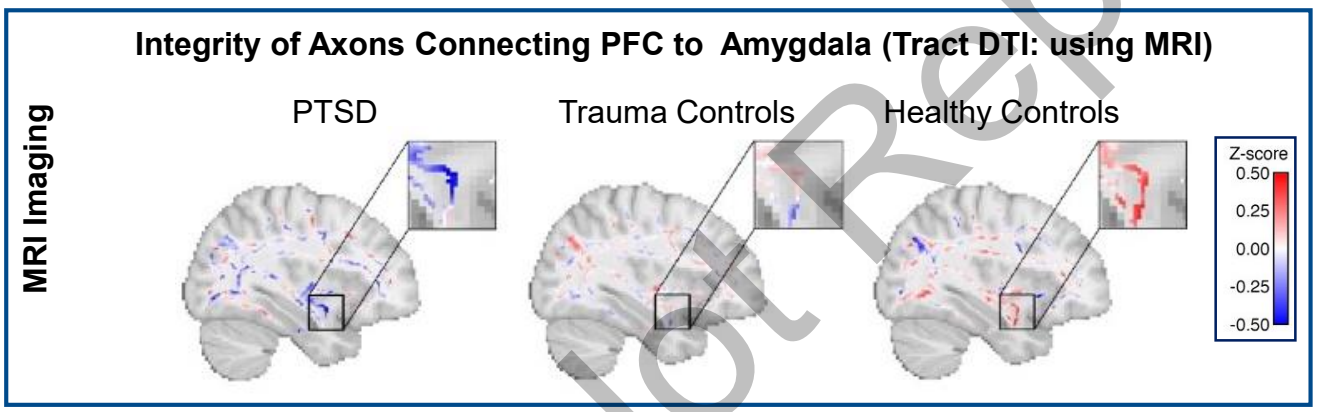


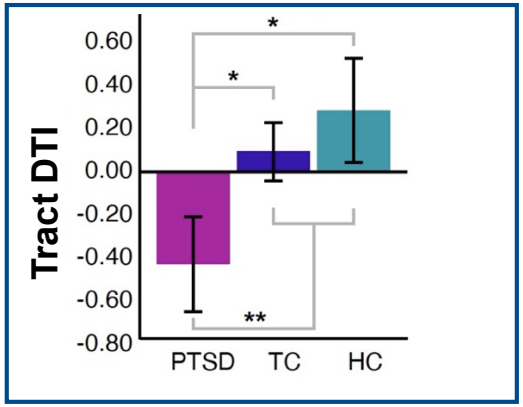
Kim et al, Circ: CV Imaging 2023

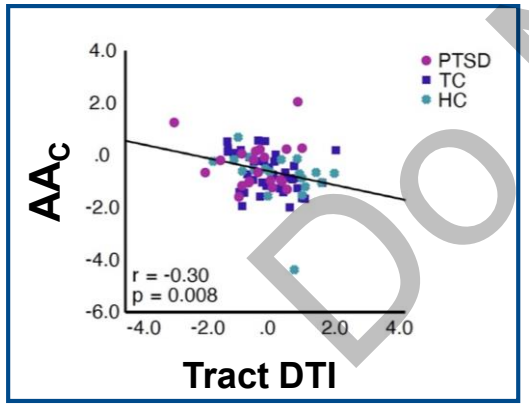
Amygdalar-cortical interactions predict atherosclerosis

