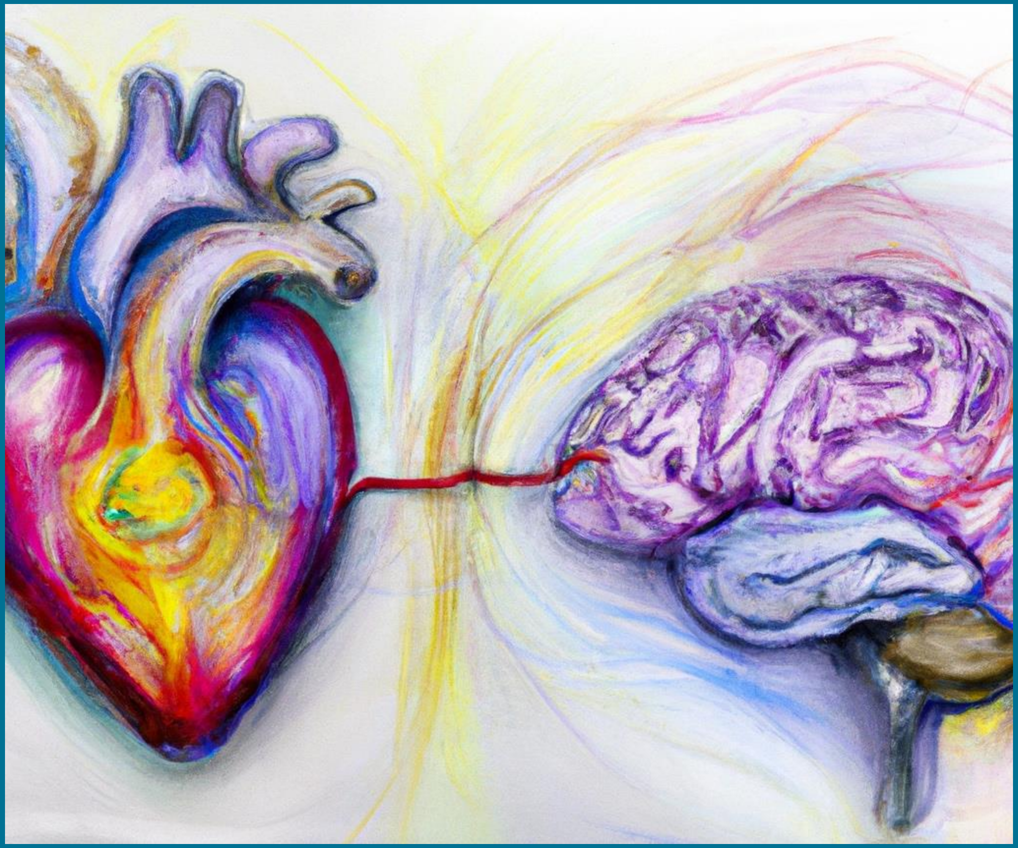

Disentangling the Links Between Stress and Cardiovascular Disease

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Director, Nuclear Cardiology
Co-Director, Cardiovascular Imaging Research Center
Associate Professor of Medicine
Massachusetts General Hospital
Harvard Medical School

MASSACHUSETTS GENERAL HOSPITAL
CORRIGAN MINEHAN HEART CENTER

Disclosures

- Related to the content of this presentation:
  - None

- Unrelated to the presentation
  - Lung Biotechnology: Research grant
  - Genentech: Consulting
  - Tourmaline Bio, Inc.: Consulting
  - Cunningham Bounds: Consulting

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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.

Mechanisms Linking Stress to Heart Disease

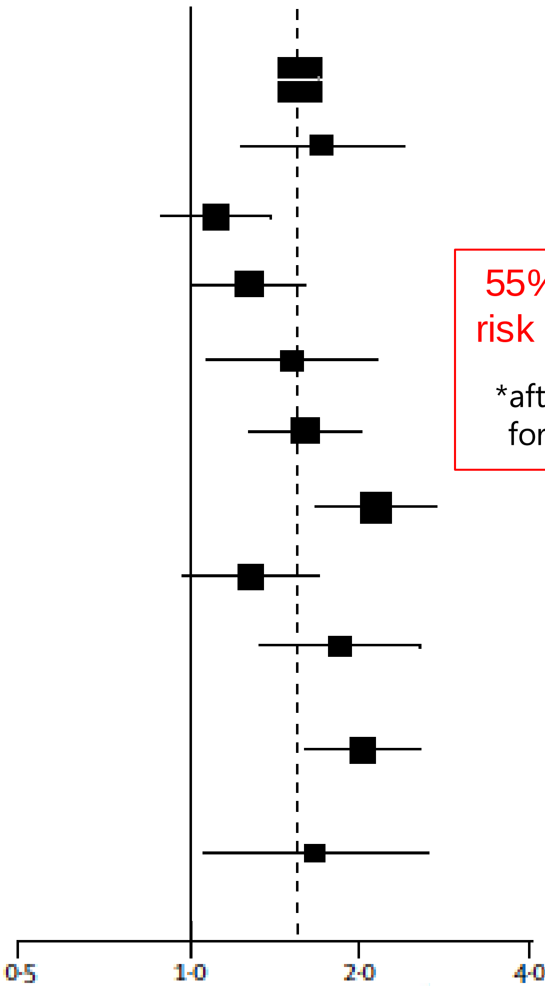
- Stress may affect behaviors and factors that increase heart disease risk:
  - Smoking
  - Physical inactivity
  - Overeating
  - HTN
  - Diabetes
  - Adiposity

- These factors do not explain the observed risk

The INTERHEART Study

Chronic Stress vs. Myocardial Infarction Risk

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)



Myocardial Infarction
(odds ratio)

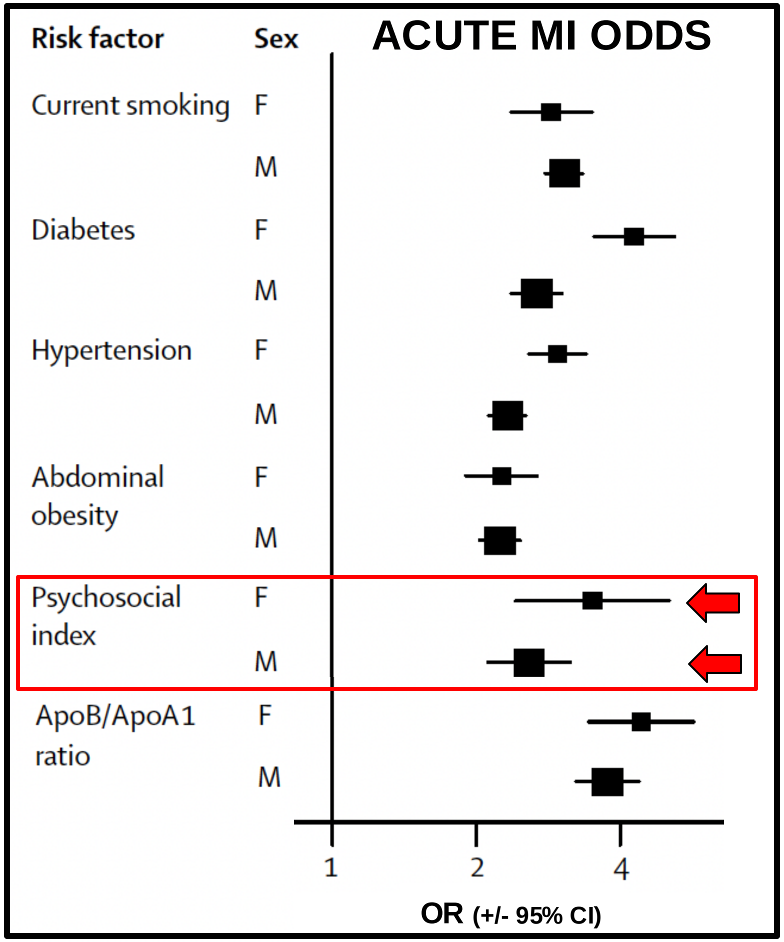
55% increased risk of Acute MI

*after adjusting for risk factors

Rosengren et al Lancet 2004

The INTERHEART Study

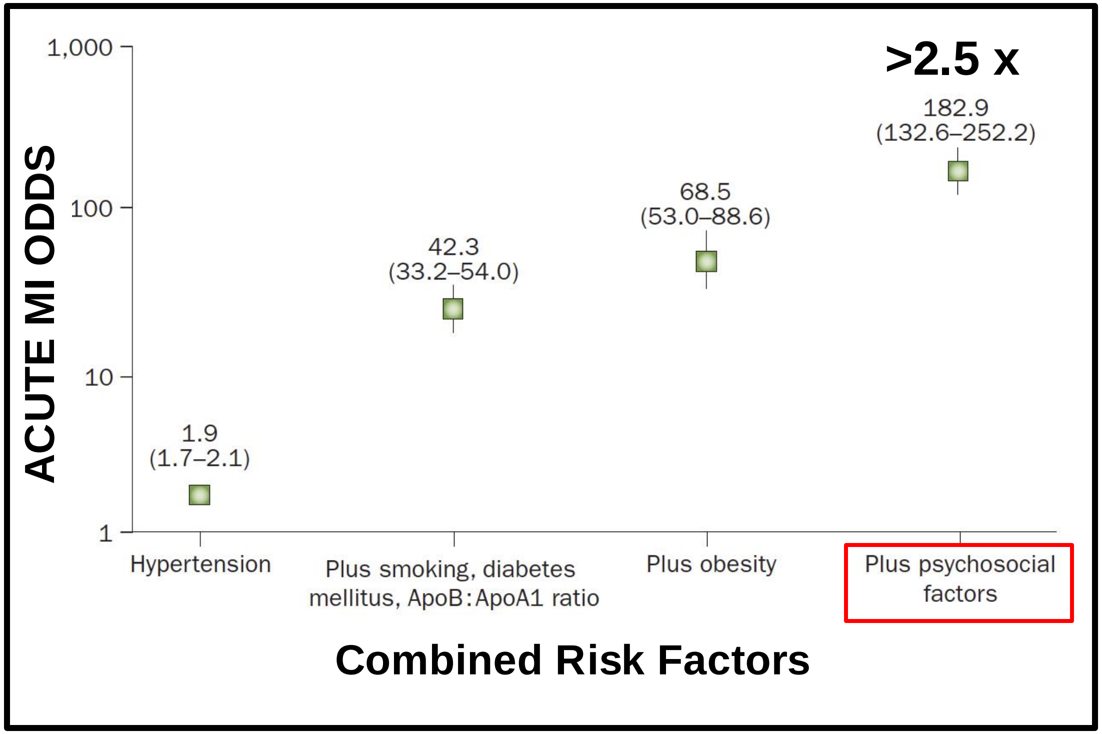
Comparing CRFs



Yusuf et al Lancet 2004

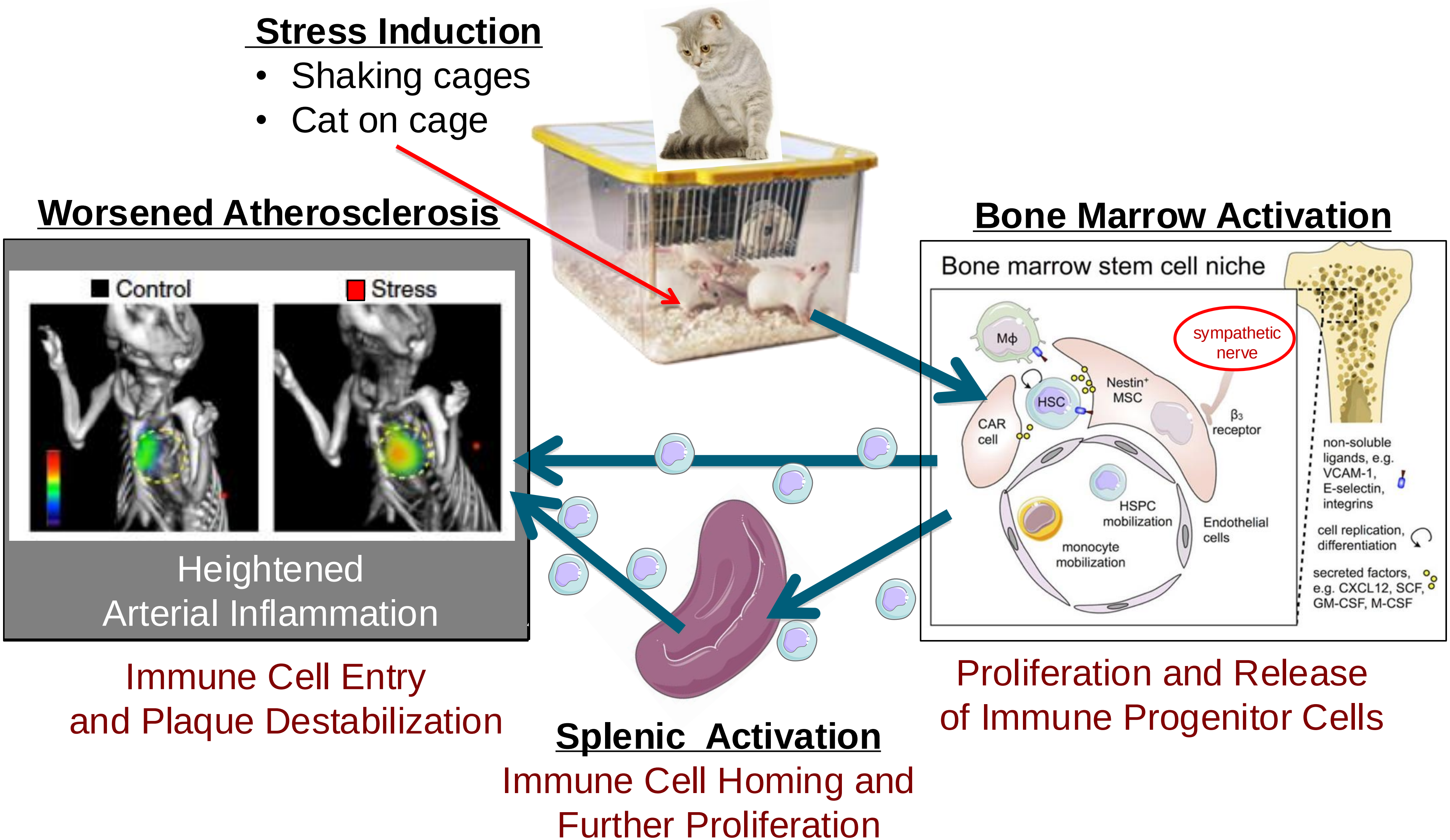
Adding Stress to CRFs

Adding stress/depression to multiple CRFs further raises MI risk by >2.5x

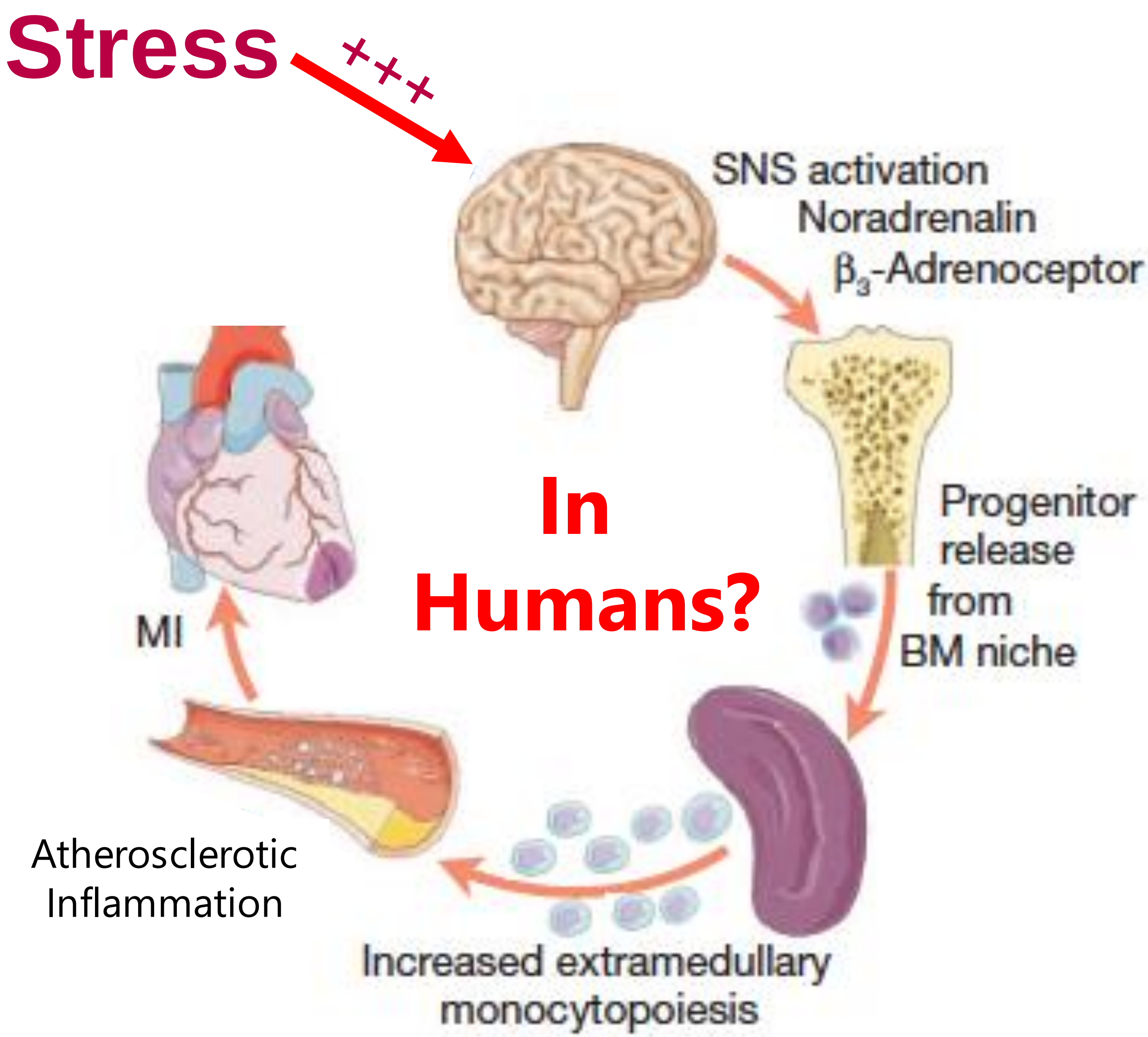


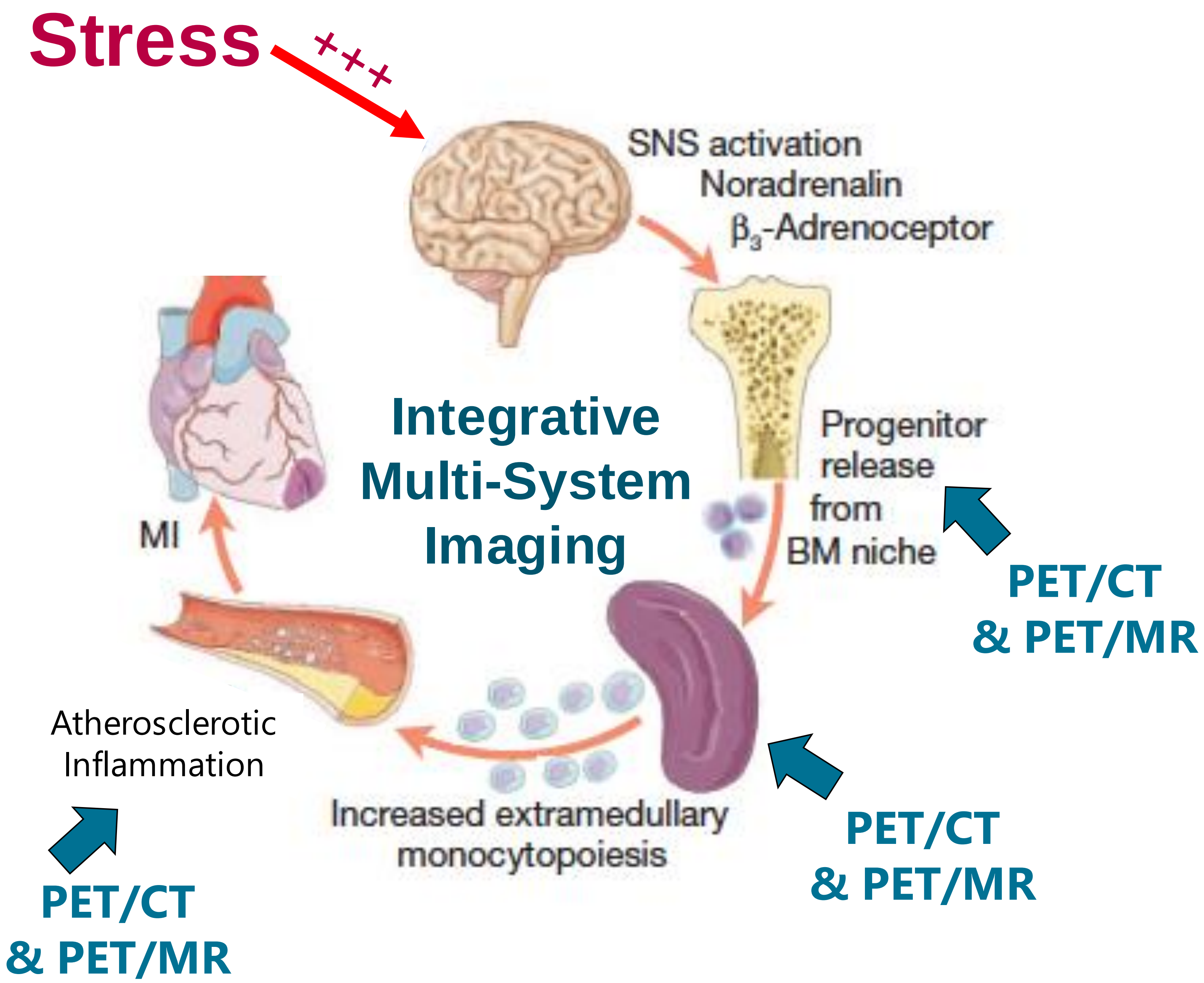
Steptoe et al Nat Rev Cardiol 2012

Chronic Stress Promotes Atherosclerotic Inflammation in Mice



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


Stress
+++
SNS activation
Noradrenalin
β_3-Adrenoceptor
Progenitor
release
from
BM niche
In
Humans?
MI
Increased extramedullary
monocytopoiesis
Atherosclerotic
Inflammation