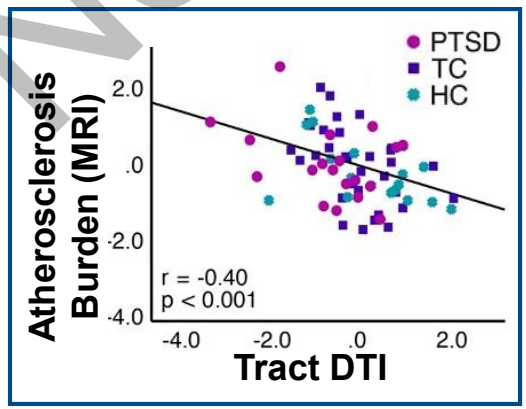


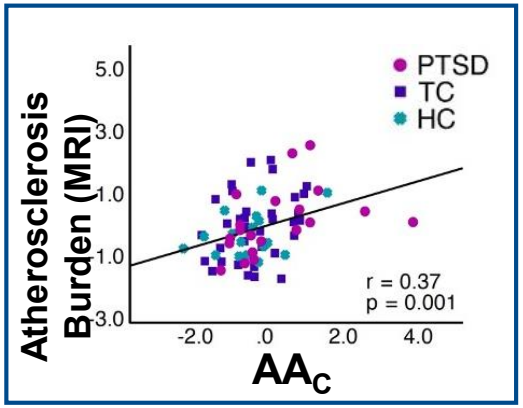






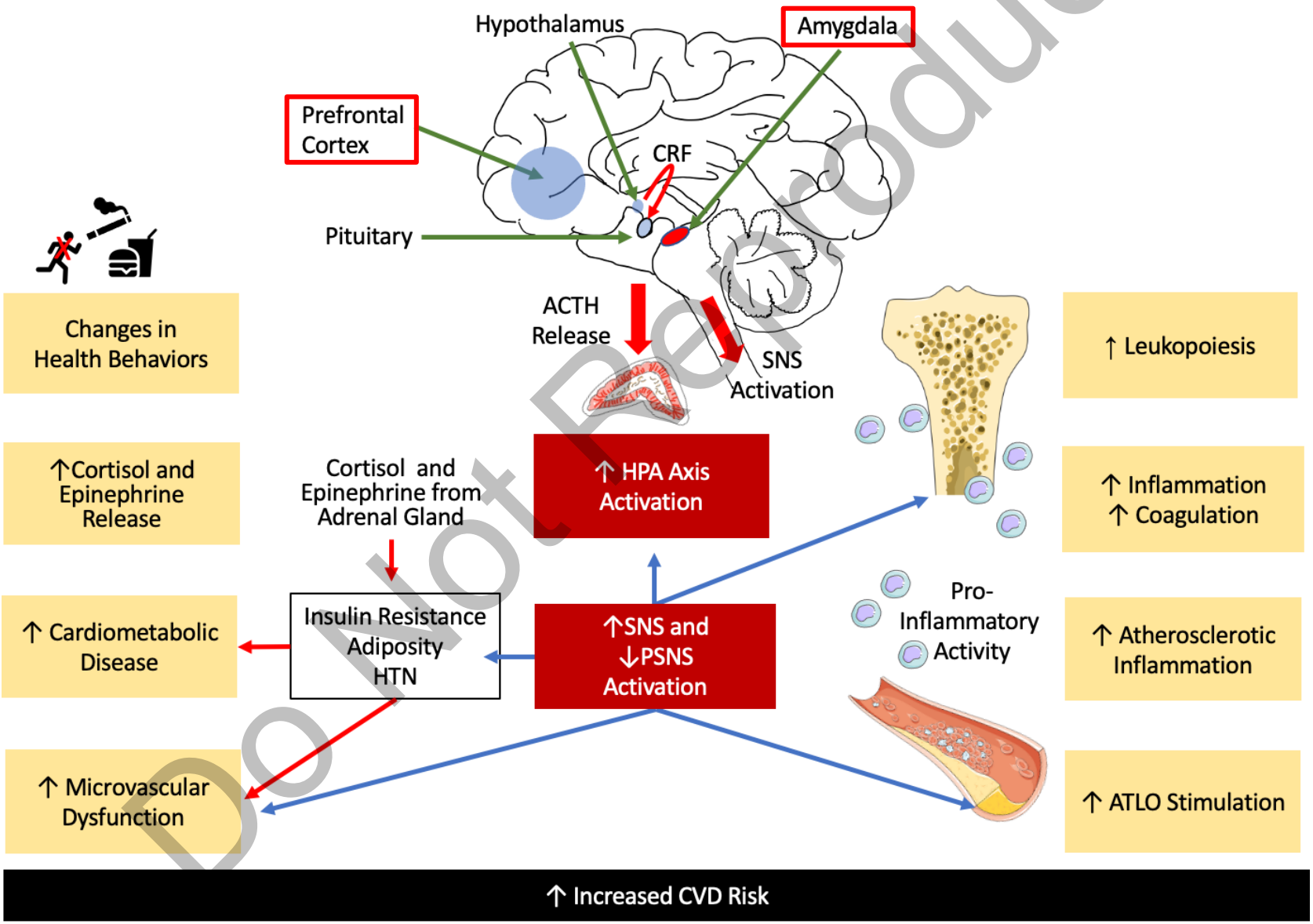






Gharios , Tawakol, Fayad. AHA 2022

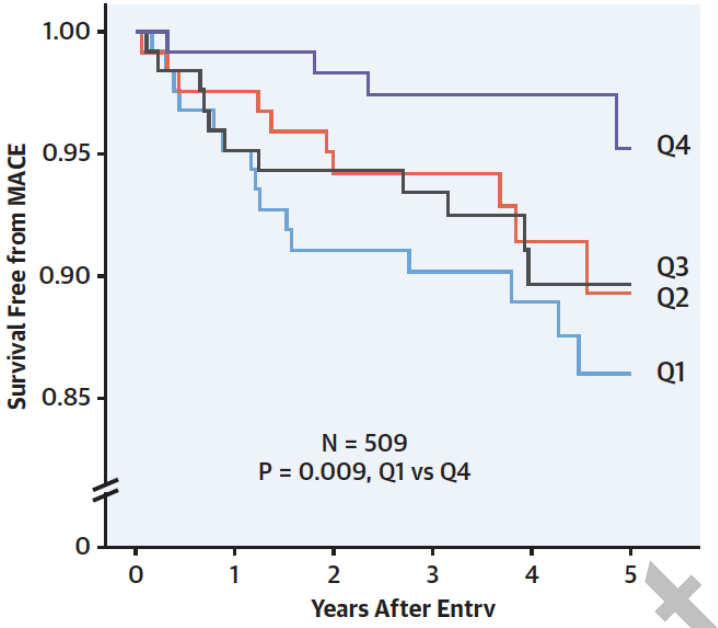
Stress-Related Pathophysiology

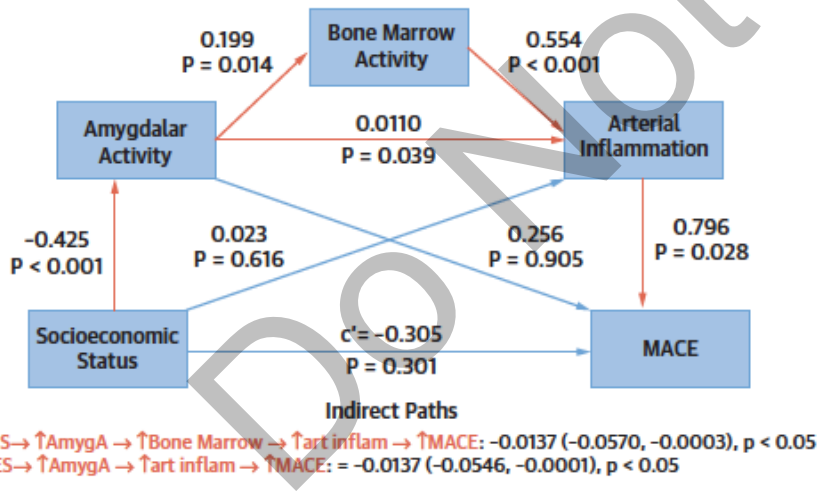


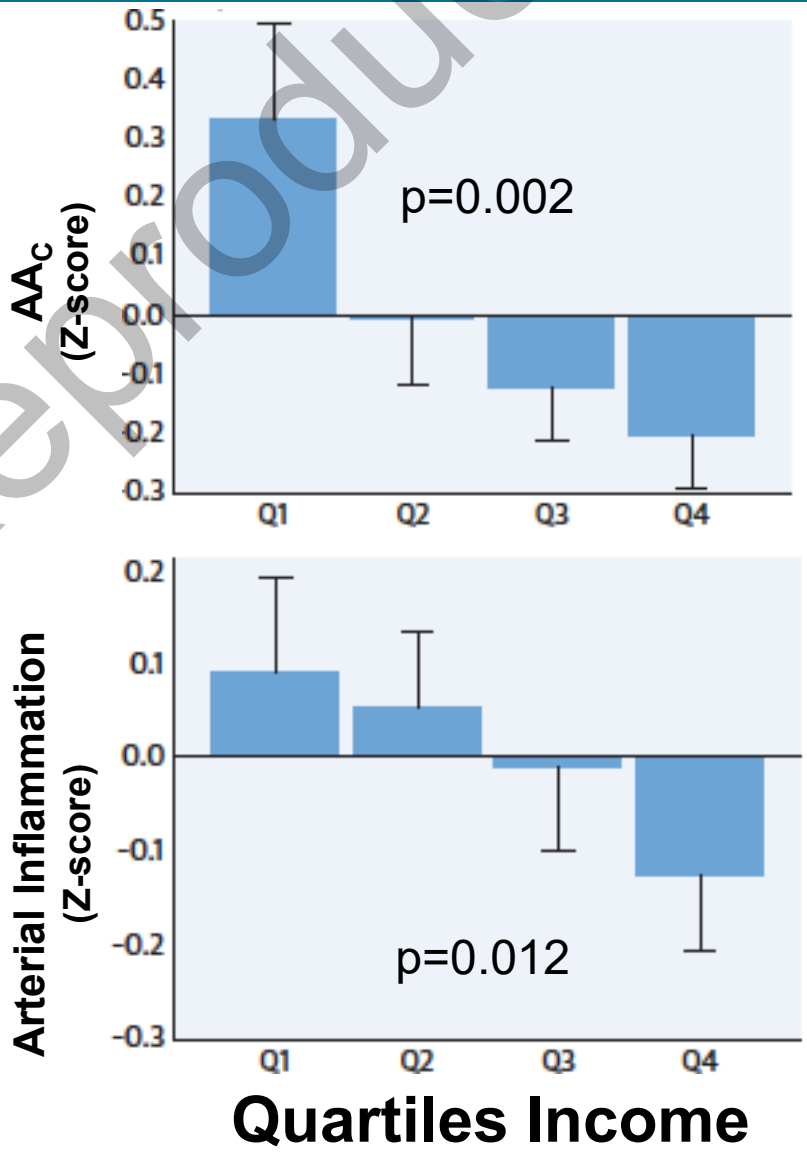
What about Chronic Stressors and CVD?

- Two well-studied stressors:
  - Low socioeconomic status (e.g. low income and high crime)
  - Chronic noise
- Well-known that both factors associate with :
  - CVD
  - Stress
- Hypothesis:
  - stress-associated pathways partially mediate the link between Noise/SES and CVD