Stress
+++
SNS activation
Noradrenalin
β_3-Adrenoceptor
Progenitor release from BM niche
PET/CT & PET/MR
Integrative Multi-System Imaging
MI
Atherosclerotic Inflammation
PET/CT & PET/MR
Increased extramedullary monocytopoiesis
PET/CT & PET/MR

Leukopoietic Tissue Activity in Humans

…Can be imaged with FDG PET

High Activity

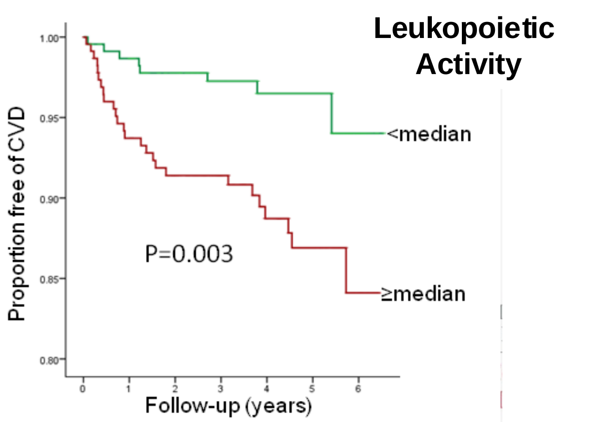
Low Activity

Emami, et al JACC Imaging 2015

…Associates with Circulating Markers of Inflammation

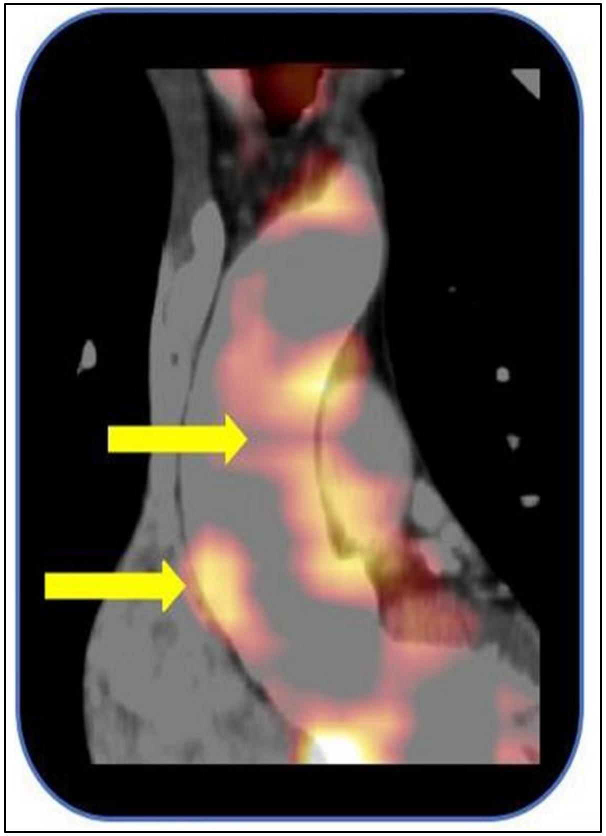
	Correlation Coefficient	p Value
Serum biomarkers		
CRP	0.62	0.002
TNF	0.19	0.46
IL-1β	0.43	0.09
Gene expression in leukocytes		
CD36	0.05	0.85
MSR-1	0.53	0.02
S100A9	0.15	0.54
TLR-2	0.19	0.45

…Associates with Risk of CVD

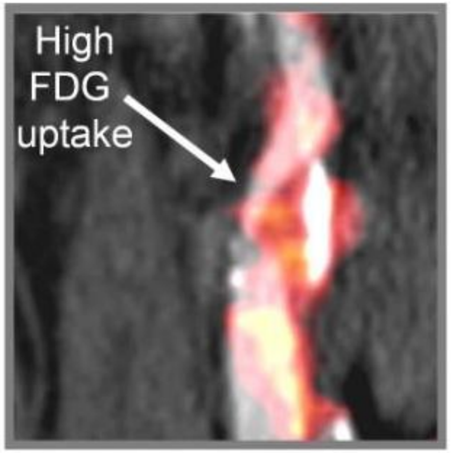


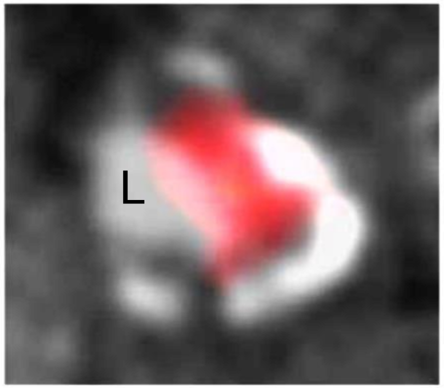
Arterial FDG Uptake Provides a Measure of Arterial Inflammation

PET/CT: Aorta

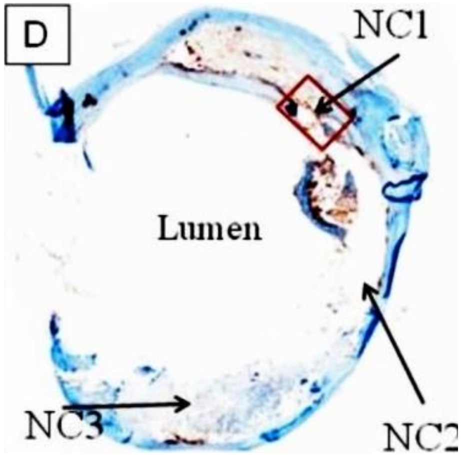


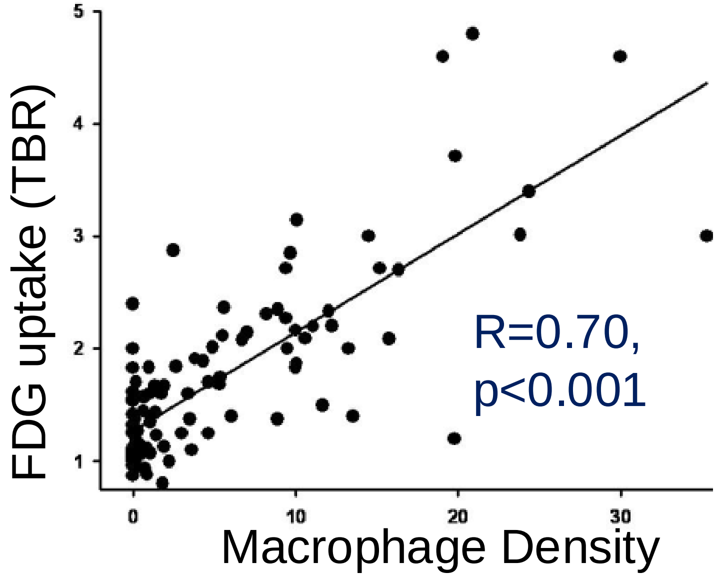
PET/CT Carotid





Histopathology





Figueroa et al Circ CV Imaging 2011

Tawakol et al JACC 2006

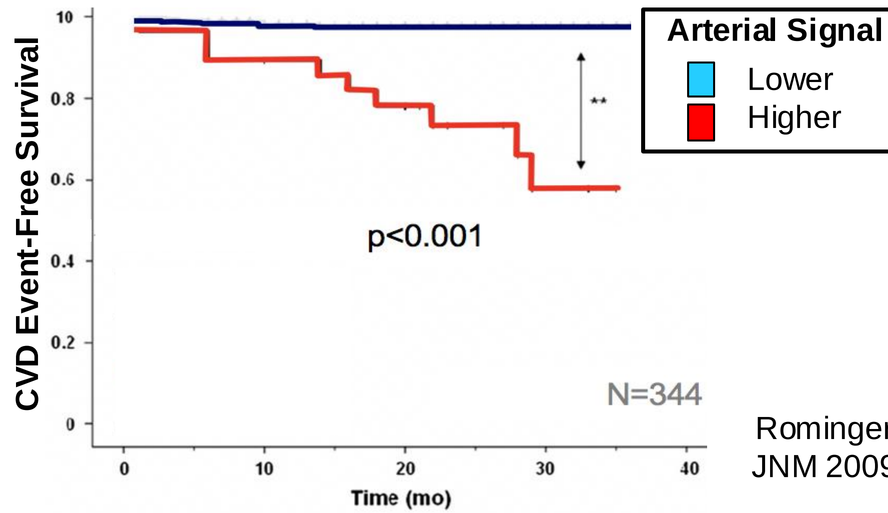
FDG PET Measures of Arterial Plaque Inflammation

Consistent Associations Between FDG Signal and Histologically-proven Arterial Inflammation in Humans

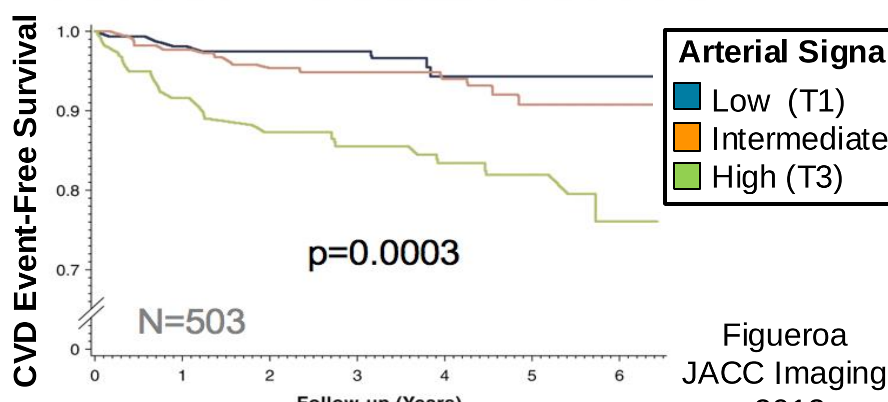
Study	(N)	Histological Measure	Imaging Parameter	r	p-value
Tawakol et al. 2006	17	Absolute CD68 staining	SUV	0.49	**<0.0001**
			TBR	0.68	**<0.0001**
		% CD68 staining	SUV	0.58	**<0.0001**
			TBR	0.7	**<0.0001**
Graebe et al. 2009	9	mRNA expression of CD68	TBR	0.71	**0.02**
Font et al. 2009	15	% CD68 staining	TBR	0.8	**<0.005**
Menezes et al. 2011	21	% CD68 staining	TBR	0.55	**0.011**
Saito et al. 2013	25	CD68 staining	SUV	NA	**0.006**
Taqueti et al. 2014	25	% CD68 staining	TBR	0.64	**<0.001**
Skagen et al. 2015	36	% inflammatory cell staining	SUV	0.52	**0.003**
			TBR	NA	**0.002**
Cocker et al. 2018	49	% CD68 staining	SUV	0.45	**0.001**
			TBR	0.51	**<0.0001**
		Number of CD45+ pixels	SUV	0.88	**<0.001**
			TBR	0.63	**0.009**
Johnsrud et al. 2019	30	% area of inflammatory cells	SUV	0.54	**0.008**
			TBR	0.58	**0.002**

Osborne et al JNC 2020

Arterial Inflammation Predicts CVD Events



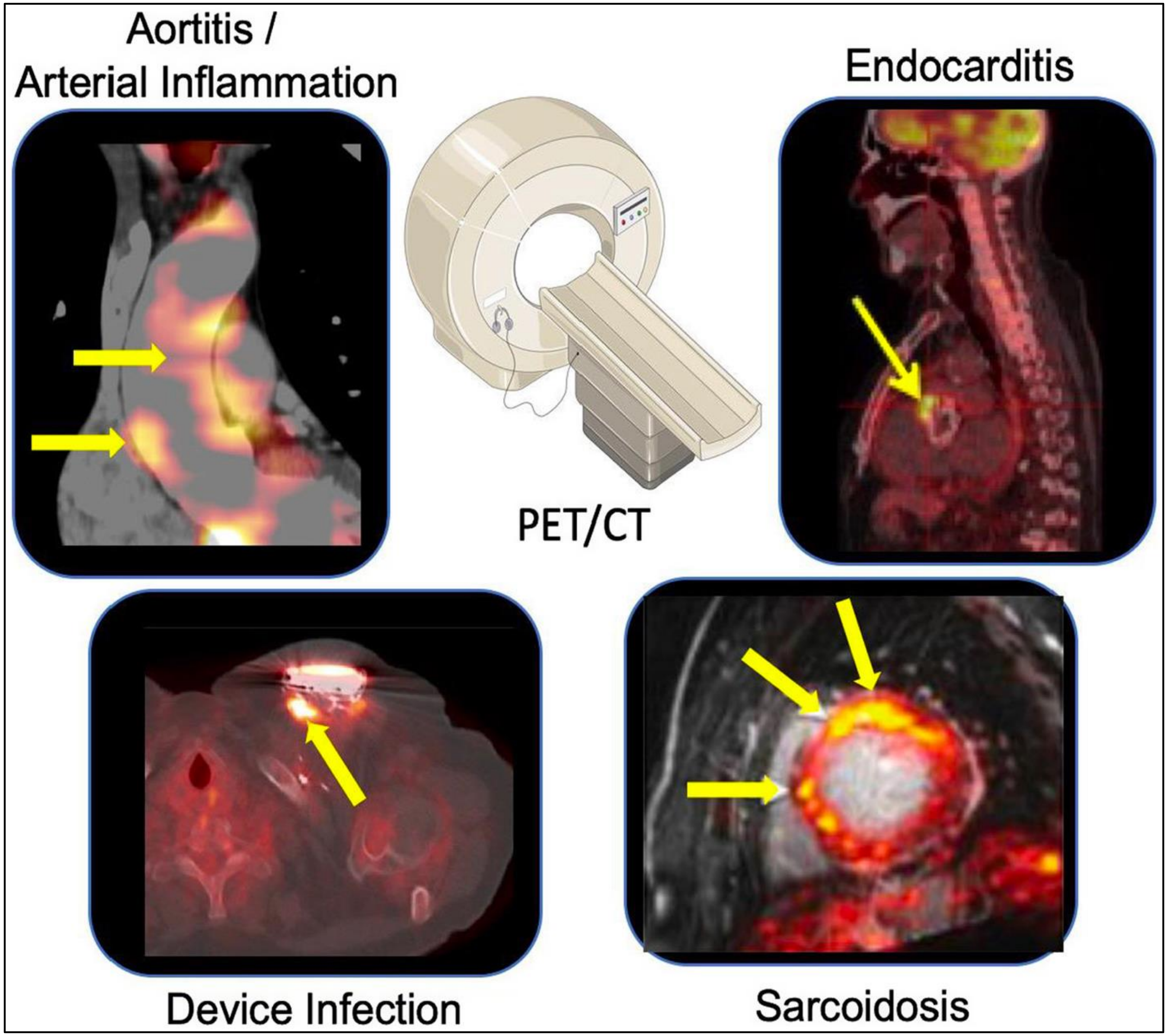
Rominger JNM 2009



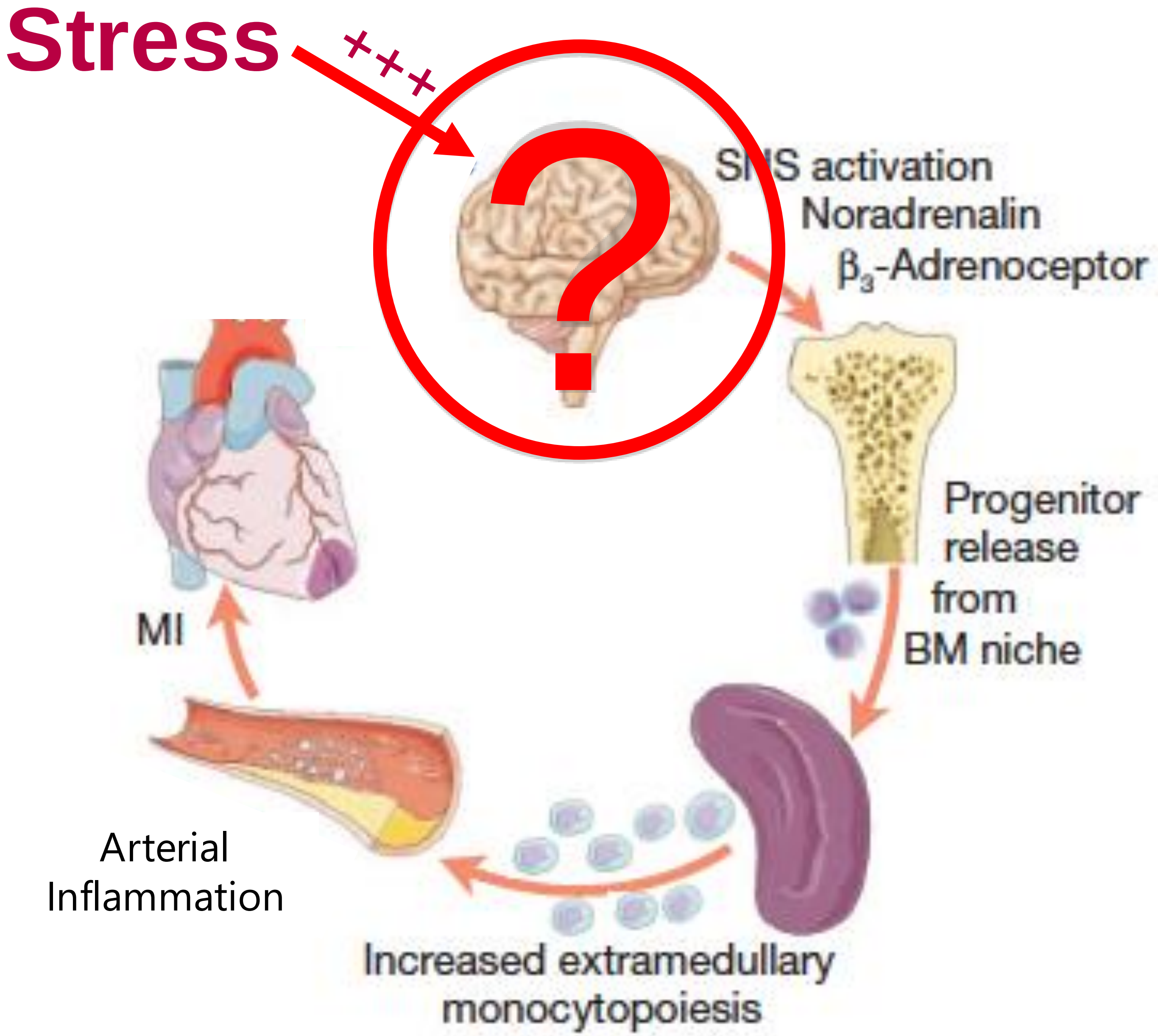
Figueroa JACC Imaging 2013

Clinical Imaging of Inflammation using FDG

Guidelines-recommended for evaluation of…



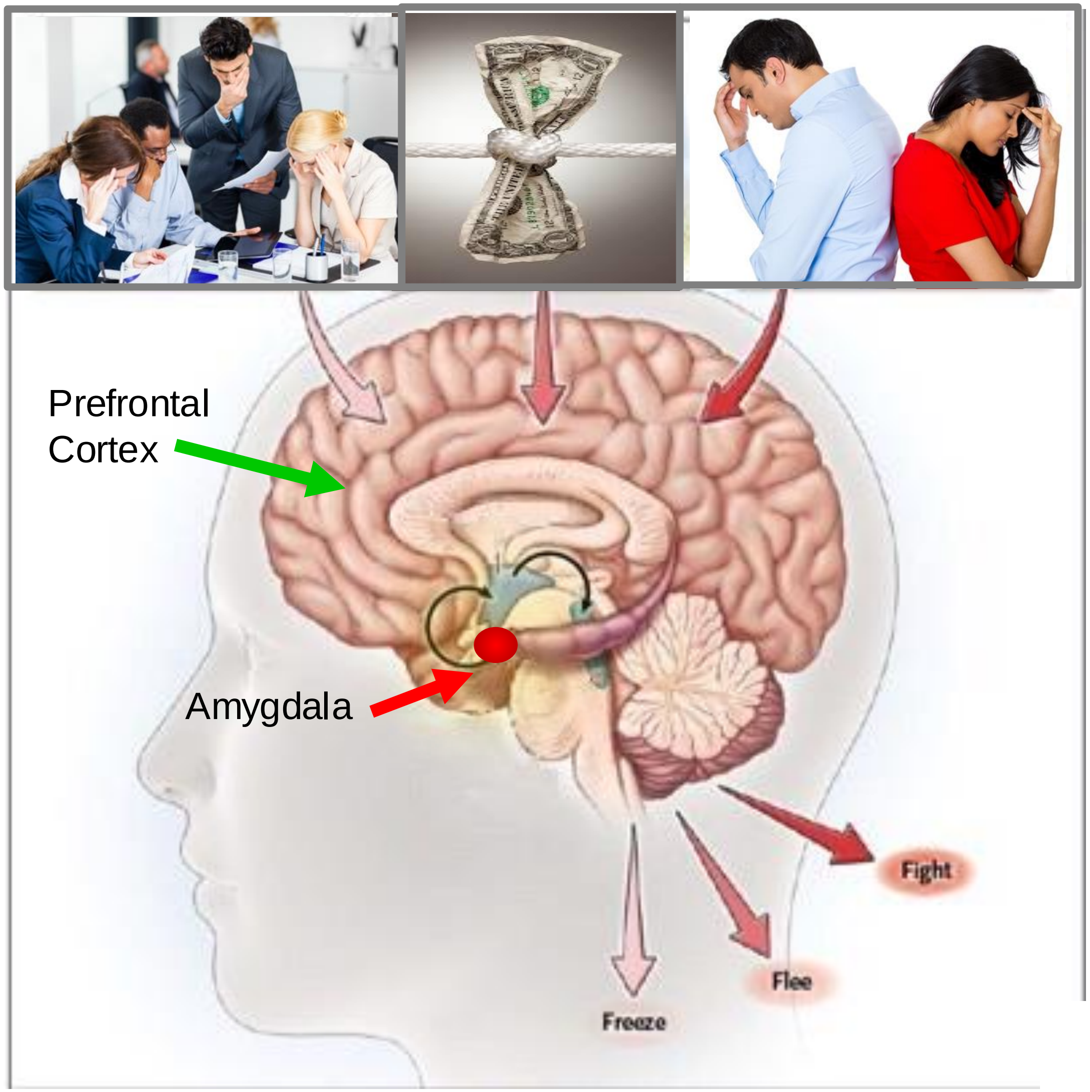
Tawakol et al
Arthritis & Rheumatology 2019


Stress
+++
?
SNS activation
Noradrenalin
β3-Adrenoceptor
Progenitor
release
from
BM niche
Increased extramedullary
monocytopoiesis
Arterial
Inflammation
MI

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

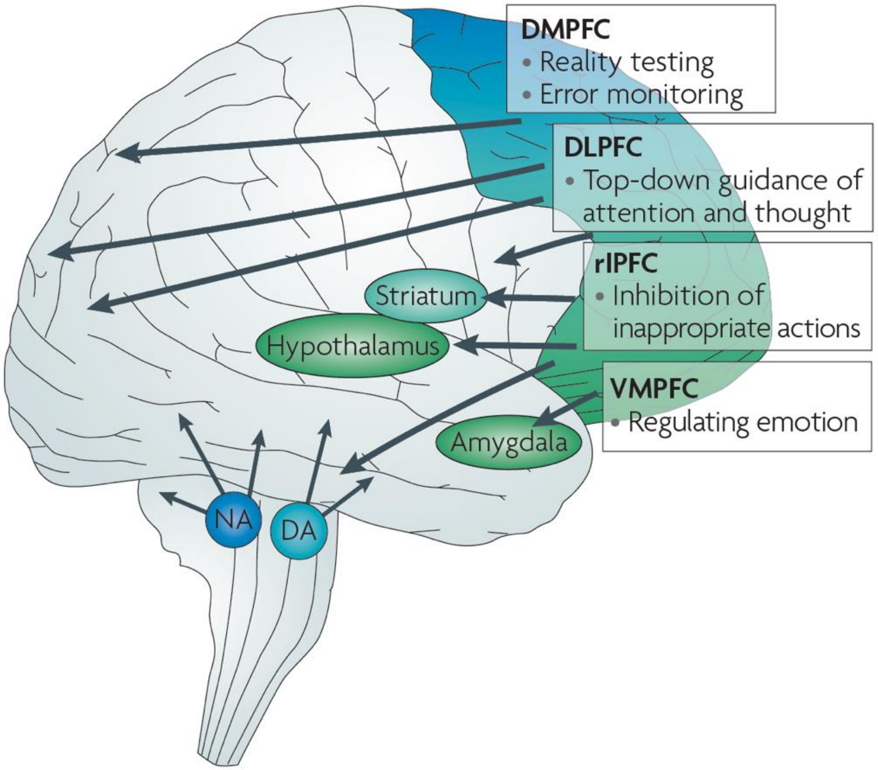


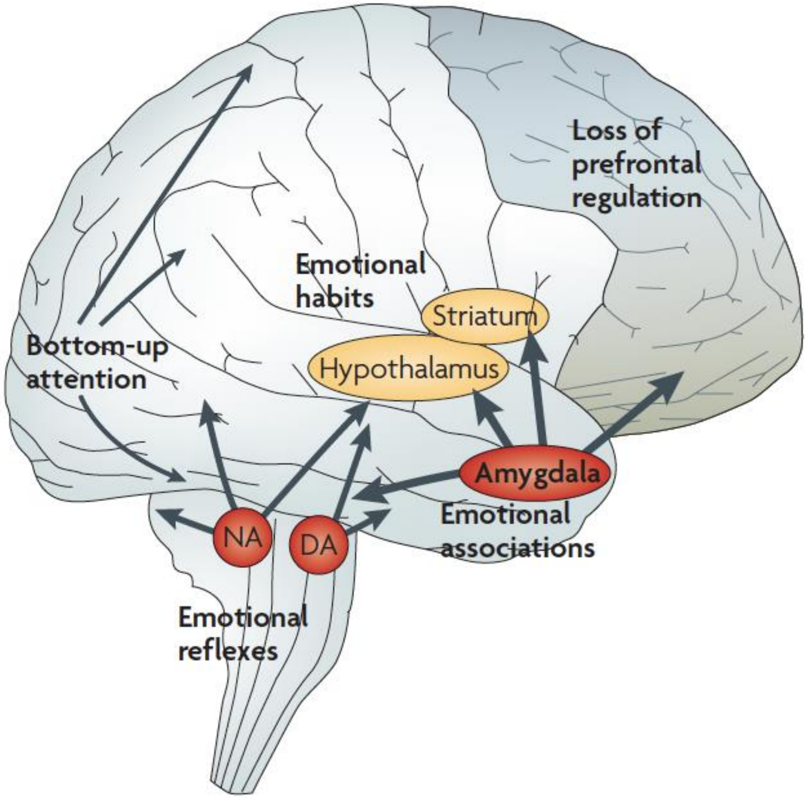
Blair et al. NEJM Dec 2014

Stress-Associated Neural Network: the switch from non-stress to stress conditions

Non-stressful Conditions
Pre-frontal Regulation

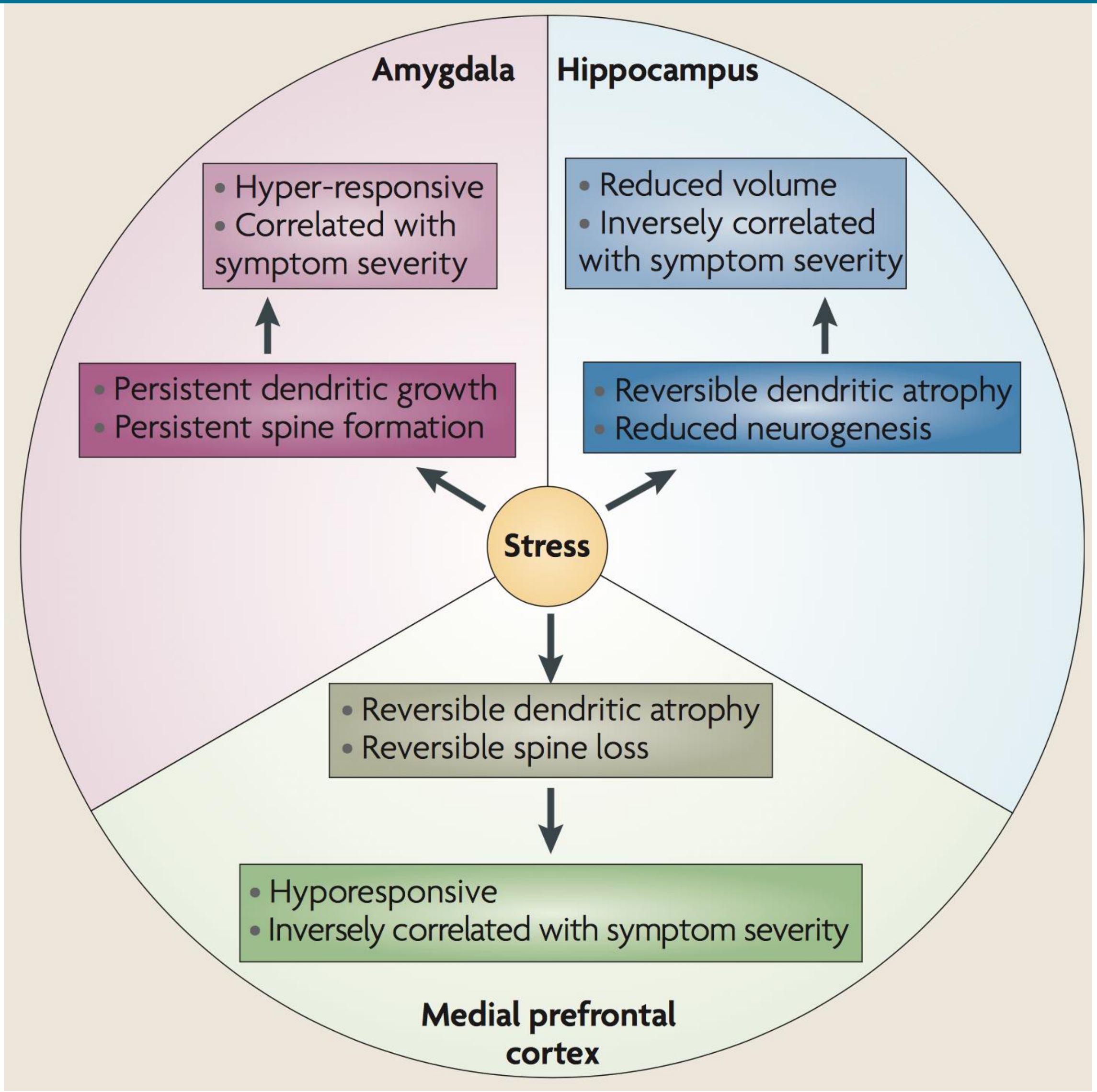
Stressful Conditions
Amygdalar Control





Anesten Nature Reviews Neuroscience 2009

Impact of Stress on Corticolimbic Structures



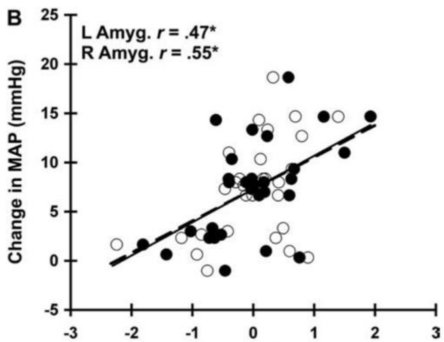
Roozendaal et al Nature Reviews Neuroscience 2009

fMRI Imaging of Amygdalar Activity

Individuals with greater amygdalar activation, by fMRI:

…have greater **stressor-evoked blood pressure reactivity**

Blood Pressure

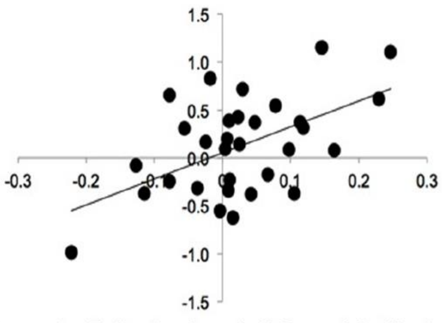


Amygdalar Activation

Gianaros et al
J. Neurosci. 2008

…produce more **inflammatory cytokines**

Inflammatory Cytokine
IL-6 Response (log pg/ml)

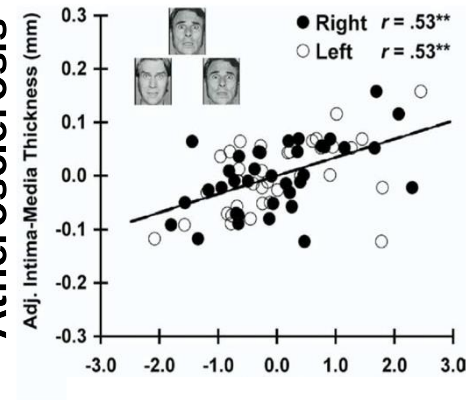


Amygdalar Activation

Muscateli et al
Brain Behav Immun 2014

…have more **atherosclerosis**

Carotid Atherosclerosis

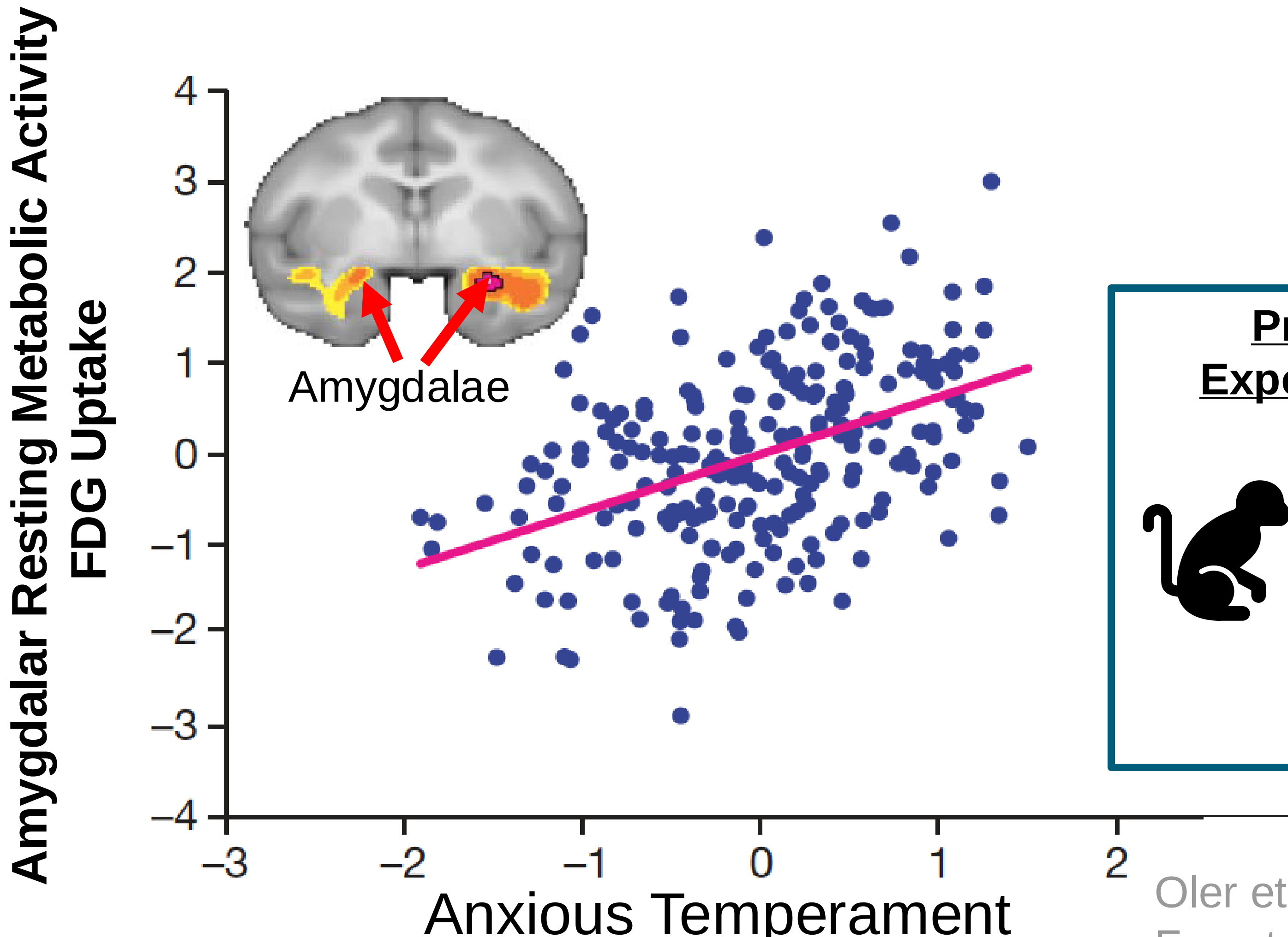


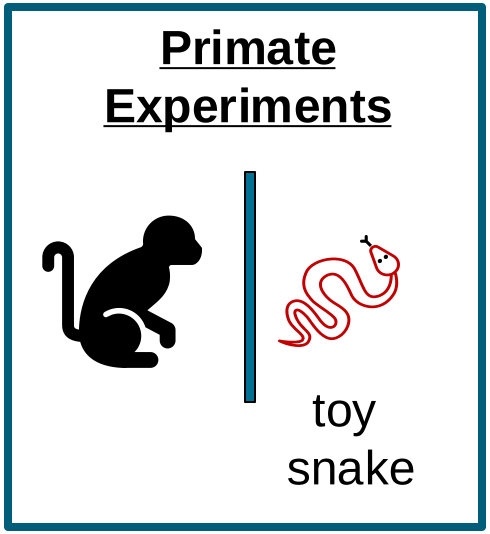
Amygdalar Activation

Gianaros et al
Biol Psych 2009

PET Imaging:
Resting amygdalar activity correlates w Stress/Anxiety

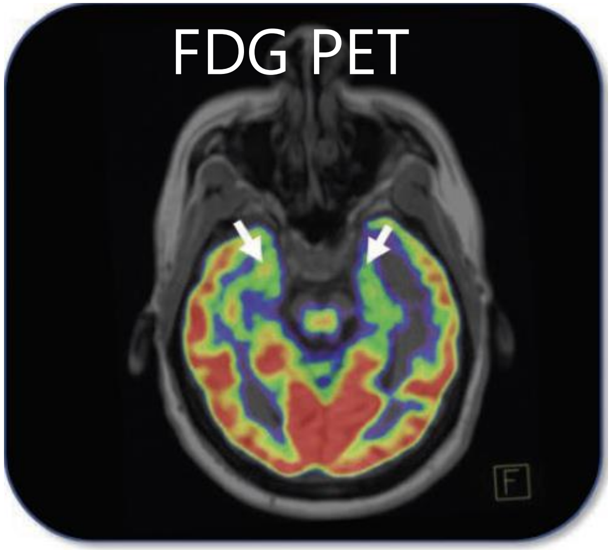
Individuals with stress have metabolically active amigdalae