Socioeconomic Status vs CVD: Involvement of Stress-Associated Mechanisms

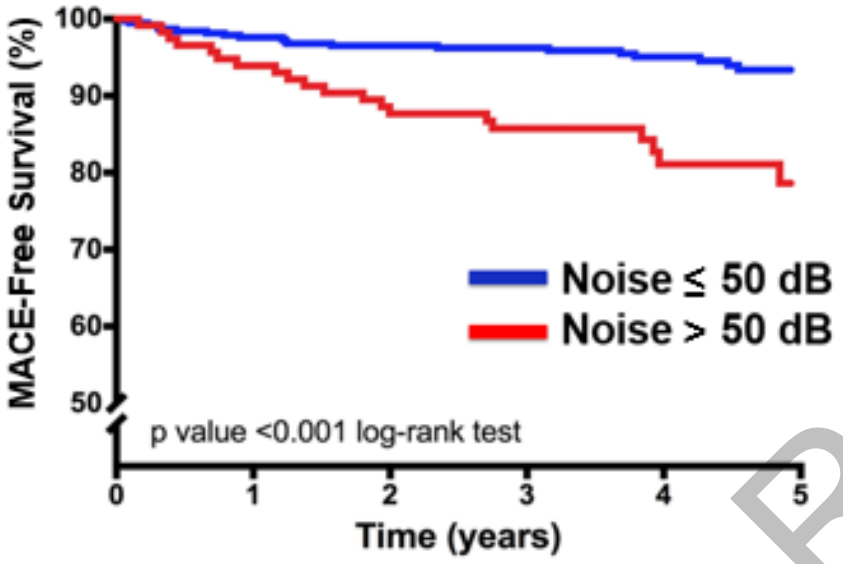


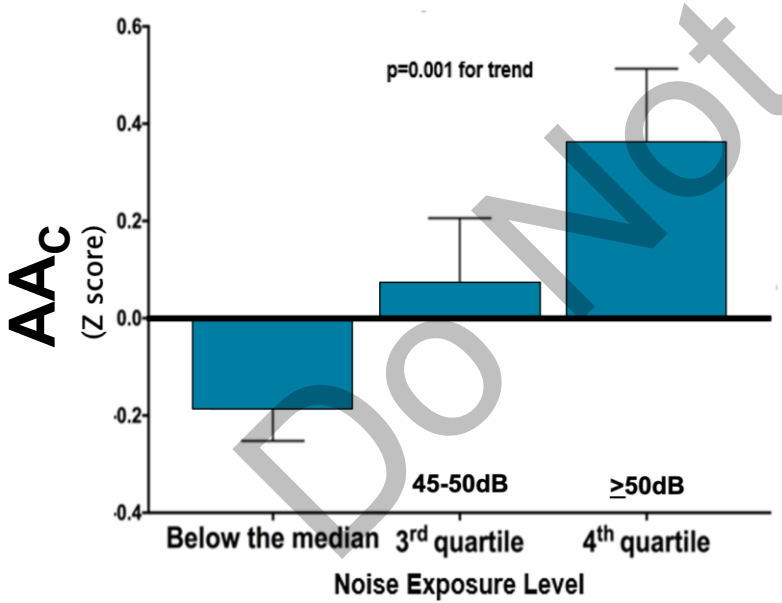


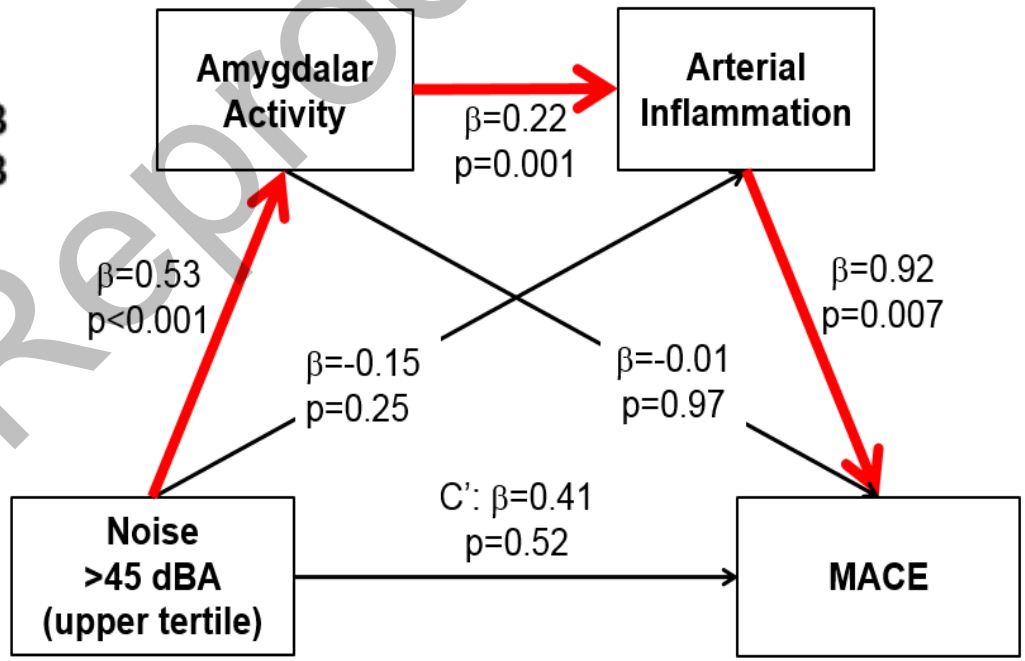


Tawakol ...Armstrong JACC 2019

Noise-Brain-CVD

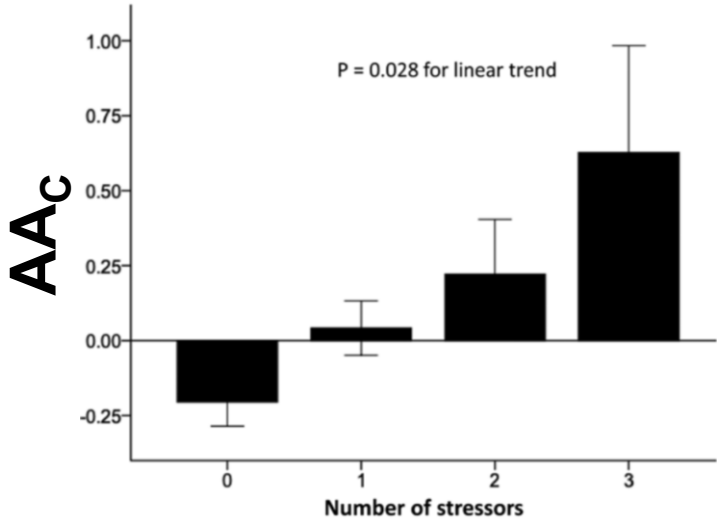


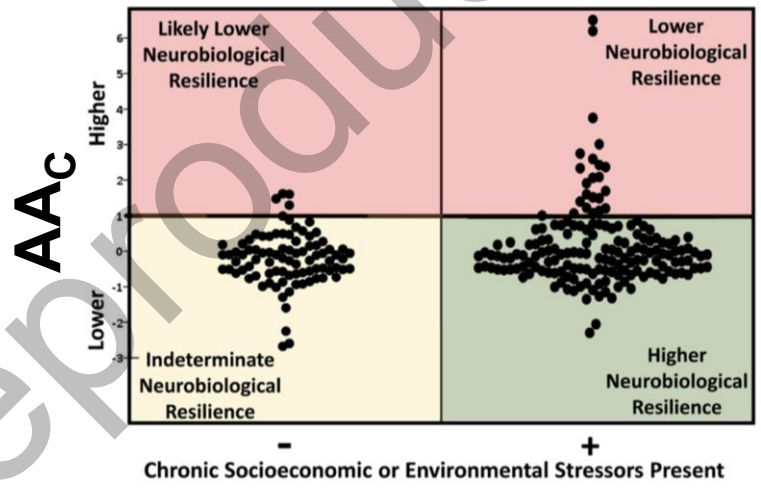




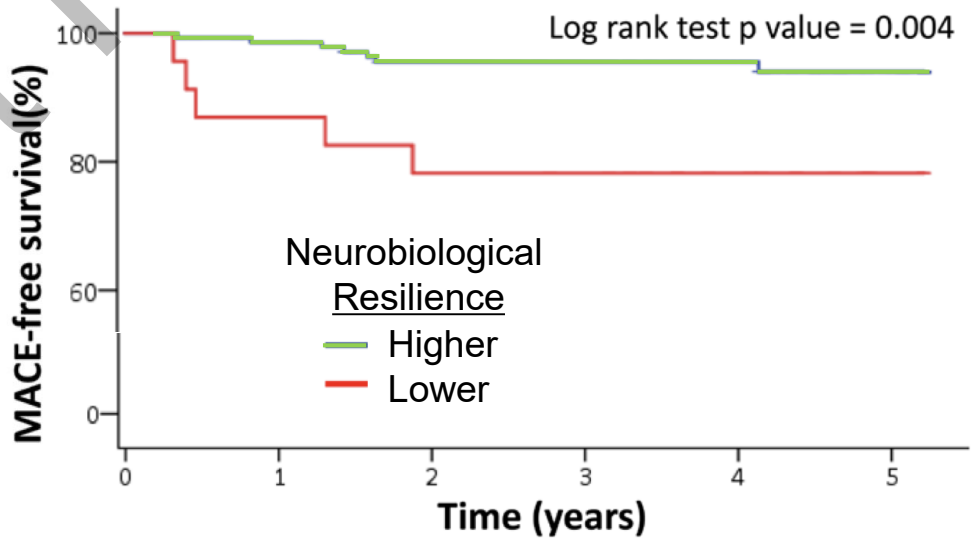
M Osborne et al
EHJ 2020

Neurobiological Resilience





Neurobiological Resilience Determines Outcomes among Stress-Exposed



Dar el al Circ Imaging 2020

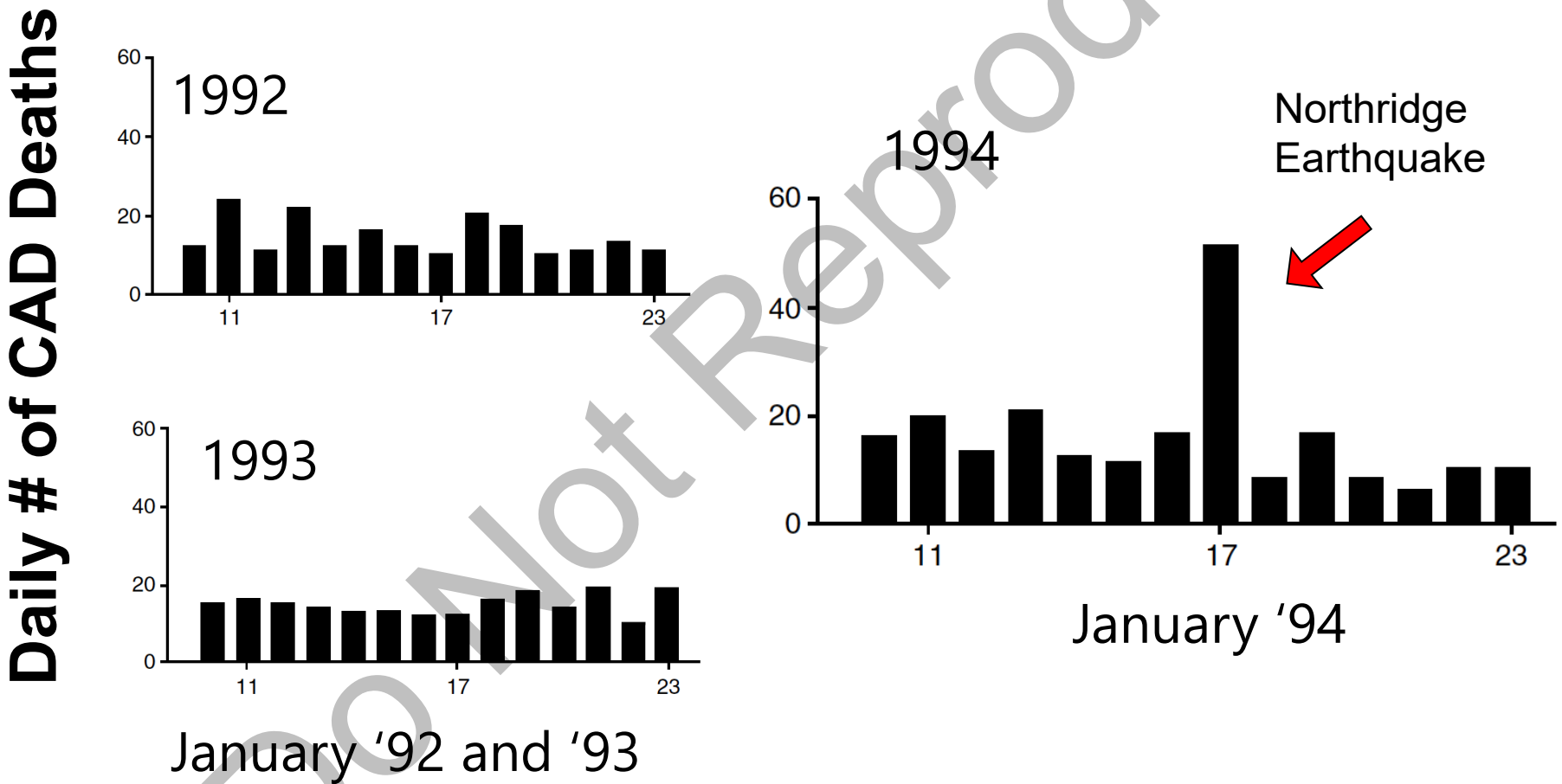
HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Acute Stress and CVD