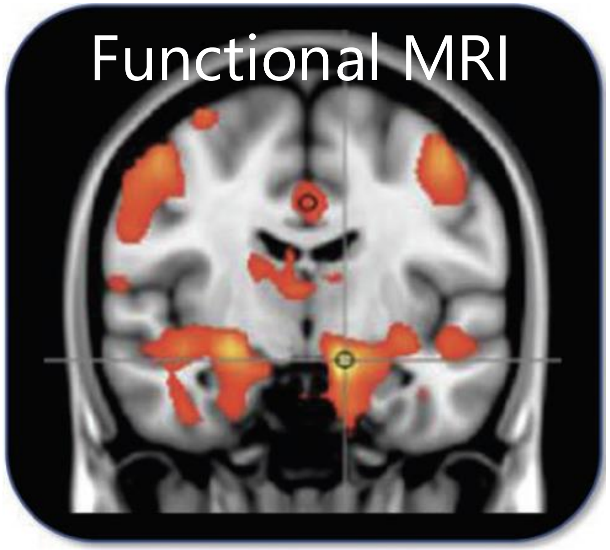
Oler et al Nature 2010
Fox et al PNAS 2012

Imaging the Neurobiology of Stress



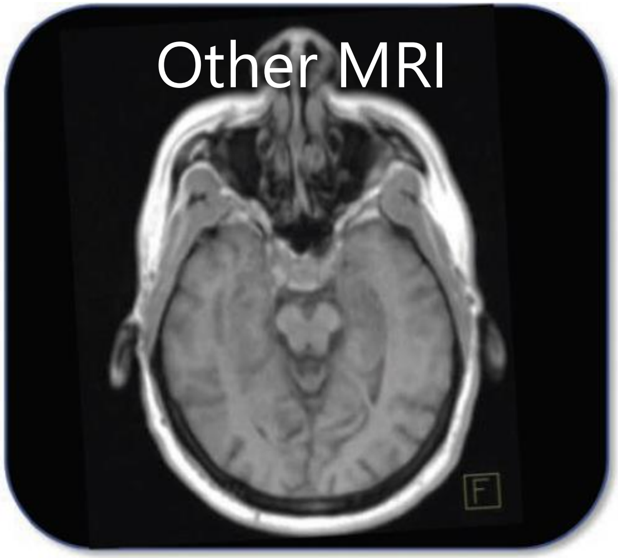
<u>Neural Metabolism</u>

High amygdalar activity (**AmygA**$_C$) *relative to counter-regulatory cortical activity*



<u>Neural Activation and Connectivity</u>

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



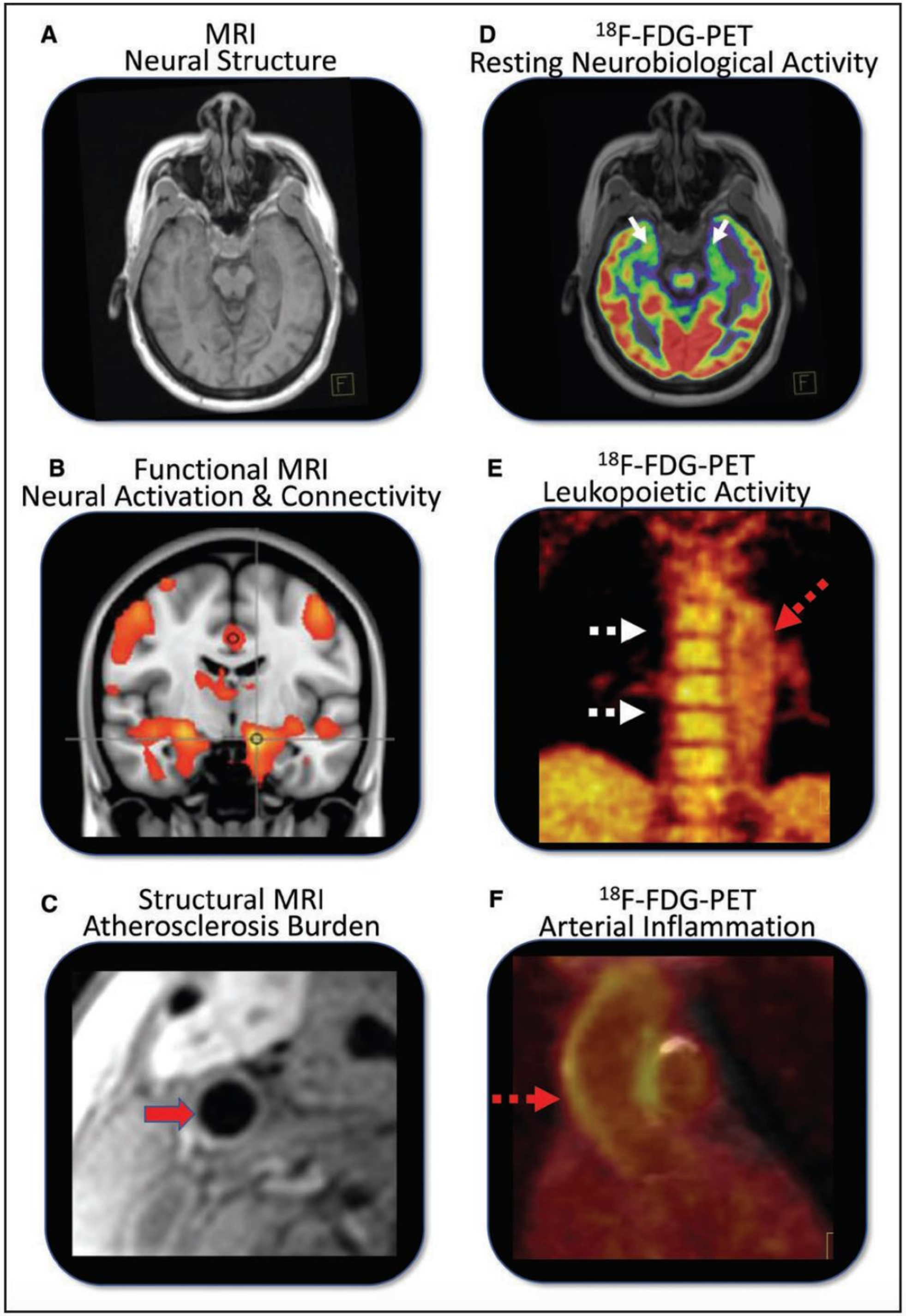
<u>Tissue Volumes</u>

- Amygdalar volume loss
- Due to loss of counterregulatory connections

<u>Diffusion Tensor Imaging</u>

- Axonal Integrity

Integrative Bio-Imaging with PET/CT and PET/MR

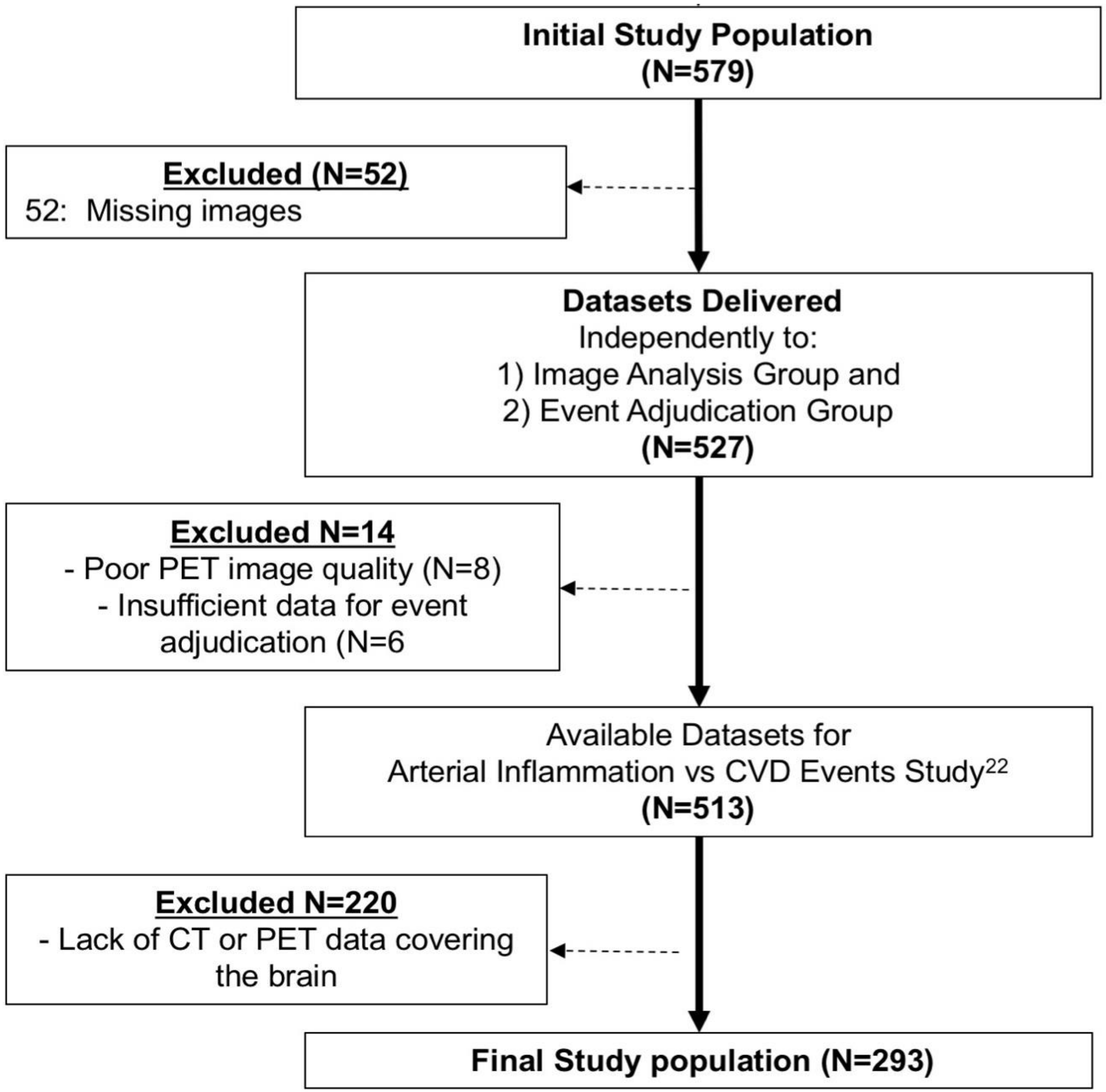


Osborne et al Circ Imaging 2020

Integrative Bio-Imaging to Study 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 integrative bio-imaging w FDG PET/CT and PET/MR to quantify:
  - Amygdalar/Cortical Activity ($AmygA_C$)
    - 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

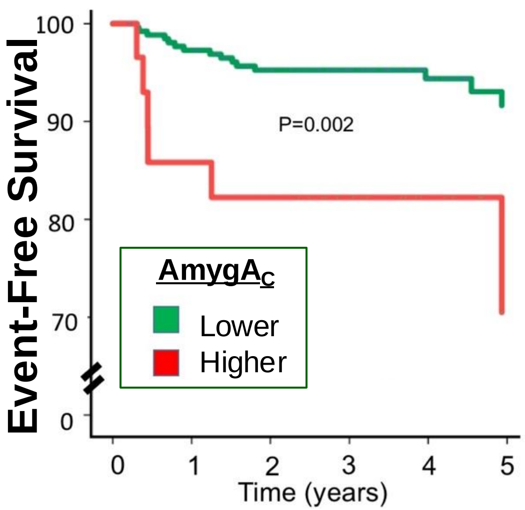
AmygA$_c$ Robustly Predicts CVD

AmygAc vs. CVD

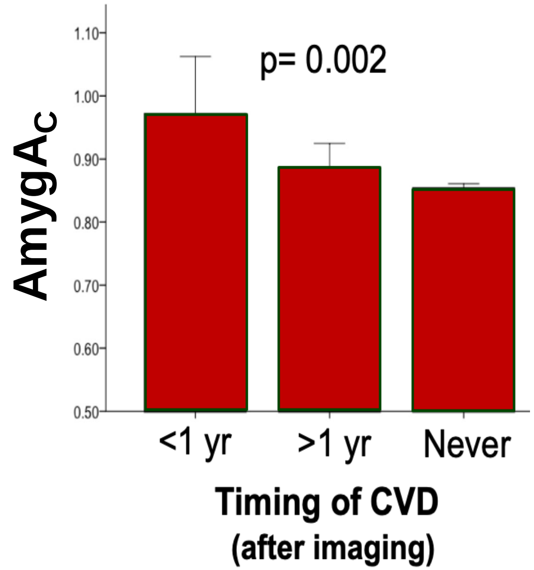
	(primary measure)	
	HR (95% CI)	p value
Univariate		
Per unit change	14·1 (4·0–50·0)	<0·0001
Per SD change	1·59 (1·27–1·98)	<0·0001
Covariates: age and sex		
Per unit change	5·0 (1·3–19·1)	0·0193
Per SD change	1·32 (1·05–1·68)	0·0193
Covariate: Framingham risk score		
Per unit change	4·5 (1·3–15·7)	0·0192
Per SD change	1·30 (1·04–1·62)	0·0192
Covariates: combined cardiac risk factors*		
Per unit change	7·6 (2·0–28·4)	0·0027
Per SD change	1·42 (1·13–1·79)	0·0027
Covariate: pre-existing atherosclerotic disease (CAC score)		
Per unit change	10·7 (2·7–42·9)	0·0008
Per SD change	1·51 (1·19–1·93)	0·0008
Covariate: history of depression or anxiety		
Per unit change	18·1 (5·0–65·5)	<0·0001
Per SD change	1·66 (1·32–2·08)	<0·0001
Covariate: antidepressant use		
Per unit change	17·3 (4·8–62·2)	<0·0001
Per SD change	1·65 (1·32–2·06)	<0·0001

AmygAc vs. More Stringently Defined Events

	HR (95% CI)	p value
Cardiovascular disease		
Per unit change	14·1 (4·0–50·0)	<0·0001
Per SD change	1·59 (1·27–1·98)	<0·0001
MACE		
Per unit change	15·9 (4·4–58·1)	<0·0001
Per SD change	1·62 (1·29–2·03)	<0·0001
AMACE		
Per unit change	23·7 (1·6–350·0)	0·0212
Per SD change	1·74 (1·09–2·78)	0·0212

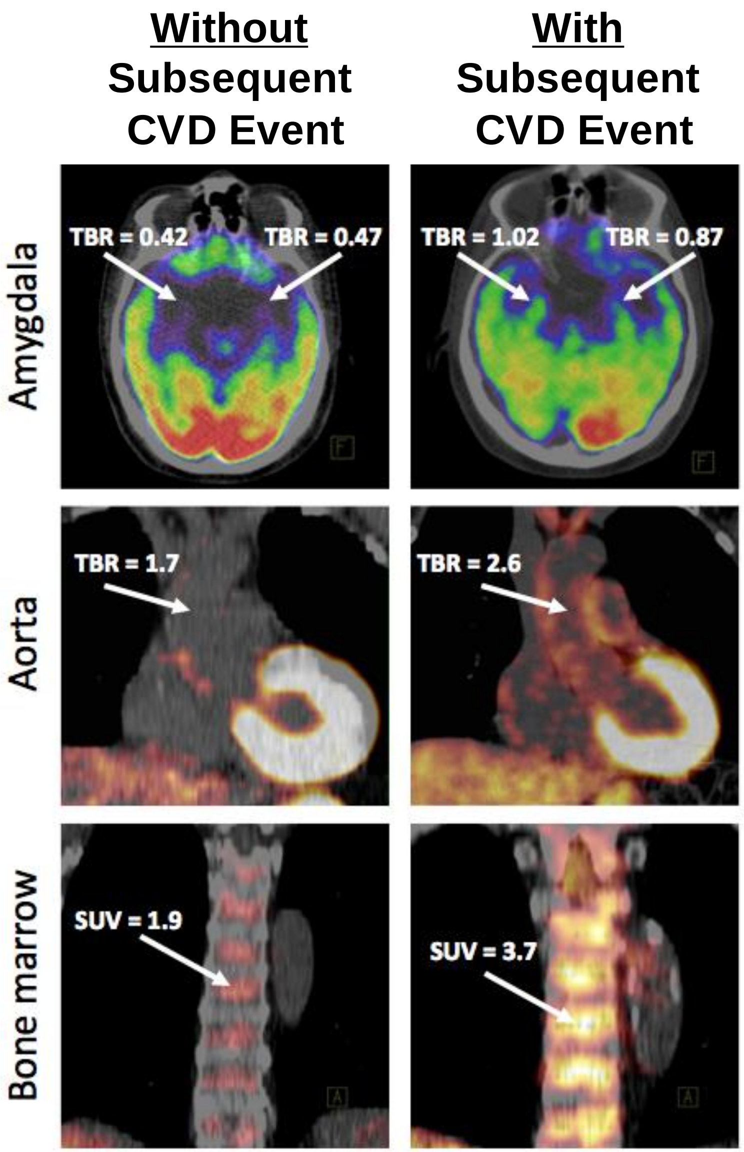


AmygA$_C$ Vs Event Timing



Tawakol et al
Lancet 2017

Amygdalar Activity vs. Activity in other Tissues



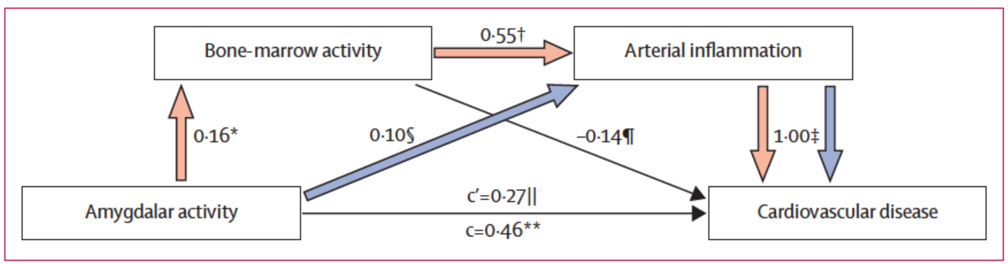
$AmygA_c$ vs Activity in Other Tissues

Comparator Tissue	Correlation with $AmygA_c$	P value
Atherosclerotic inflammation	0.44	**<0.001**
Bone marrow activity	0.42	**<0.001**
Control tissue (Subcutaneous Fat)	0.02	0.79

Tawakol et al Lancet 2017

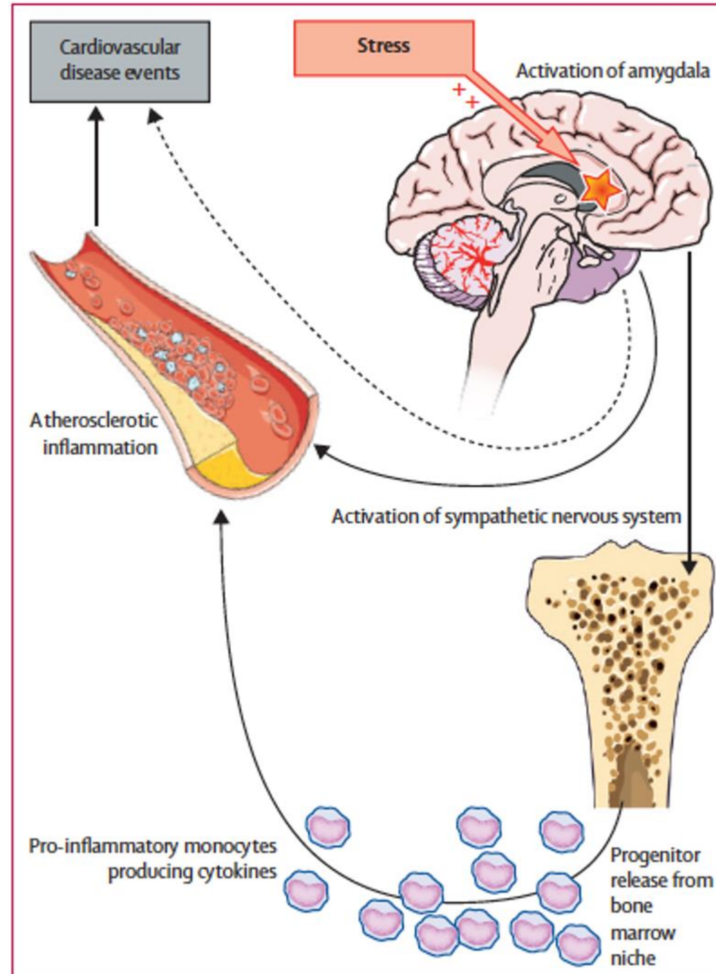
Path Analysis

Serial Mediator Paths



Supports Path Predicted in Mice

Proposed Mechanism

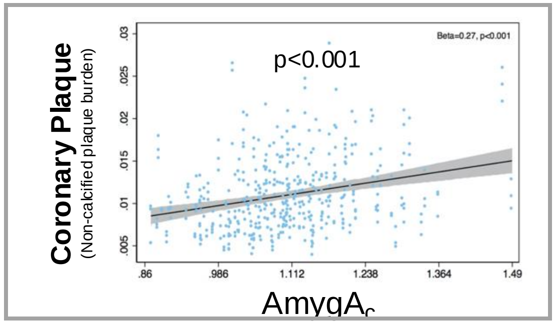


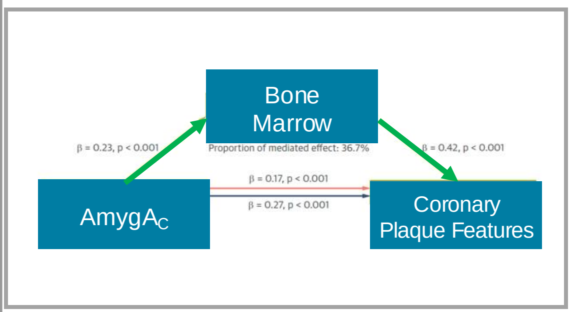
Tawakol et al Lancet 2017

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

(out of >200 studies mentioning Amygdala and Cardiovascular Disease since January 2017)

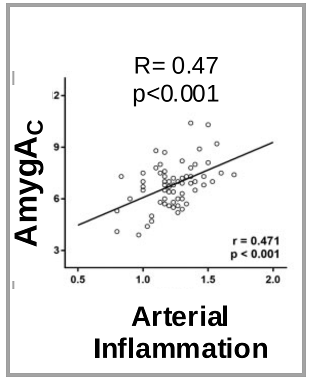
SNA vs. high-risk coronary plaques

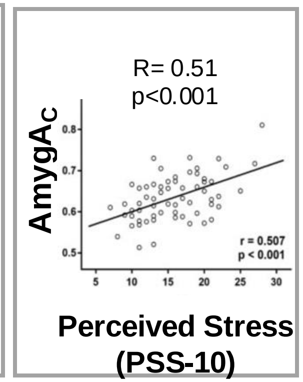




Goyal et al JACC CV Imaging 2020

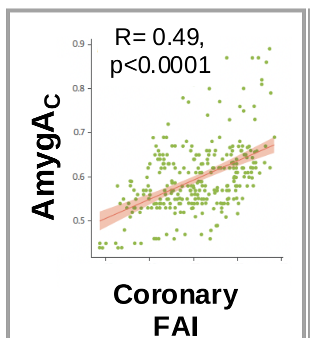
SNA vs. Stress and Inflammation

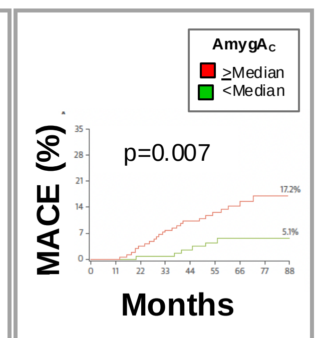




Kang et al EHJ 2021

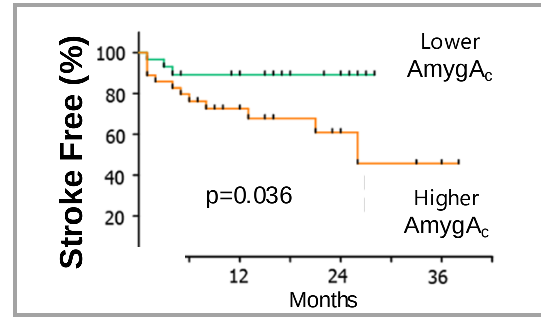
SNA vs Cor Inflam. and Events

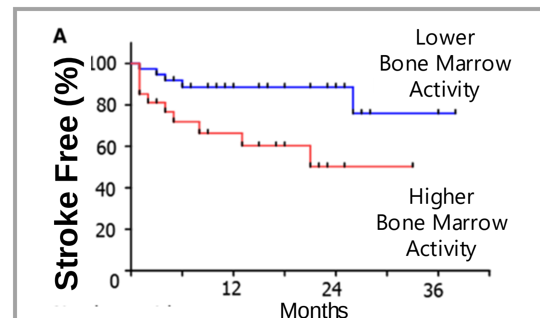




Dai et al, JACC: CV Imaging 2023

SNA vs. <u>recurrent</u> events

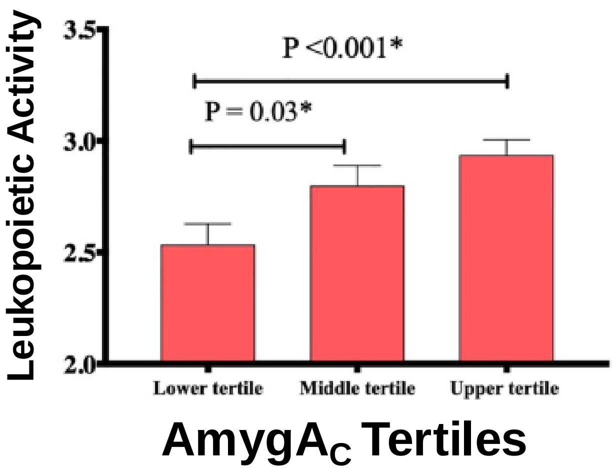


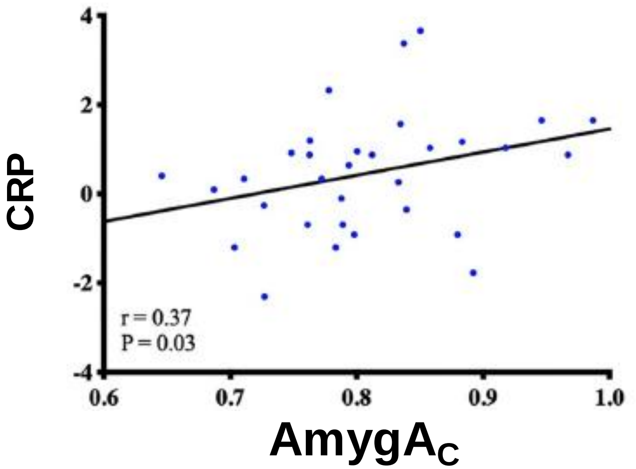


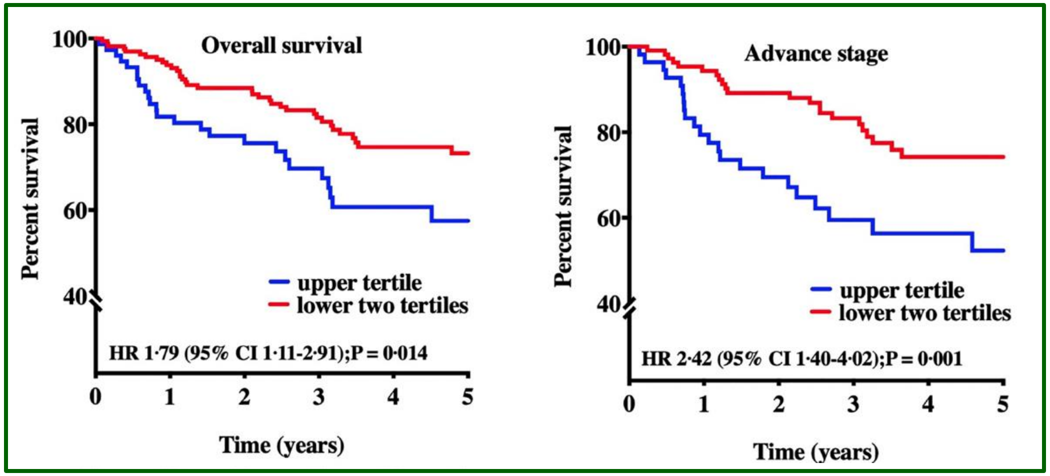
Kim et al, Circ: CV Imaging 2023

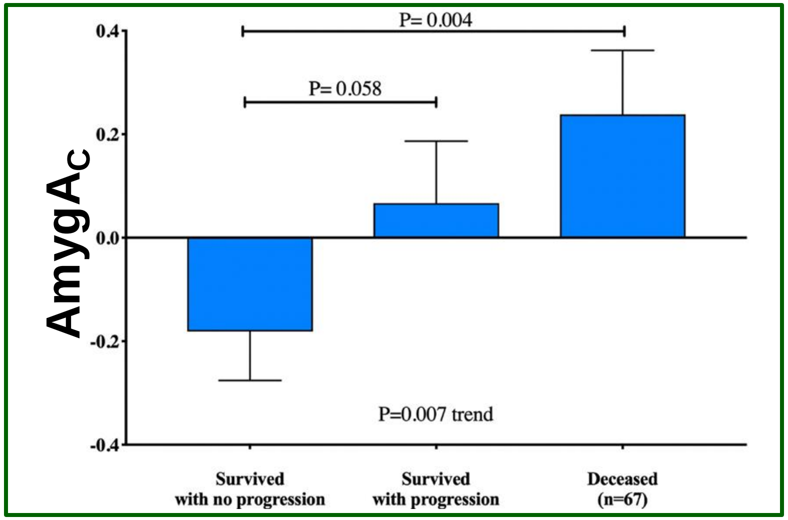
Stress-Cancer Link

240 patients with head and neck cancer who underwent 18F-FDG-PET/CT imaging as part of **initial cancer staging**.



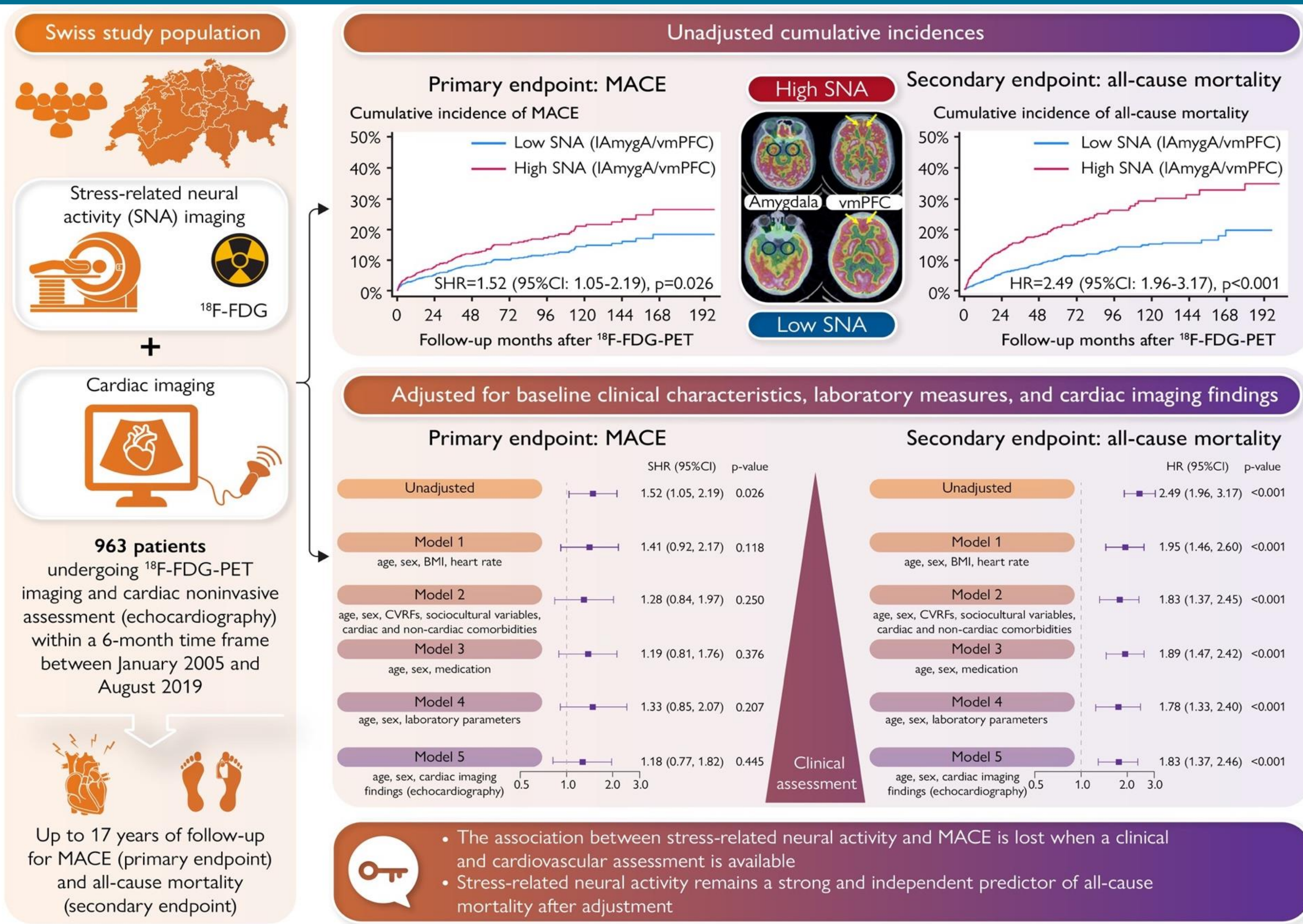






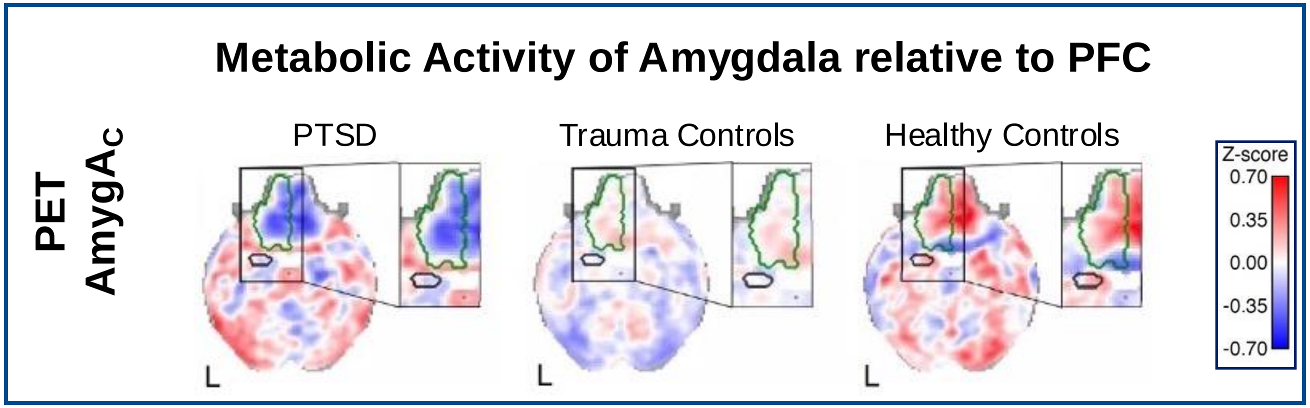
MO Hassan et al
PLOS One 2023

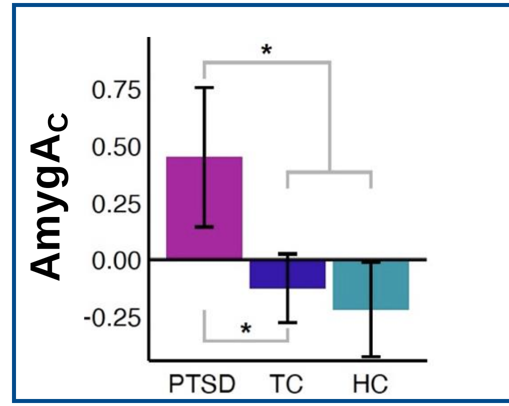
SNA : Strong and Independent Predictor of All-Cause Mortality

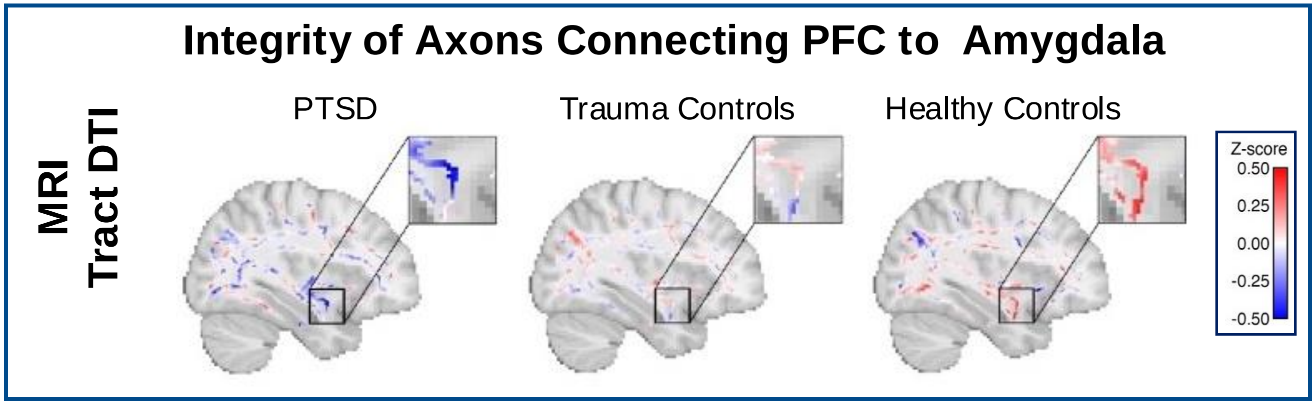


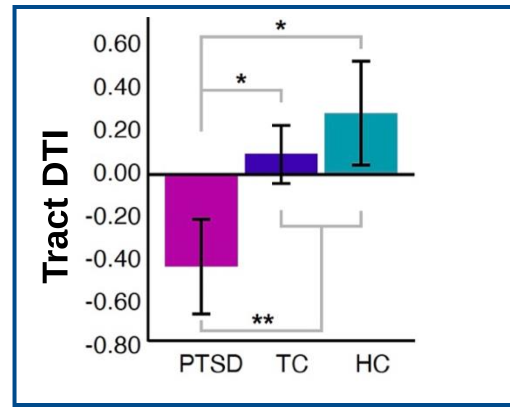
Mikail et al EHJ 2024

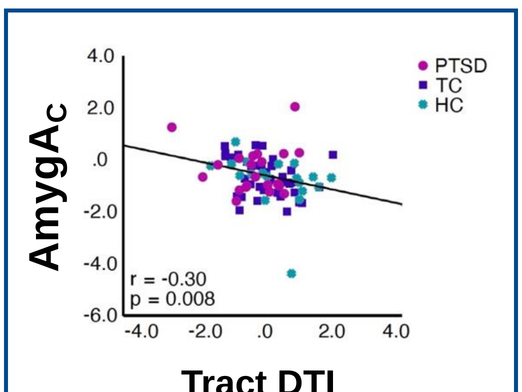
Amygdalar-cortical interactions predict atherosclerosis