MASSACHUSETTS GENERAL HOSPITAL

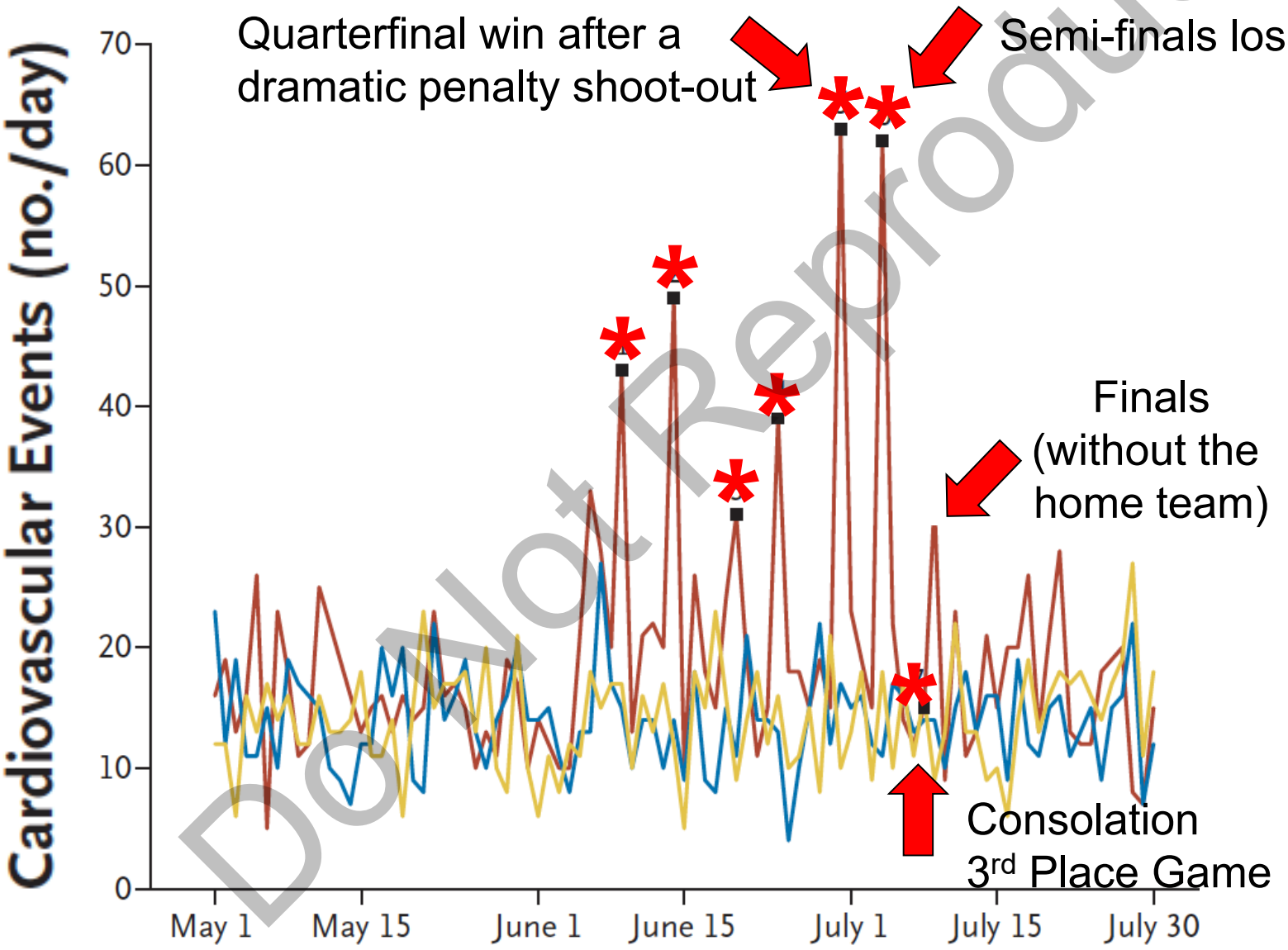
CORRIGAN MINEHAN HEART CENTER

Acute Stress and CVD: Earthquake



Leore, Poole & Kloner NEJM 1996

Acute Stress and CVD: World Cup



Ibert-Lampen et al NEJM 2008

CVD Events Surge after Elections

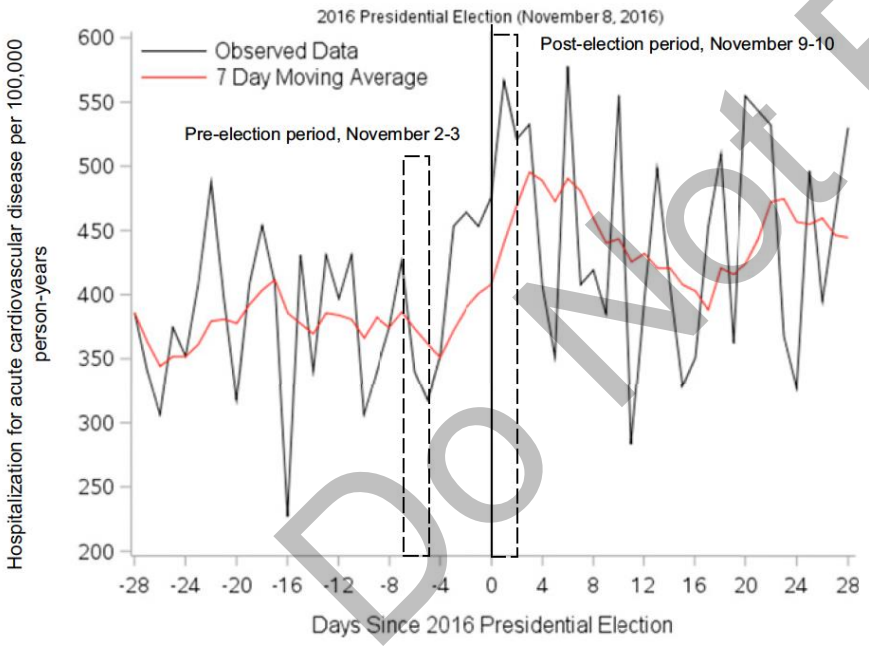
PNAS

RESEARCH ARTICLE | BIOLOGICAL SCIENCES | FREE ACCESS

Sociopolitical stress and acute cardiovascular disease hospitalizations around the 2016 presidential election

Matthew T. Mefford, Murray A. Mittleman, Bonnie H. Li, +8, and David R. Williams Authors Info & Affiliations

October 12, 2020 | 117 (43) 27054-27058 | https://doi.org/10.1073/pnas.2012096117



JAMA Network Open

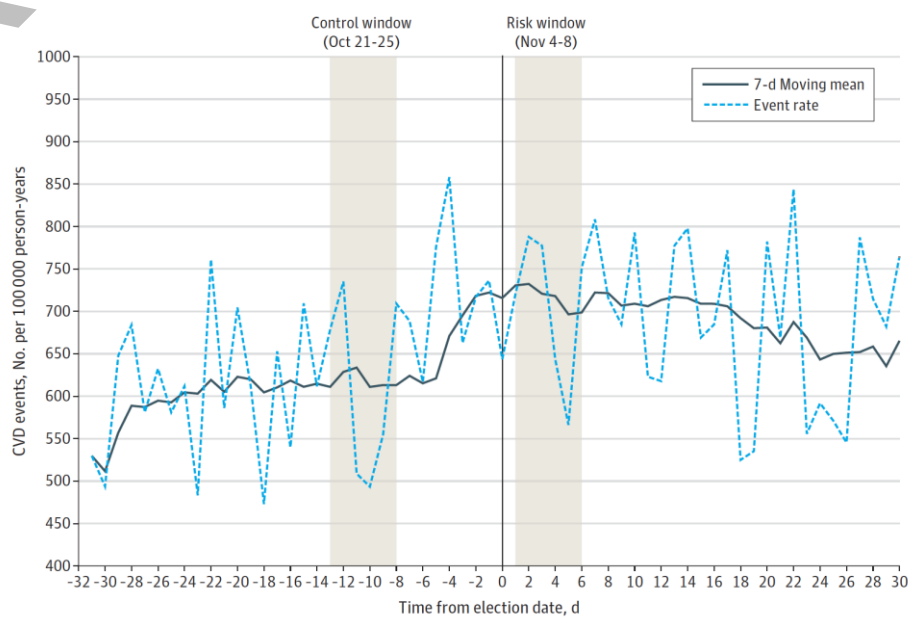
Association of the 2020 US Presidential Election With Hospitalizations for Acute Cardiovascular Conditions

Matthew T. Mefford, PhD[1]; Jamal S. Rana, MD, PhD[2,3]; Kristi Reynolds, PhD, MPH[1,4]; Omesh Ranasinghe, MPH[1]; Murray A. Mittleman, MD, DrPH[5,6]; Jennifer Y. Liu, MPH[3]; Lei Qian, PhD[1]; Hui Zhou, PhD[1]; Teresa N. Harrison, SM[1]; Alan C. Geller, MPH[7]; Richard P. Sloan, PhD[8]; Elizabeth Mostofsky, ScD[5]; David R. Williams, PhD[7,9]; Stephen Sidney, MD[3]