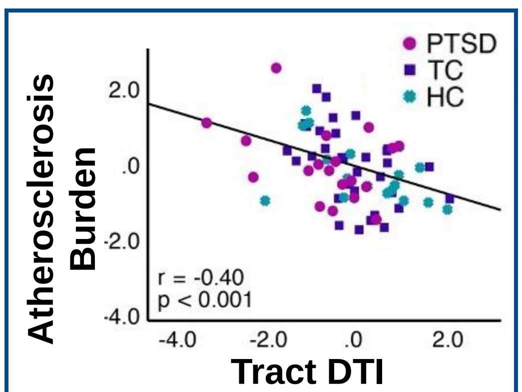


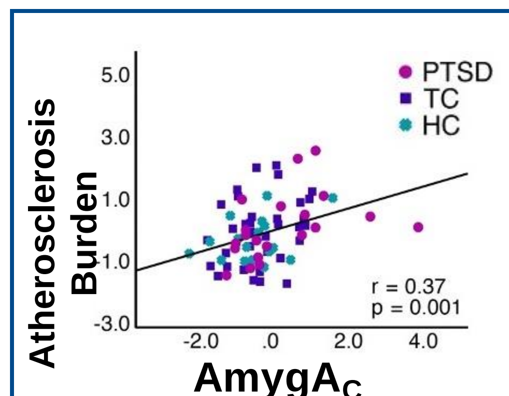


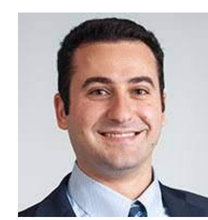












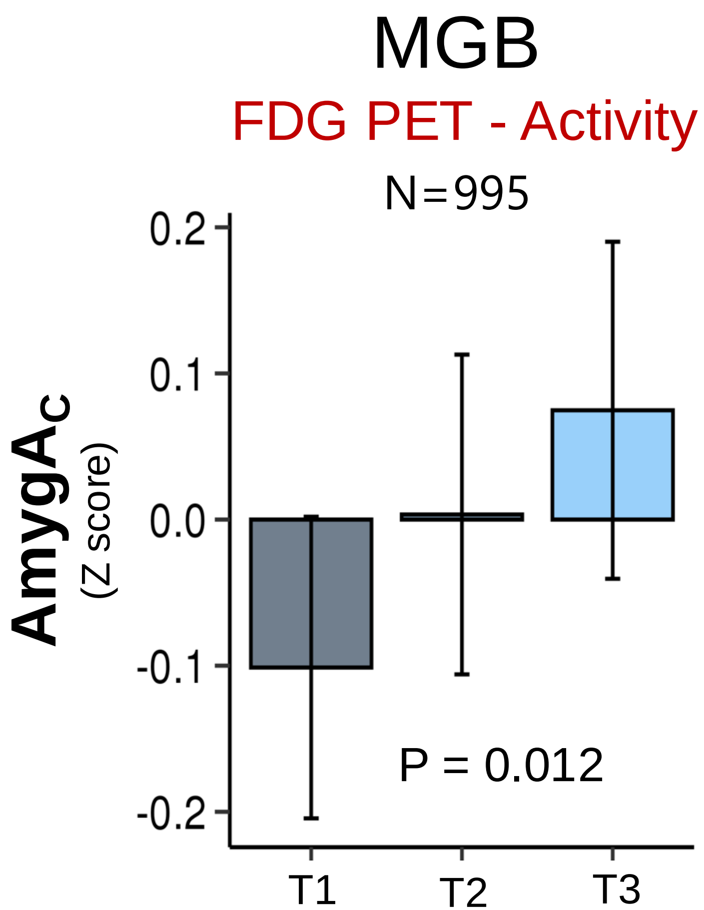
Gharios ,
et al.
AHA 2022

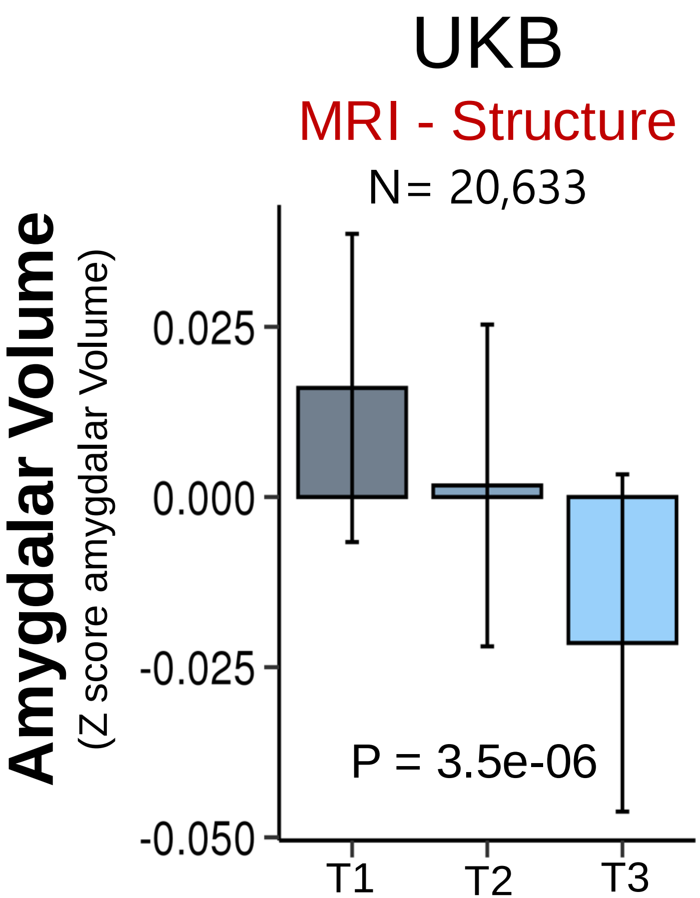
Hypothesis:

If stress is causally related to CVD…

…then a genetic predisposition to stress syndromes should independently associate with cardiovascular disease events.

Genetic Predisposition to Stress Disorders vs Brain Activity and Structure

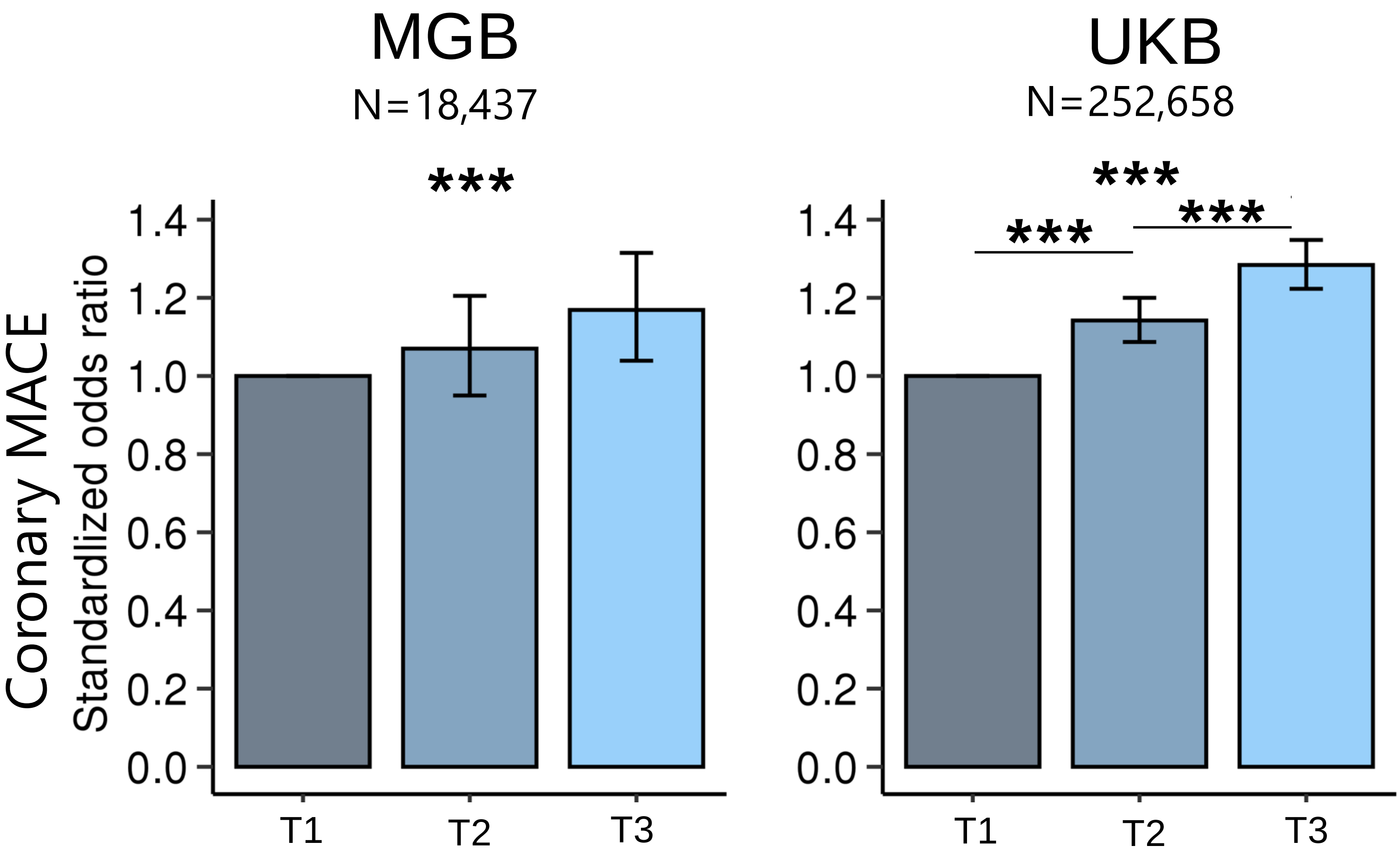




Stress-Sensitivity Polygenic Risk Score (tertiles)

S Abohashem, M Osborne, et al AHA 2020

Genetic Predisposition to Stress Disorders vs CV Events

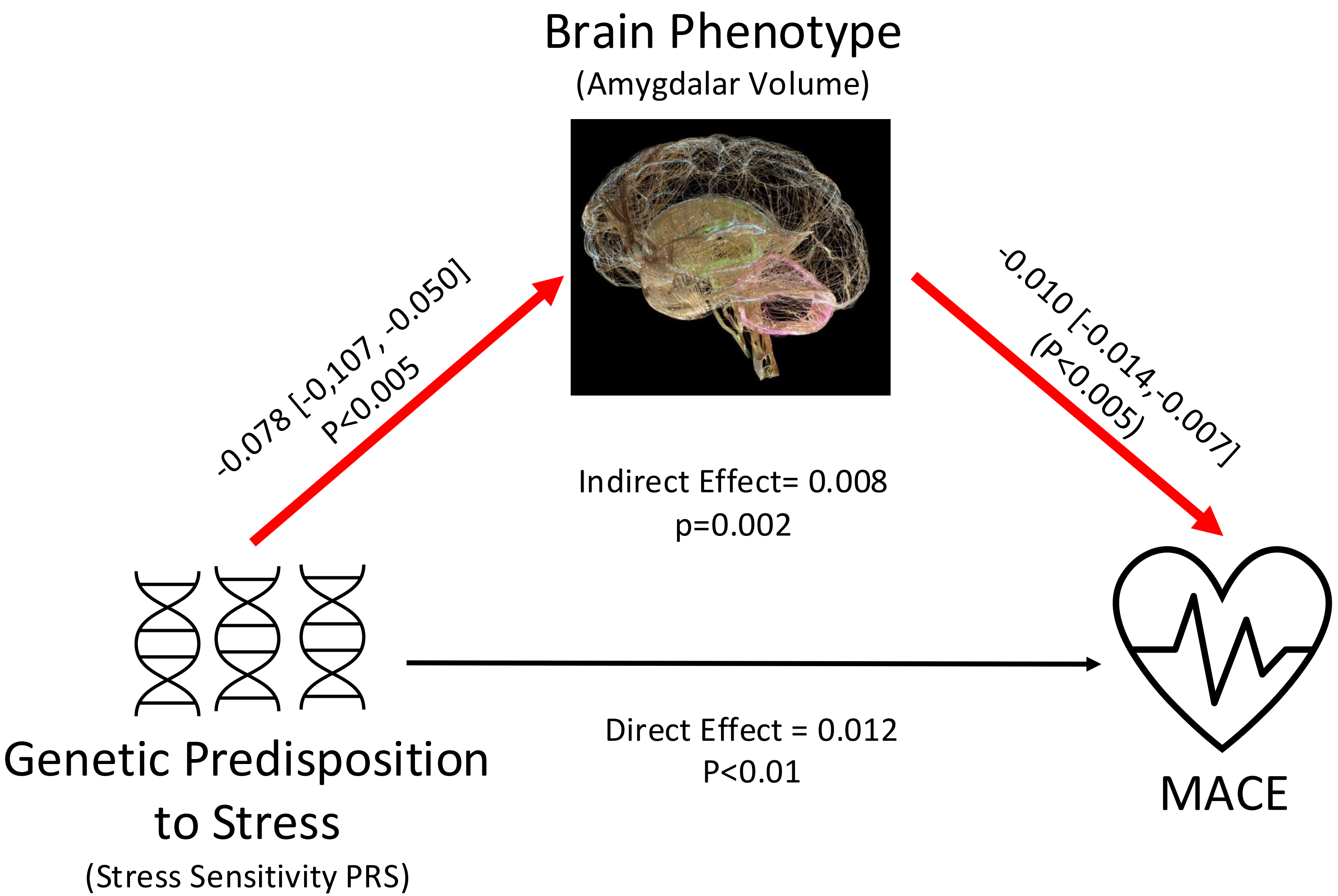


Stress-Sensitivity Polygenic Risk Score (tertiles)