Author Affiliations | Article Information

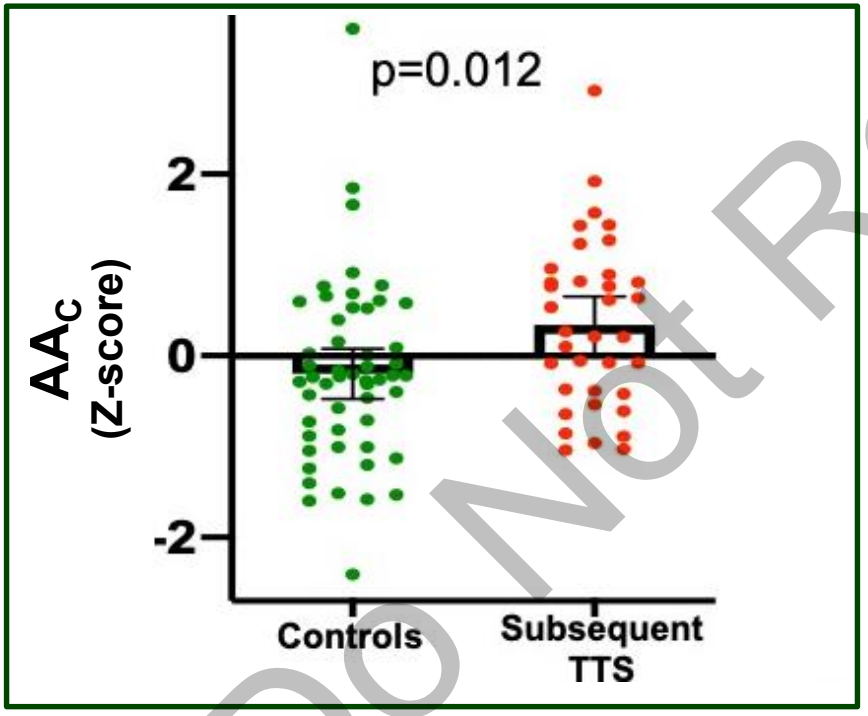
JAMA Netw Open. 2022;5(4):e228031. doi:10.1001/jamanetworkopen.2022.8031

Figure 1. Hospitalization for Acute Cardiovascular Disease (CVD) Events per 100 000 Person-Years in the Month Preceding and After the 2020 Presidential Election



AA_C vs. Risk of Takotsubo Syndrome (TTS)

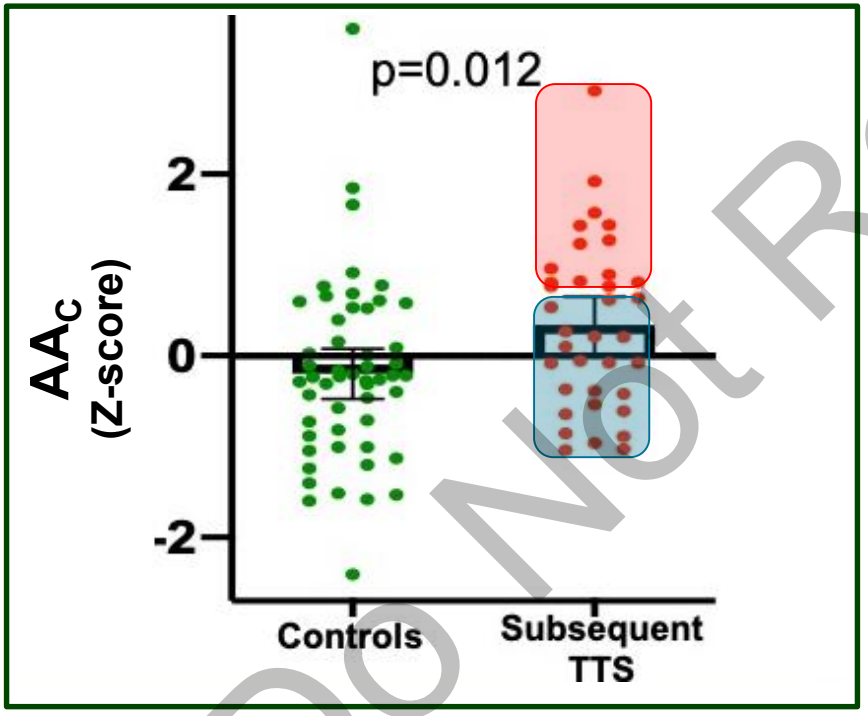
- 104 Individuals who underwent FDG-clinical PET/CT
- 41 subsequently developed TTS (med 2.5 years after imaging)
- 63 matched controls.

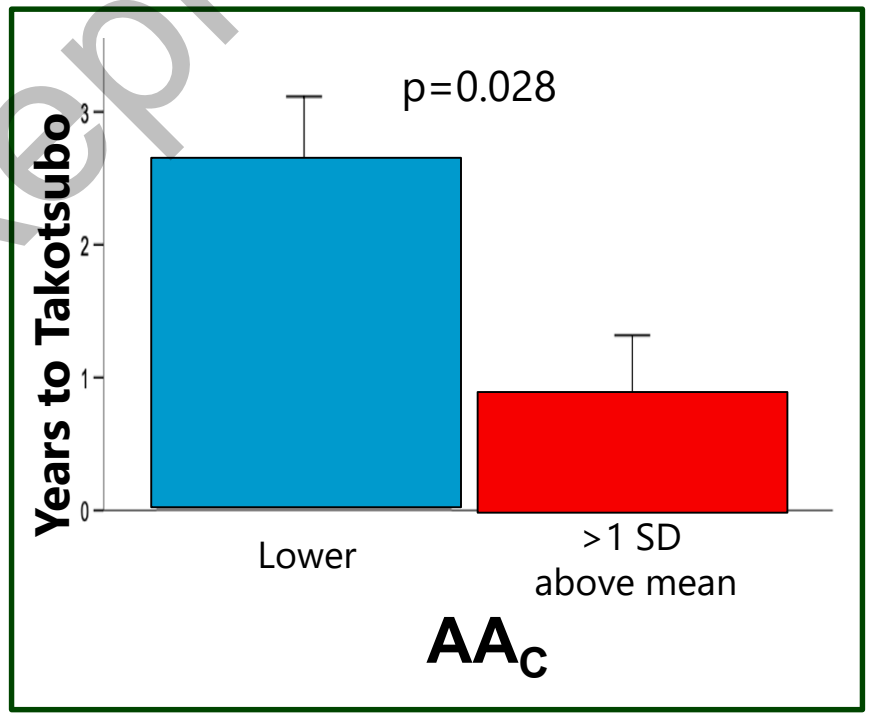


A Radfar, et al European Heart Journal 2021

AA_C vs. Risk of Takotsubo Syndrome (TTS)

- 104 Individuals who underwent FDG-clinical PET/CT
- 41 subsequently developed TTS (med 2.5 years after imaging)
- 63 matched controls.





A Radfar, et al European Heart Journal 2021

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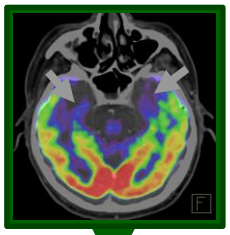
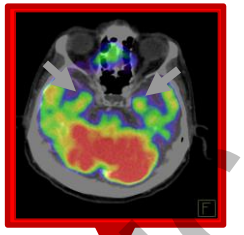
Lower AA_C
More
Neurbiologically
Resilient





Higher AA_C
Less
Neurbiologically
Resilient

Lower susceptibility
of neural centers to
activation by stressful events

Higher susceptibility
of neural centers to
activation by stressful events

Emotional and/or physical stressors

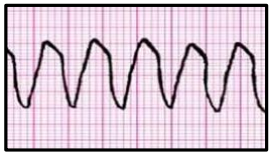
Less neural activation and lesser systemic response to stress

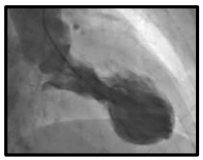
Triggered neural activation and exaggerated systemic response to stress

Fewer Physiologic consequences of stress

Sympathetic system surge
Inflammation
Hypercoagulability

Benign / Resilient Course





ACS **Sudden Death** **Arrhythmia** **Takotsubo**

HARVARD MEDICAL SCHOOL
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Impact of Interventions on Stress-Associated Neural Activity

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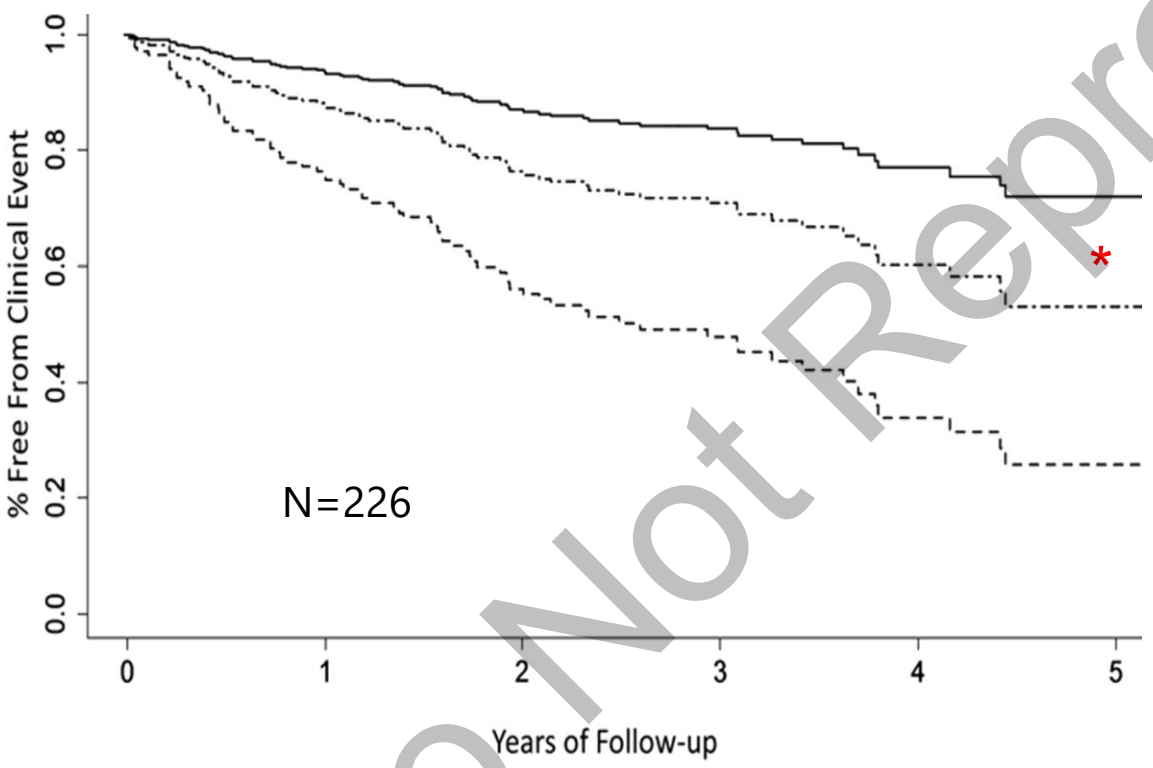
Stress Reduction may Impart CVD Benefits