*** p<0.005

S Abohashem, M Osborne, et al AHA 2020

Mediation (Path) Analysis



Mental Stress can Induce Clinically Important Ischemia

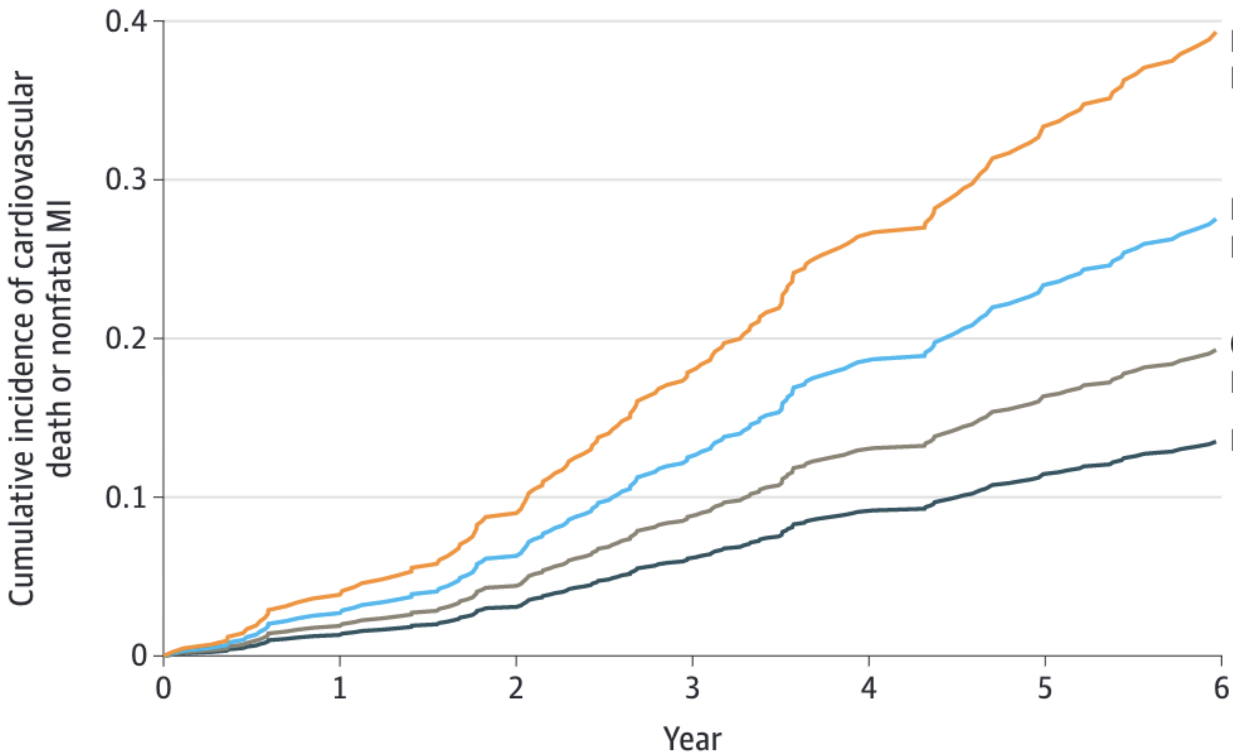
Conventional Exercise Stress Test

+

Mental Stress Test

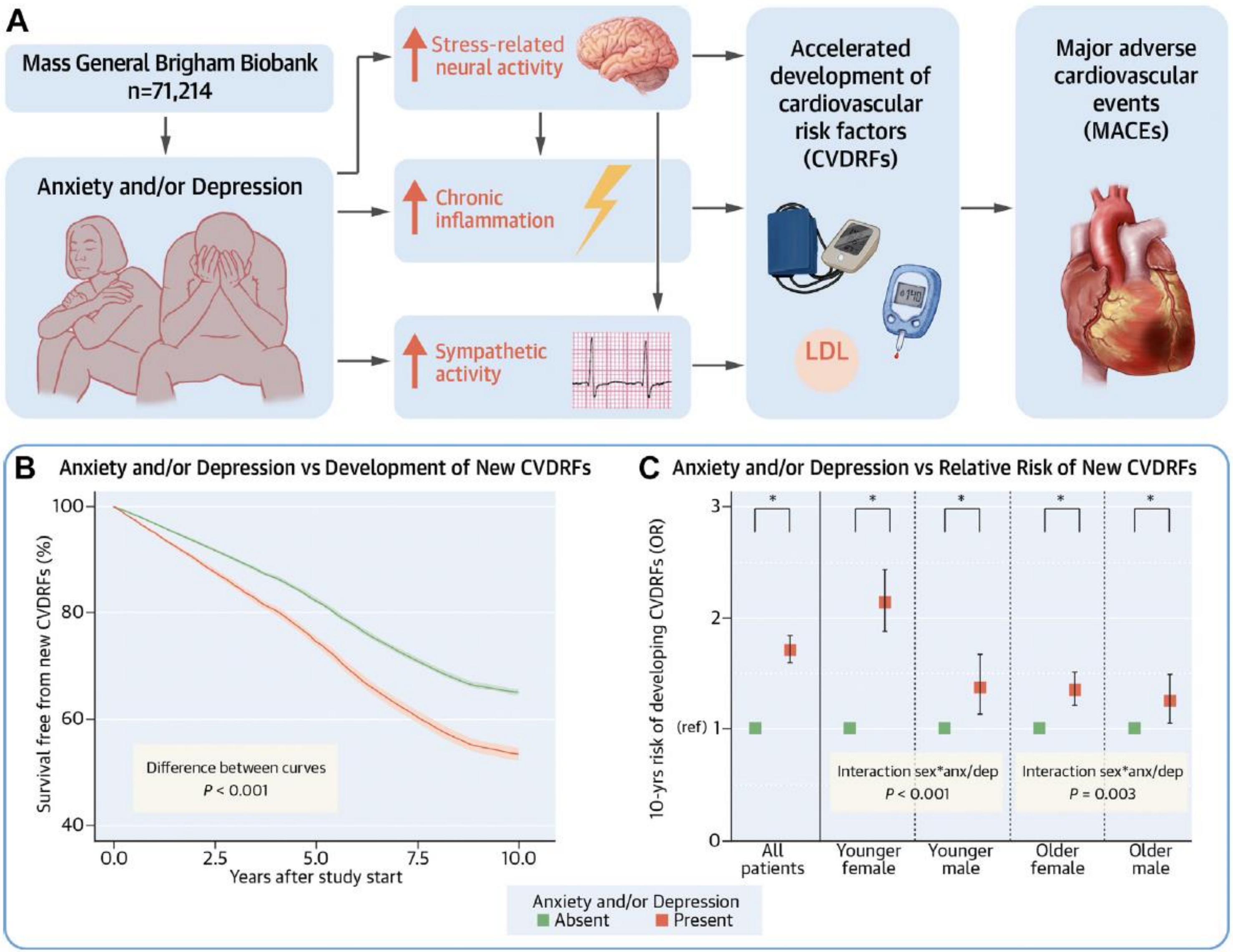
+

Myocardial Perfusion Imaging



Vaccarino et al JAMA 2021

Stress and Depression Accelerate Gain of CVD Risk Factors



G Civieri et al
JACC Adv 2024

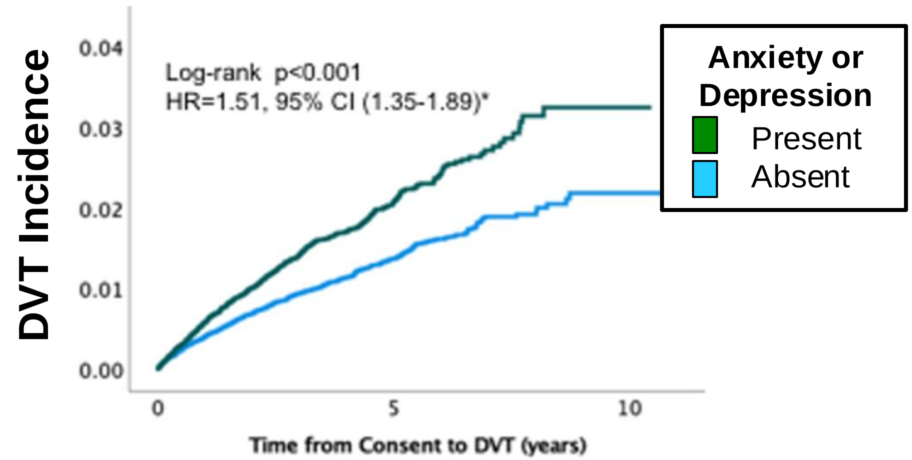
Stress/Depression-Thrombosis Link

Anxiety or Depression vs DVT Risk

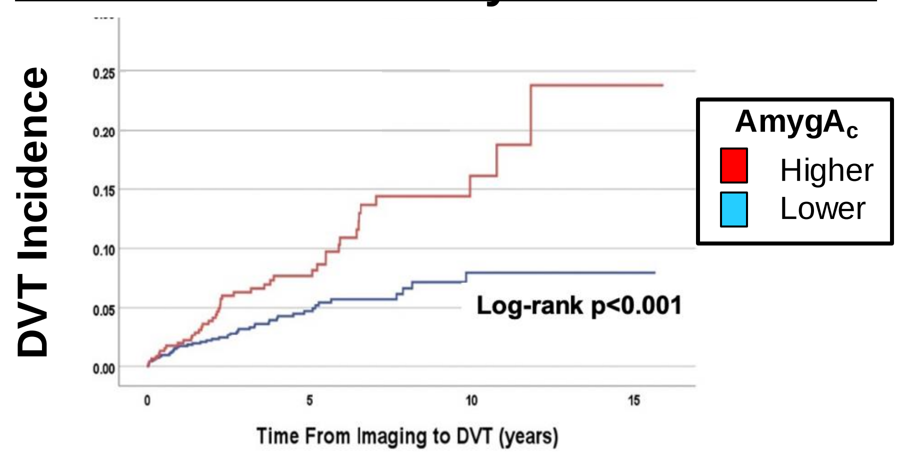
Model Covariables		Anxiety Disorders		Depression	
		Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)	p-value
Univariable analysis	None	1.803 (1.612-2.016)	5.6 x 10^{-25}	1.651 (1.474-1.849)	4.0 x 10^{-18}
+ Demographic factors	+Age, Sex, Race	1.970 (1.759-2.207)	8.4 x 10^{-32}	1.756 (1.566-1.968)	4.6 x 10^{-22}
+ CVD risk factors	+Hypertension, Diabetes, Hyperlipidemia, Smoking	1.658 (1.469-1.871)	2.6 x 10^{-16}	1.504 (1.331-1.700)	6.0 x 10^{-11}
+ DVT risk factors	+Cancer history, Long term aspirin use, Oral contraceptive use	1.530 (1.354-1.728)	8.5 x 10^{-12}	1.427 (1.261-1.614)	1.6 x 10^{-8}

Rosovsky et al AJH 2024

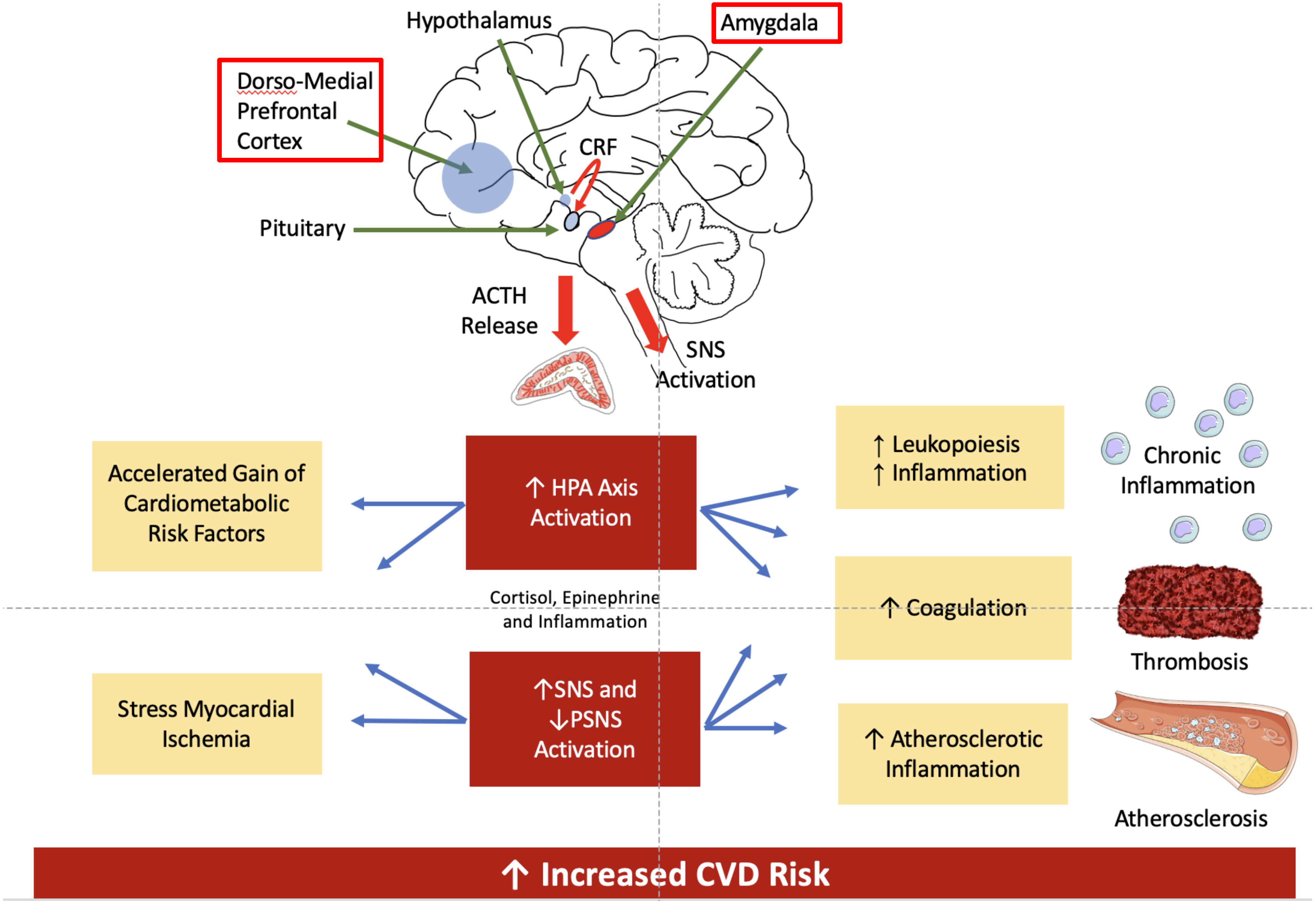
Anxiety or Depression vs Thrombosis



Stress Neural Activity vs. Thrombosis



Stress-Related Pathophysiology

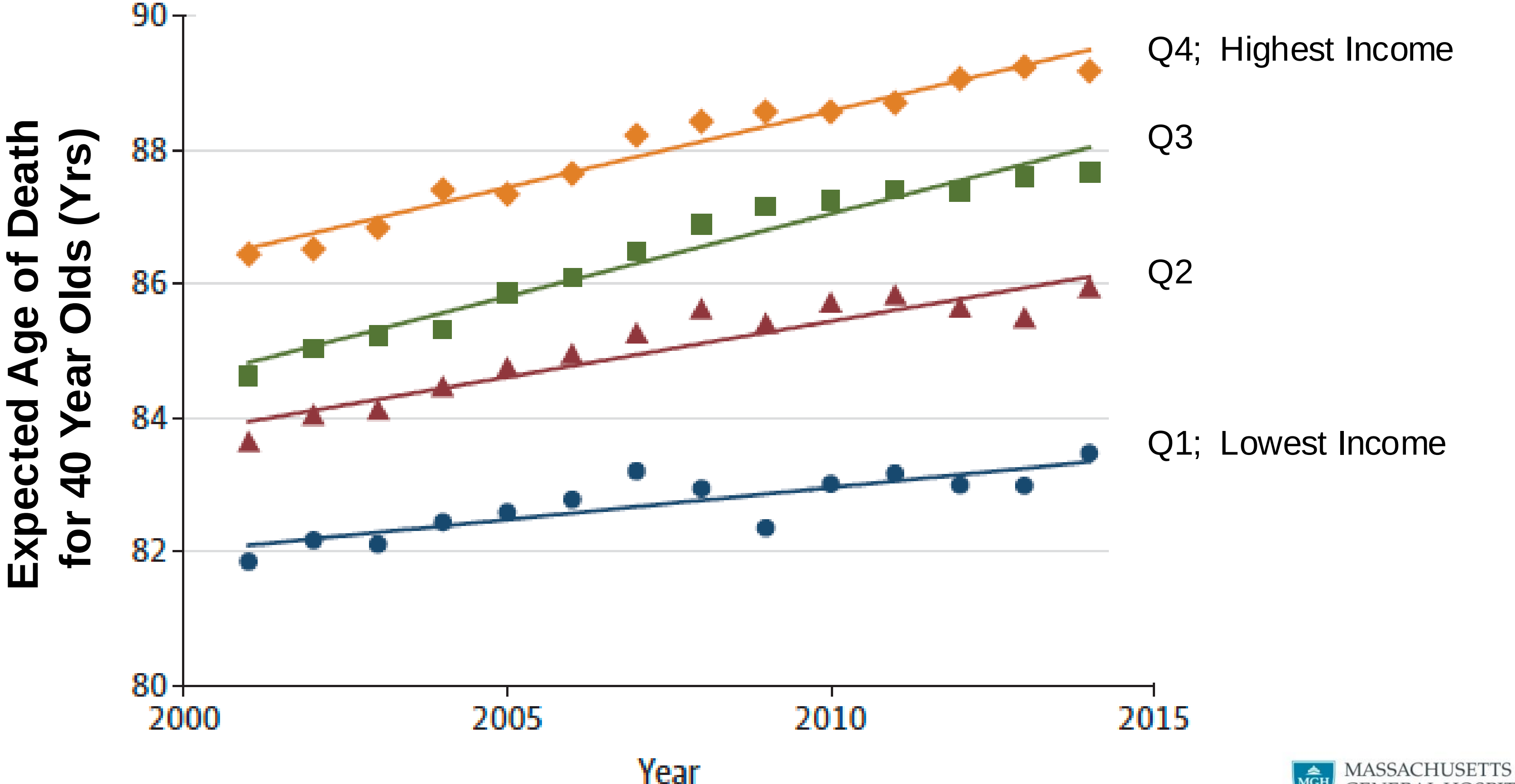


What about Chronic Stressors and CVD?

- 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

Income vs Health

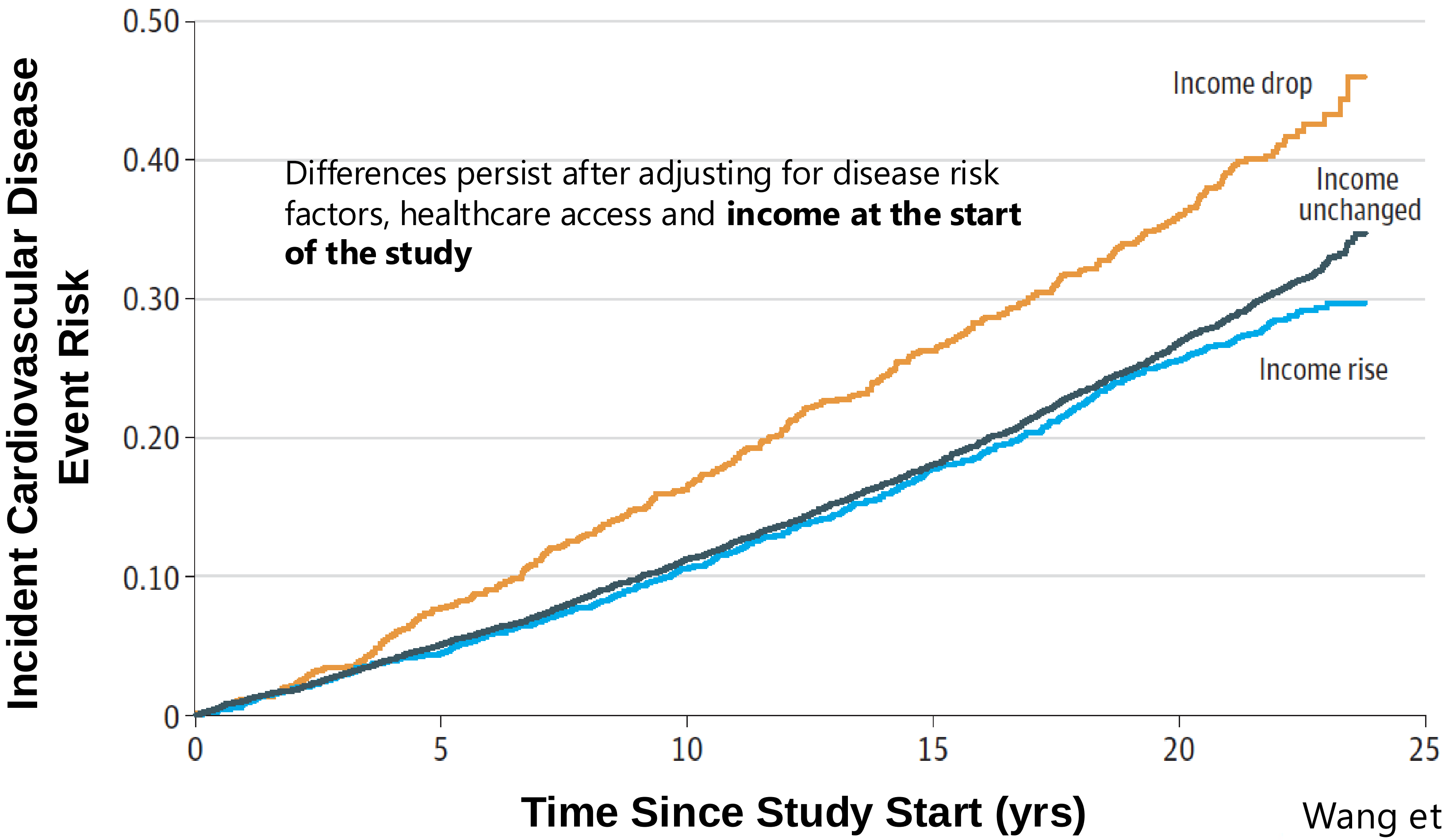
Income vs Age of Death



Chetty et al JAMA 2014

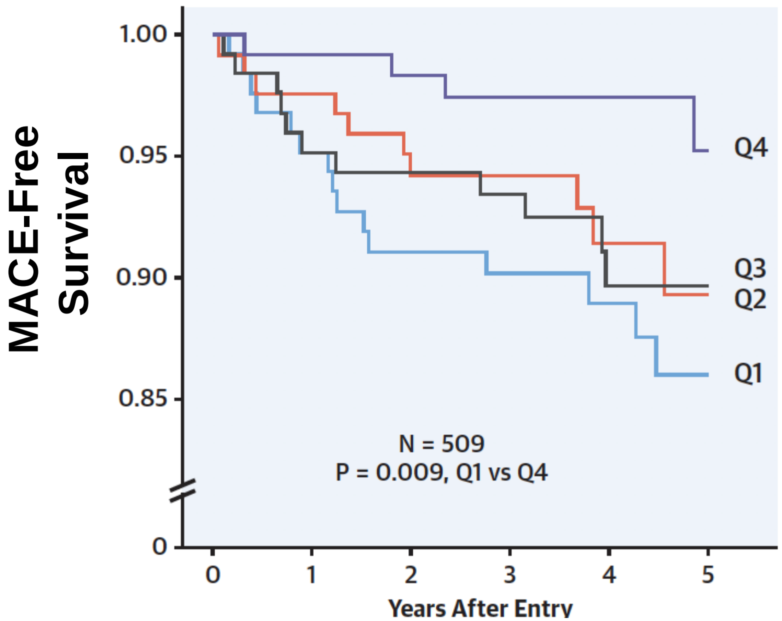
Income vs Health

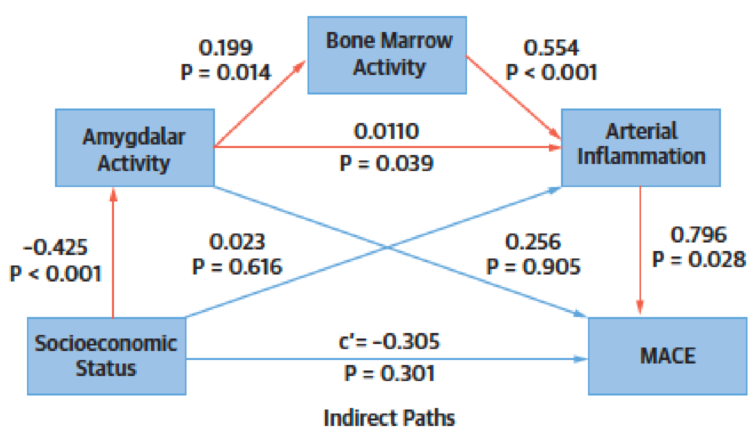
Change in Income vs Cardiovascular Disease