226 Subjects with recent CVD events
Standard Cardiac Rehab (exercise) vs Enhanced Cardiac Rehab (Exercise + SR)



Exercise (CR) and Stress Reduction

* Exercise (CR) Alone

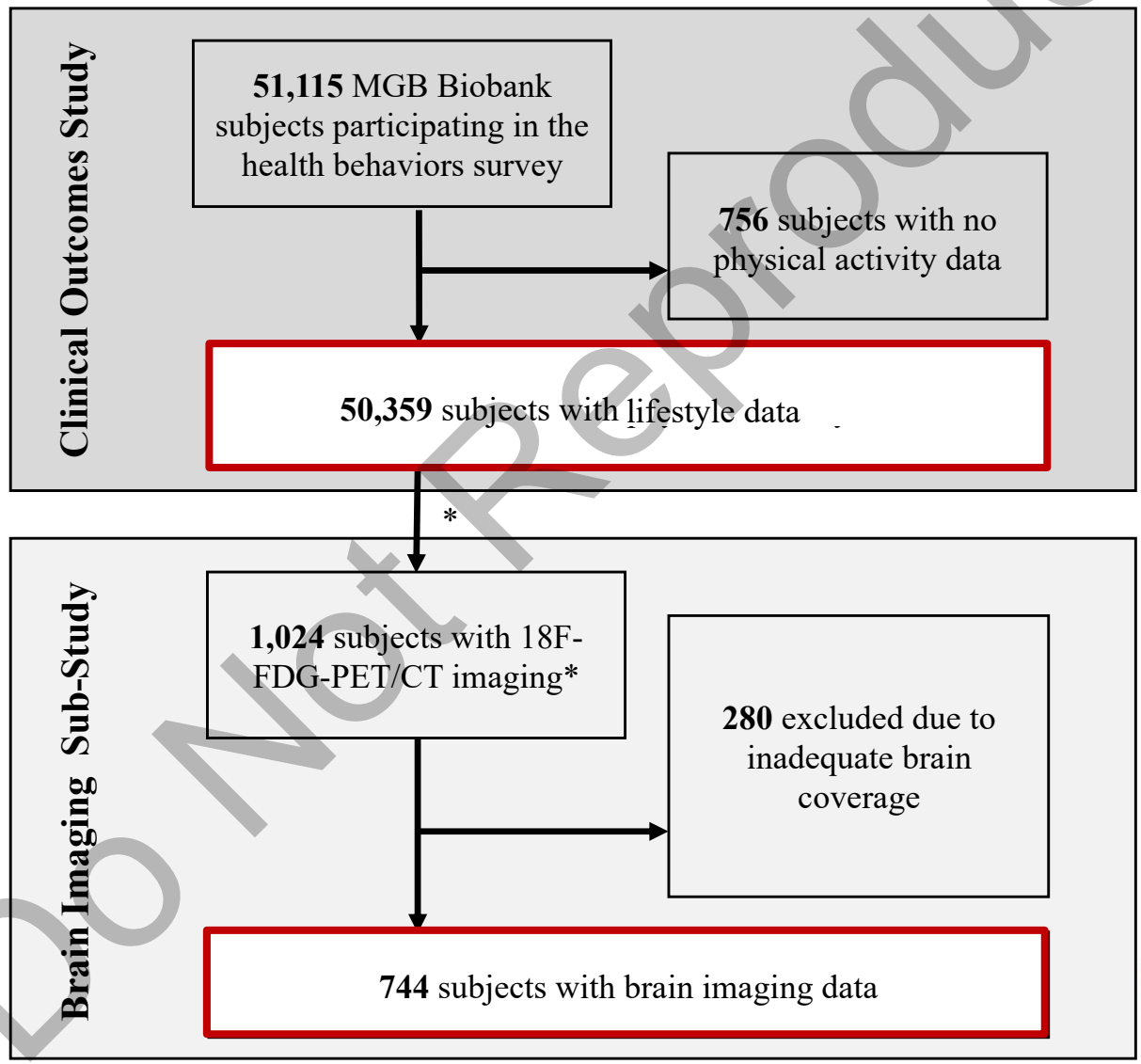
No Intervention

* P=0.025

>50% relative risk reduction for:
CR + Stress Reduction vs.
CR alone

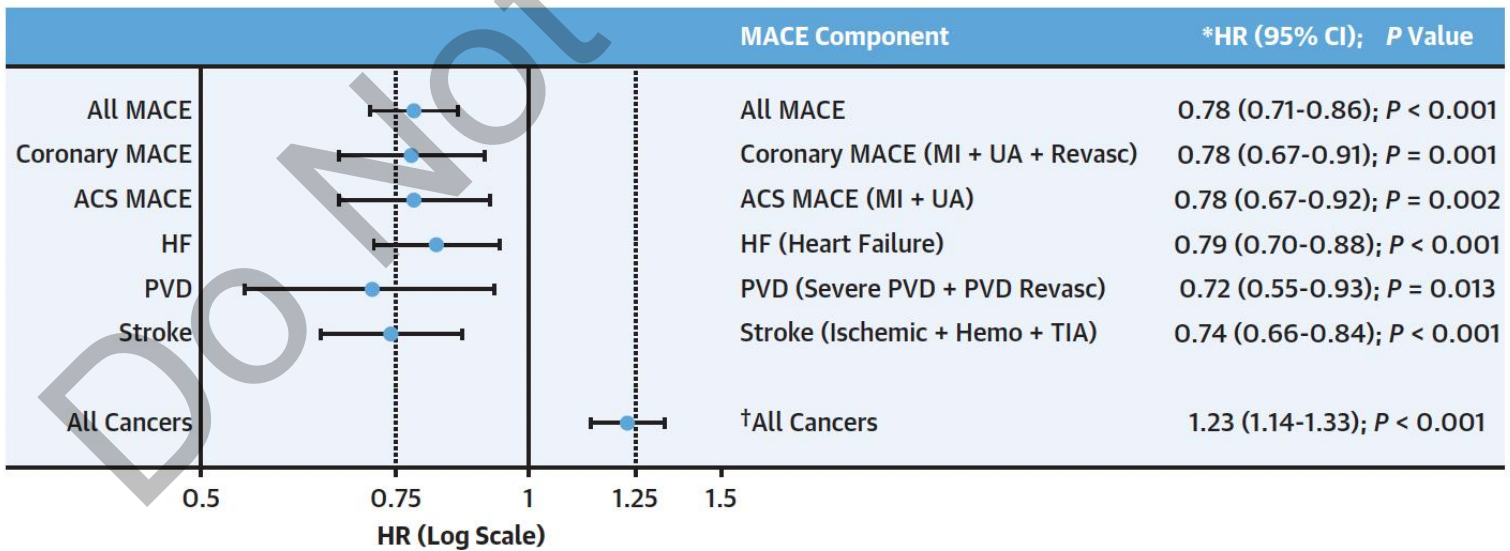
Blumenthal et al Circulation 2016

Evaluation of Lifestyle Factors : MGB Biobank Heart-Mind Study



Light/Mod Alcohol vs MACE

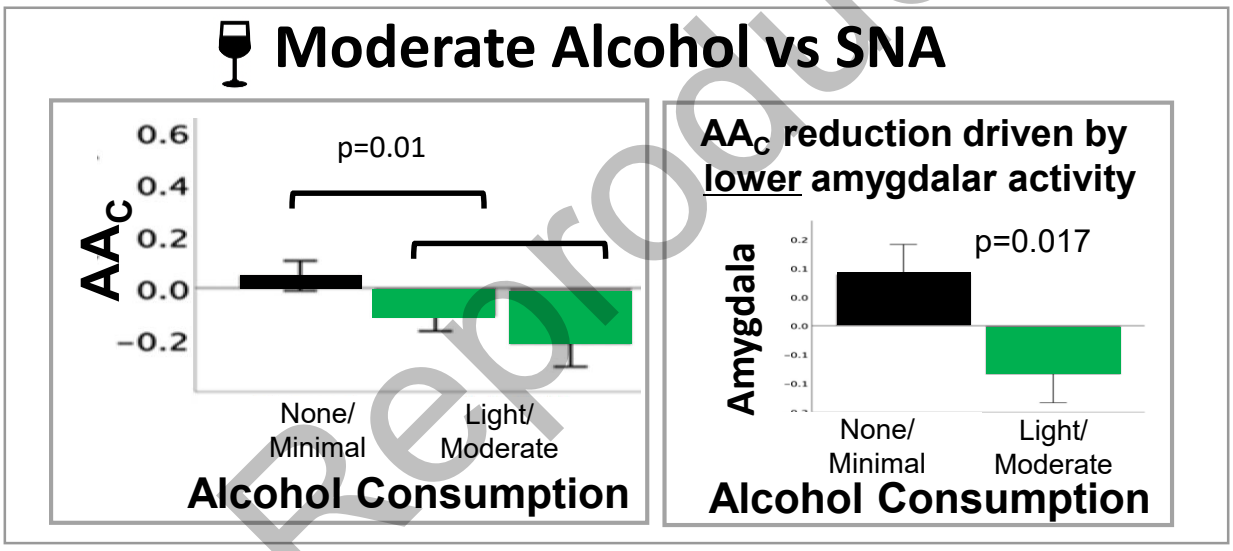
	Covariable Themes	Covariables	10-year MACE	P-Value
Light/moderate vs Low Alcohol consumption	+ CVD risk factors (primary analysis)	Age, sex, HTN, DM, HLD, smoking	0.81 (0.75-0.88)	**P<0.001**
	+ Health behaviors	Exercise, Sleep disorders	0.83 (0.77-0.90)	**P<0.001**
	+ Socioeconomic factors	Employment, Education, income	0.84 (0.77-0.91)	**P<0.001**
	+ Psychological factors	Depression, Anxiety	0.84 (0.77-0.91)	**P<0.001**
	+ Medical comorbidities	Charlson index	0.87 (0.80-0.94)	**P<0.001**



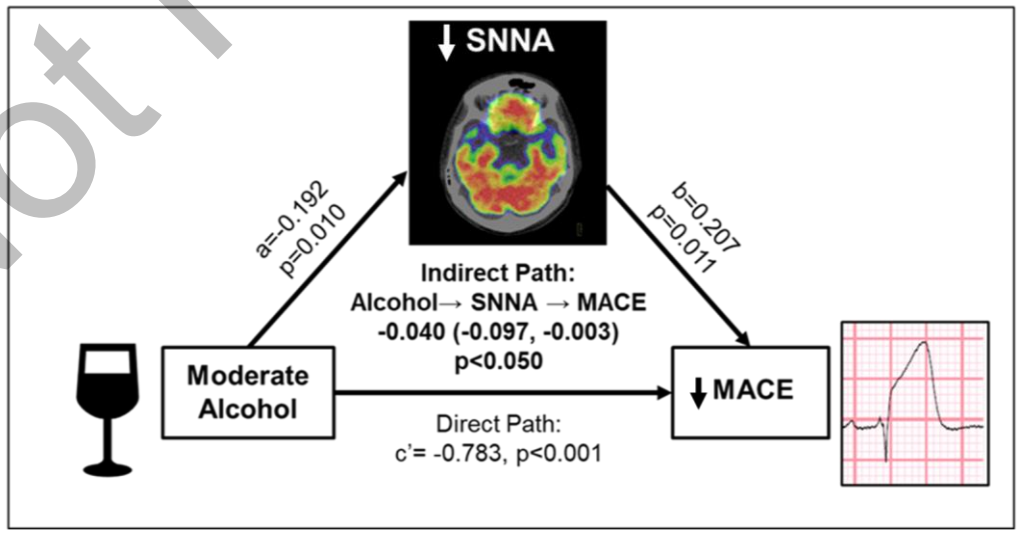
Mezue et al JACC 2023

Light/Mod Alcohol vs. Stress-Associated Neural Activity

Alcohol vs Stress-Associated Neural Activity



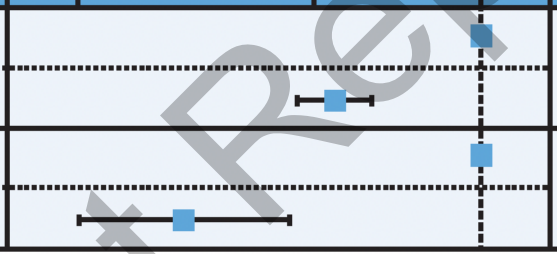
Moderate Alcohol Reduces MACE visa Decreased Stress-Associated Neural Network Activity



Mezue et al AHA 2021

Light/Mod Alcohol vs MACE

Greater effect in individuals with anxiety

B Population (n)	Alcohol Intake	10-Year MACE HR* (0.5 / 0.75 / 1)	HR (95% CI)	*P* Value for Difference	*P* Value for Interaction
Individuals Without Pre-Existing Anxiety (29,651)	none/minimal		0.78 (0.73-0.83)	< 0.001	0.003‡
	light/moderate				
Individuals With Pre-Existing Anxiety† (4,067)	none/minimal		0.60 (0.50-0.72)	< 0.001	
	light/moderate				

~double the reduction in MACE risk

Mezue et al JACC 2023

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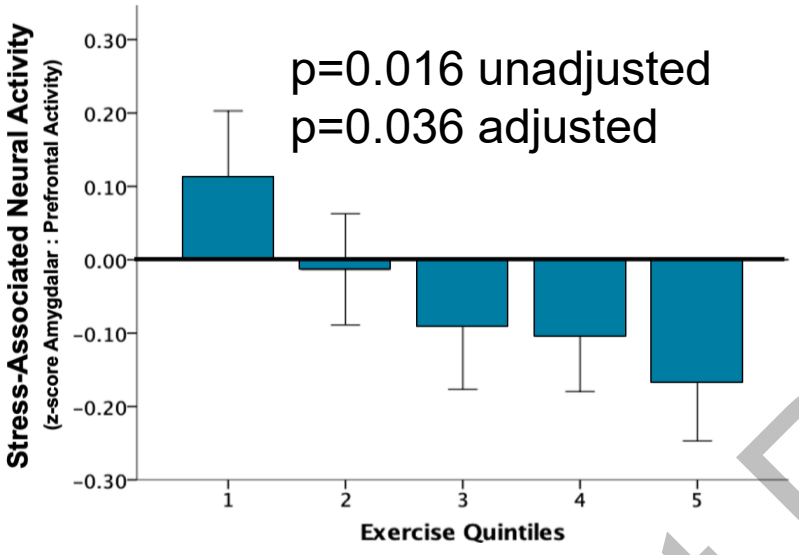
- Mod alcohol associates with decreased CVD risk
  - in part by attenuating stress-related pathways

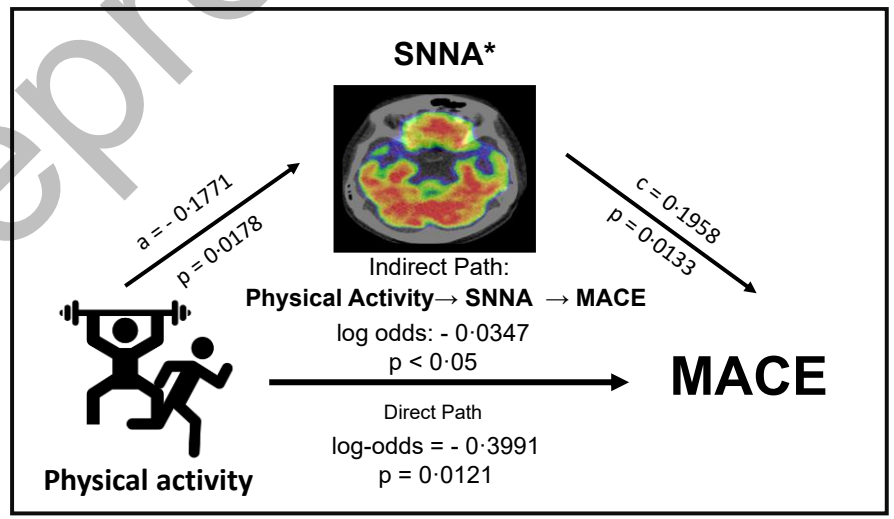
- No safe levels of alcohol

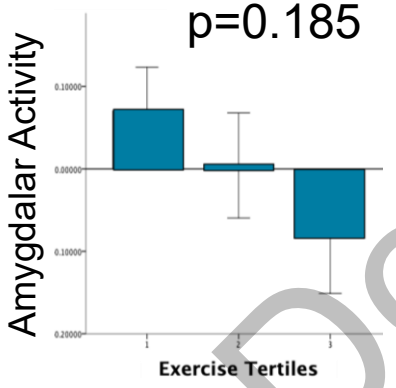
- Need therapies that reduce stress-associated neural mechanisms without the side effects of alcohol.

Relationship between Exercise and Stress-Associated Neural Activity

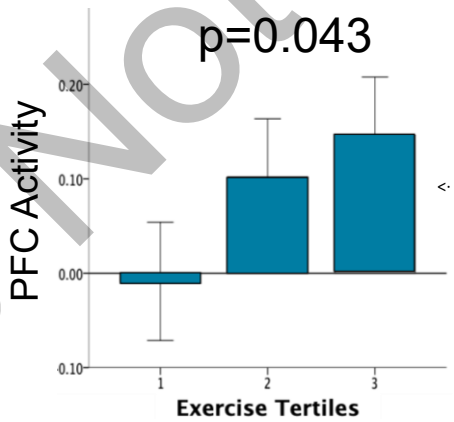


p=0.016 unadjusted
p=0.036 adjusted





p=0.185



p=0.043

Zureigat et al ACC 2021

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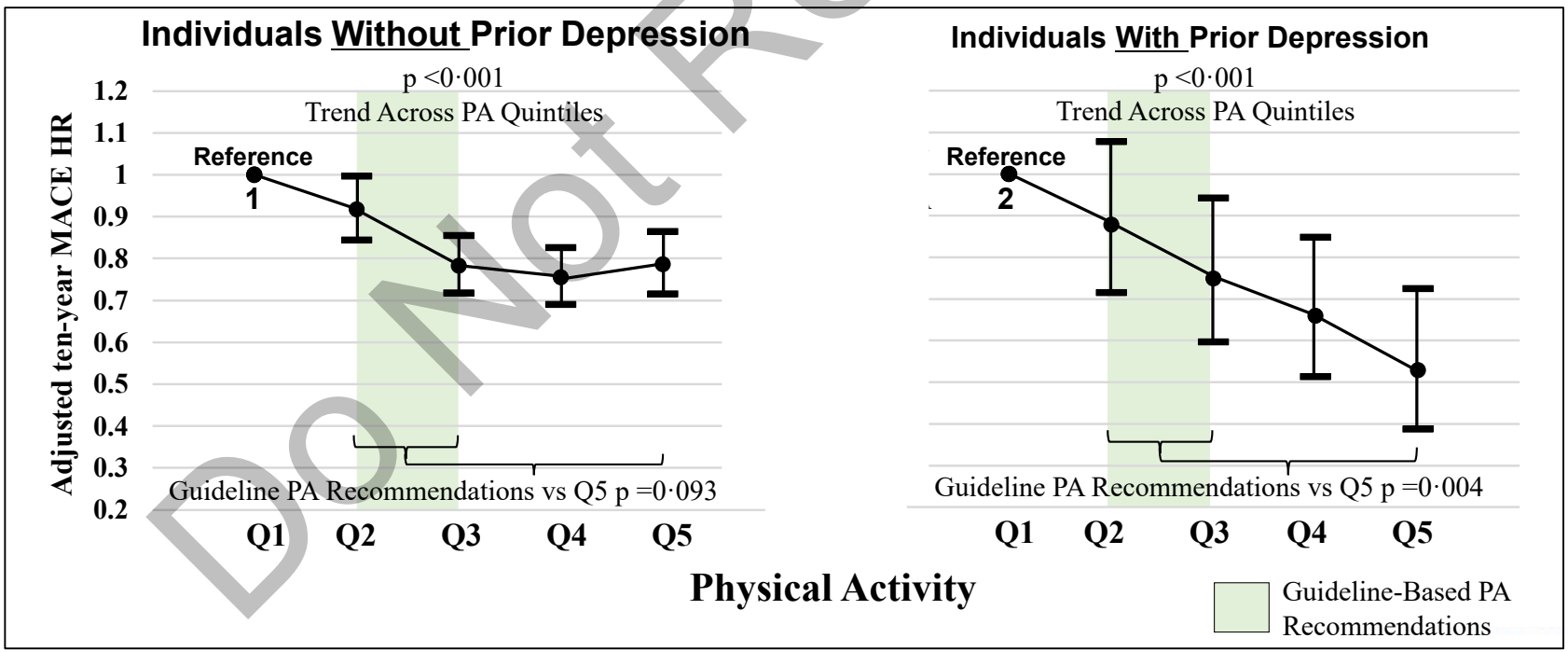
Physical Activity vs Cardiac Events: Greater Impact in those w Depression

Pre-existing Depression (n)	Physical Activity recommendations^ (MET-min/wk)	Coronary MACE HR† (0·5 – 0·75 – 1 – 1·25)	Incidence (percentage)	HR [95% CI]	*p for difference*	*p for interaction¶*
Absent* (n=45,065)	<	-12%	605 (4·9%)	1	**0·015**	**0·046**
	≥		994 (3·2%)	0.880 [0·794, 0·975]		
Present (n=5,042)	<	-33%	129 (7·0%)	1	**0·003**	
	≥		106 (3·9%)	0·673 [0·519, 0·873]		



Key Points

- Stress:
  - a common, important risk factor for CVD
  - attributable risk on par with HTN, smoking, DM
- Associates with:
  - higher stress-associated neural network activity
  - leukopoietic activity & systemic inflammation
  - arterial inflammation and noncalcified plaque
  - CVD events
- Its impact might be modifiable
- Large trials are needed in order to:
  - Prove causation and
  - Determine efficacy of interventions

Key Points

For individuals with high atherosclerotic risks and high stress, reasonable to recommend :

- Stress reduction approaches
- Exercise
- Healthy sleep

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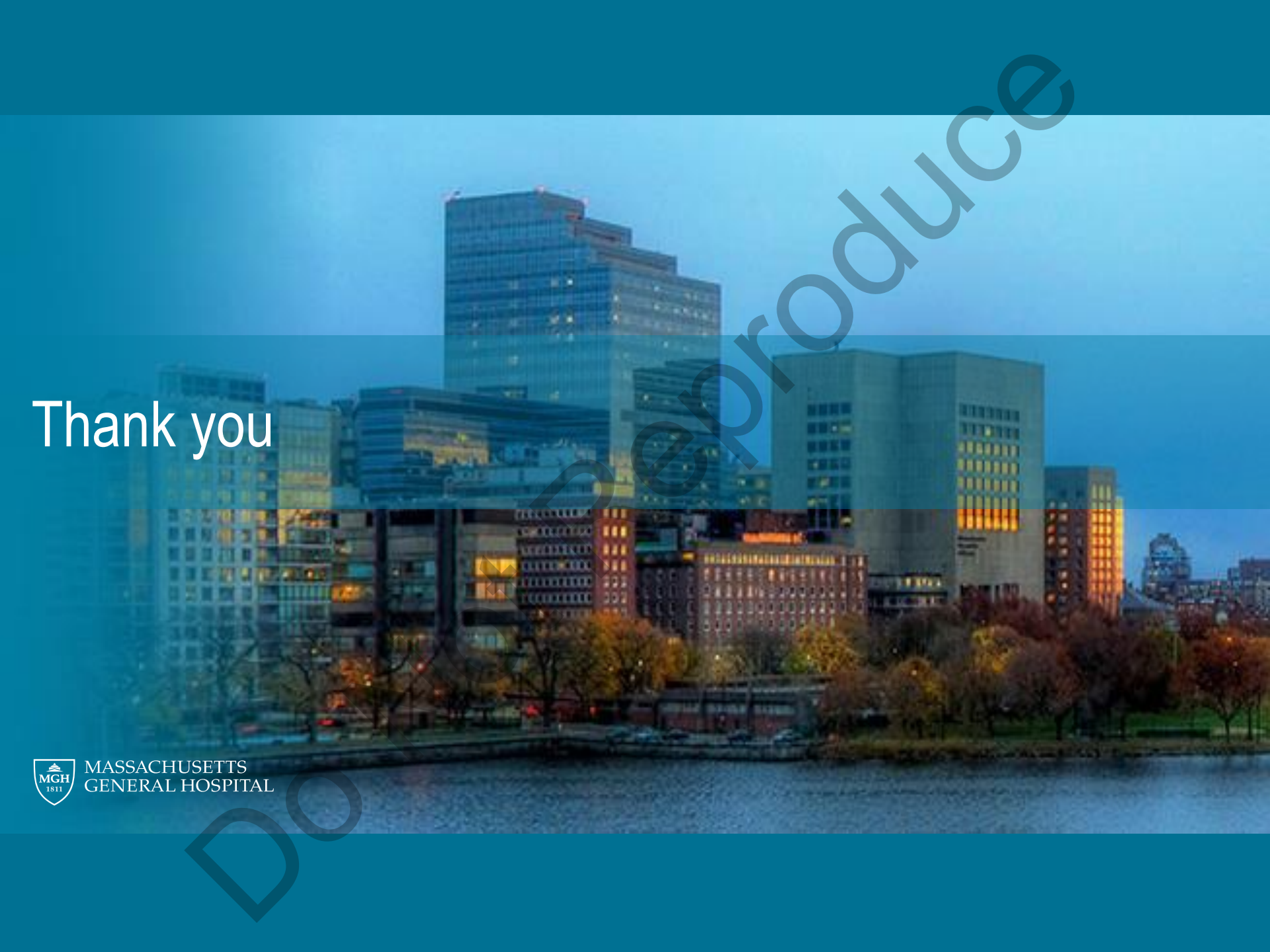
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