Wang et al
JAMA Cardiol
2019

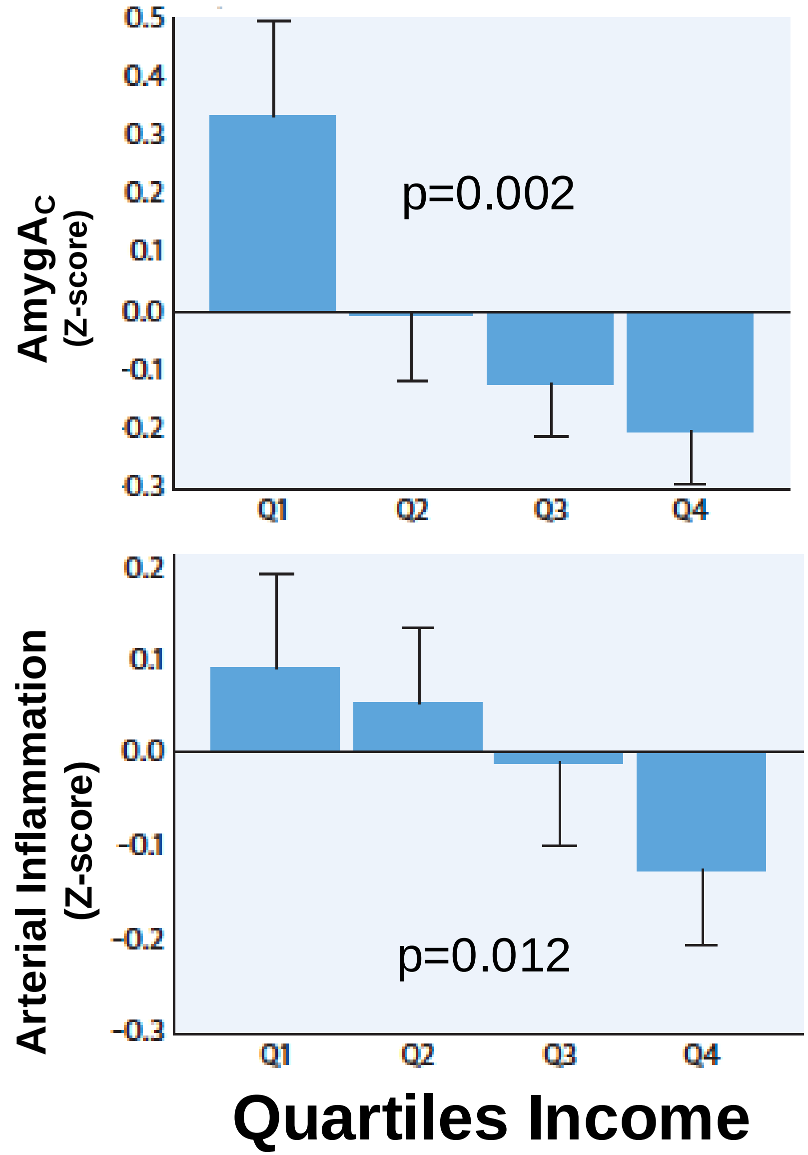
Socioeconomic Status vs CVD: Involvement of Stress-Associated Mechanisms





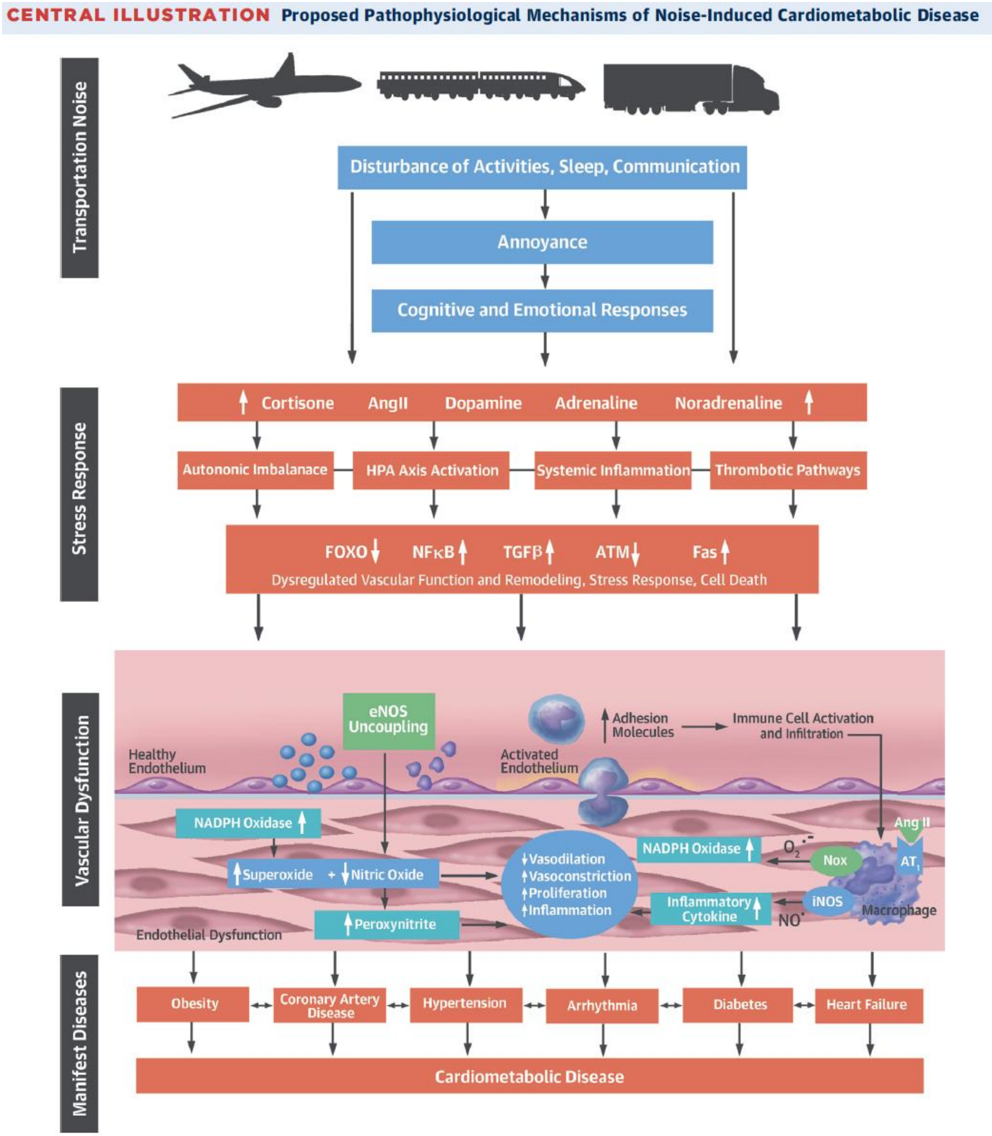
Indirect Paths

1) ↓SES→ ↑AmygA → ↑Bone Marrow → ↑art inflam → ↑MACE: -0.0137 (-0.0570, -0.0003), p < 0.05
2) ↓SES→ ↑AmygA → ↑art inflam → ↑MACE: = -0.0137 (-0.0546, -0.0001), p < 0.05



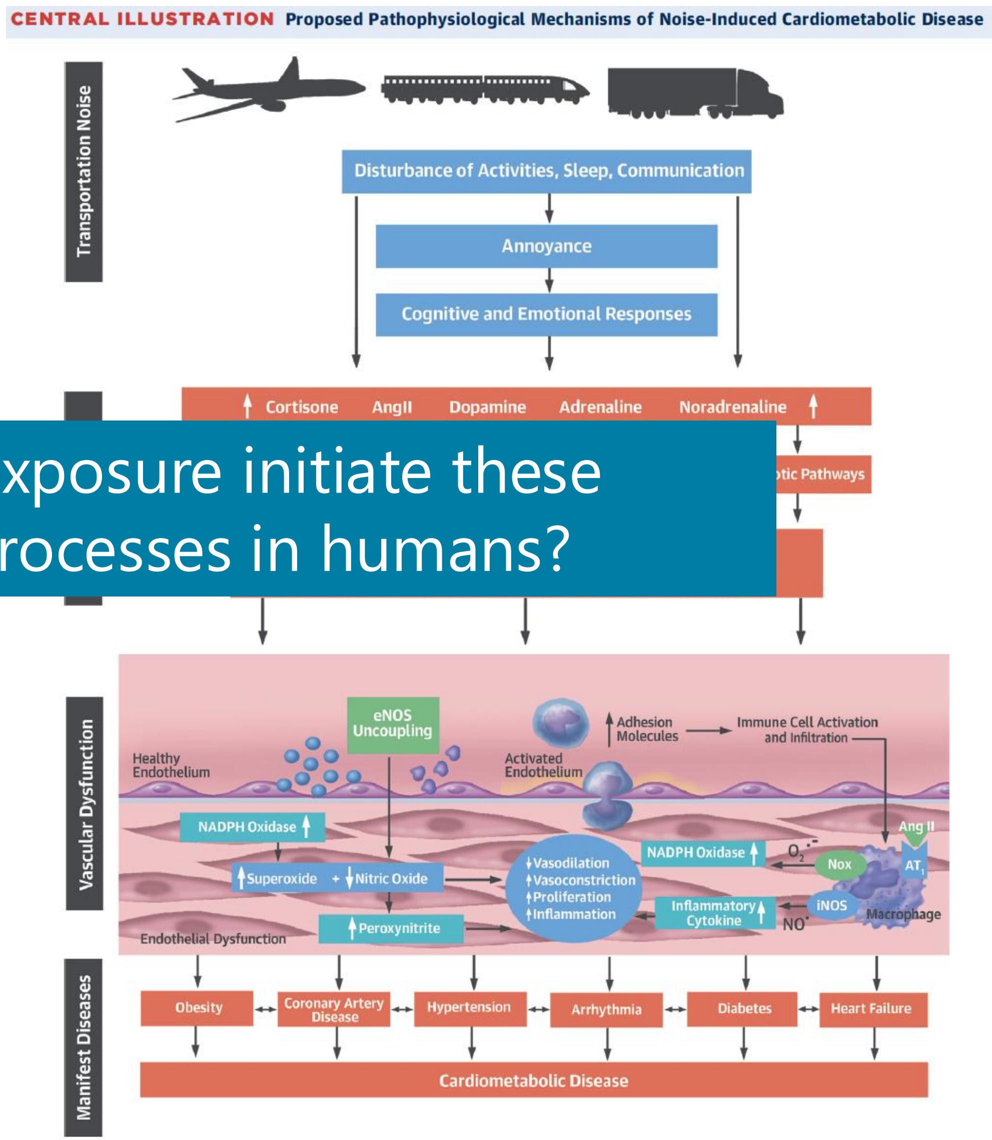
Tawakol et al JACC 2019

Noise and CVD



Münzel, T. et al. J Am Coll Cardiol. 2018;71(6):688-97.

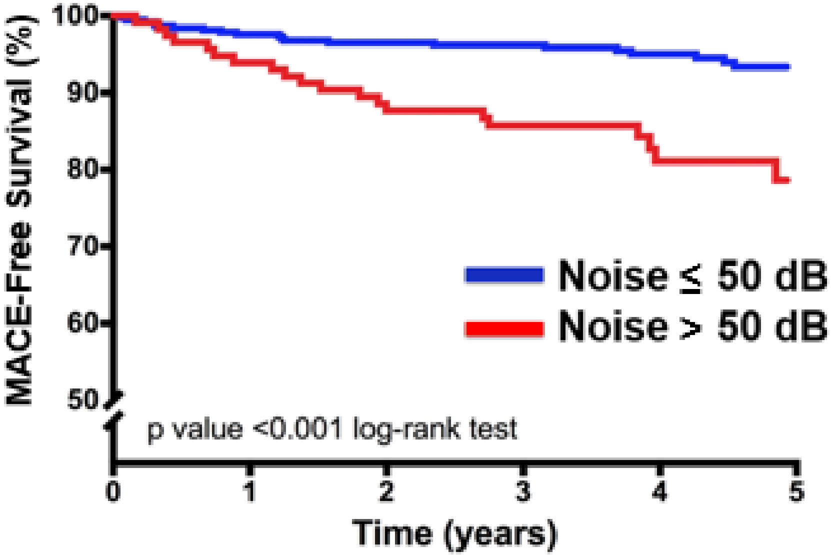
Noise and CVD

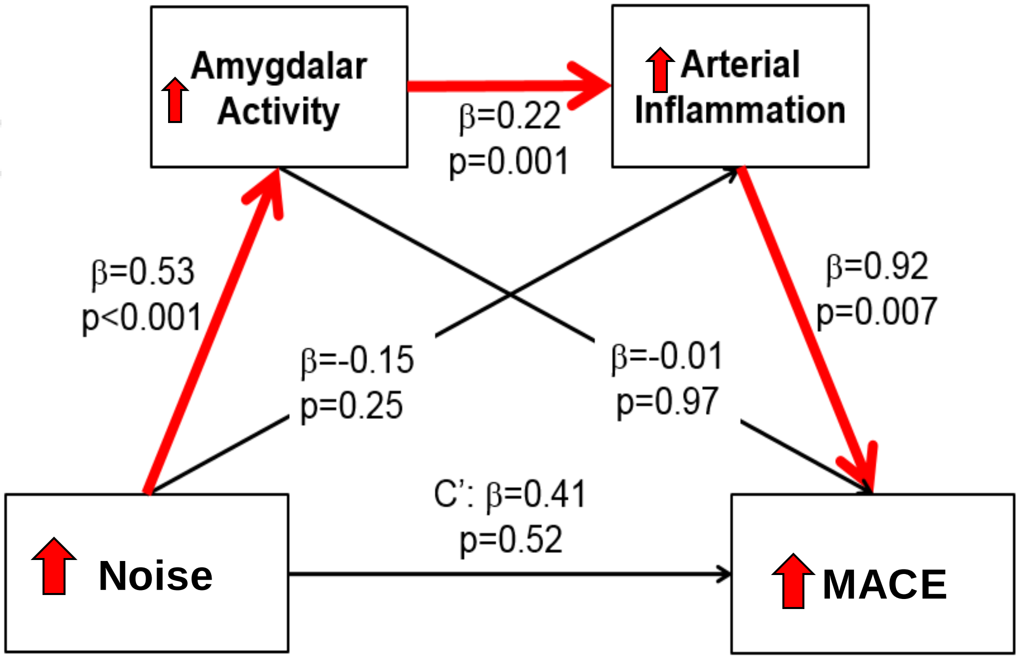


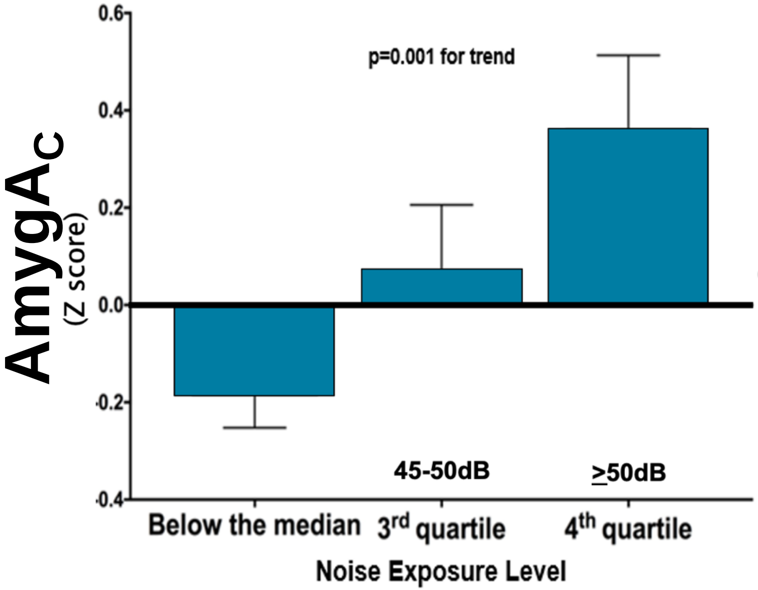
Münzel, T. et al. J Am Coll Cardiol. 2018;71(6):688-97.

How does noise exposure initiate these pathobiological processes in humans?

Noise-Brain-CVD

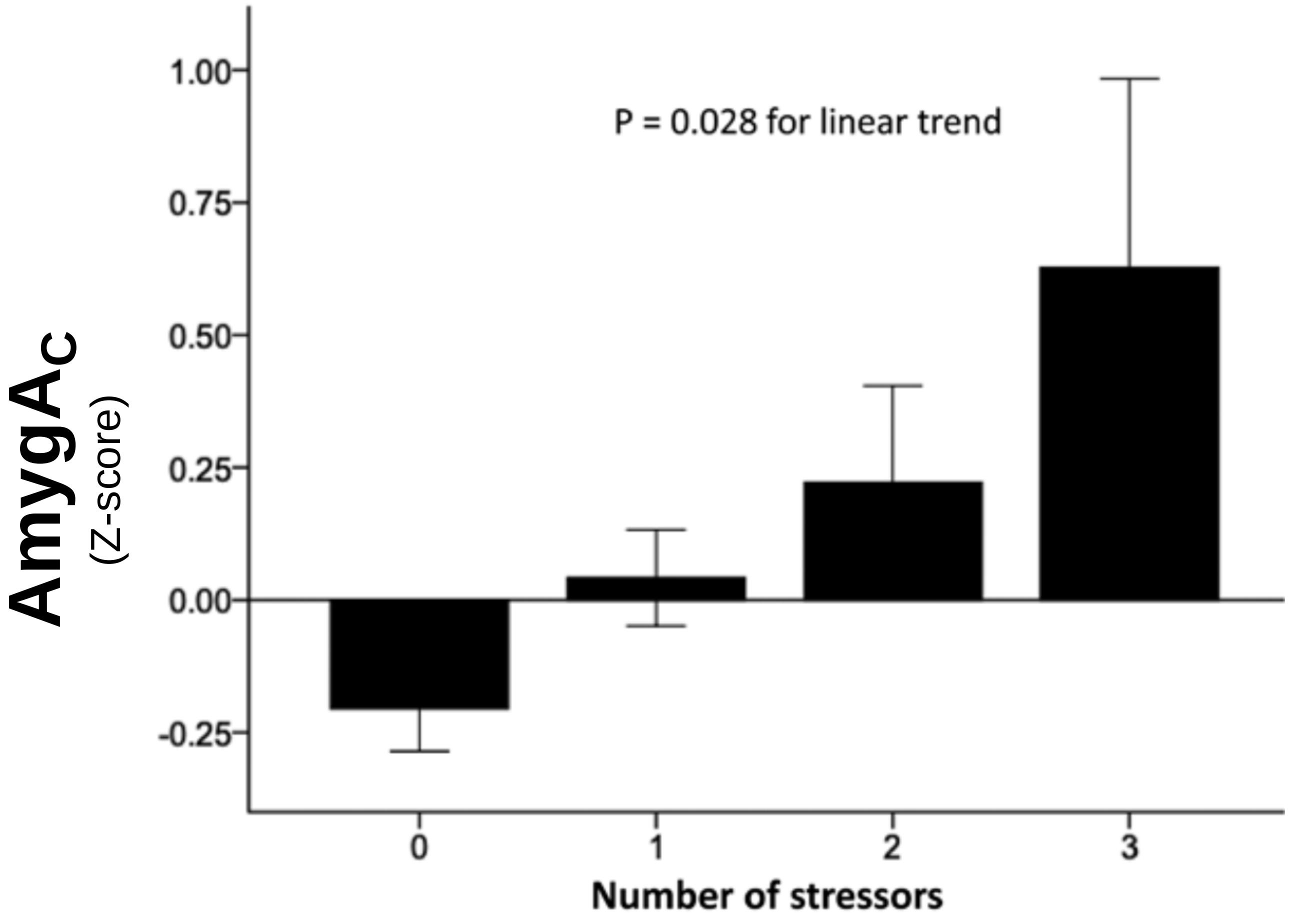






M Osborne et al
EHJ 2020

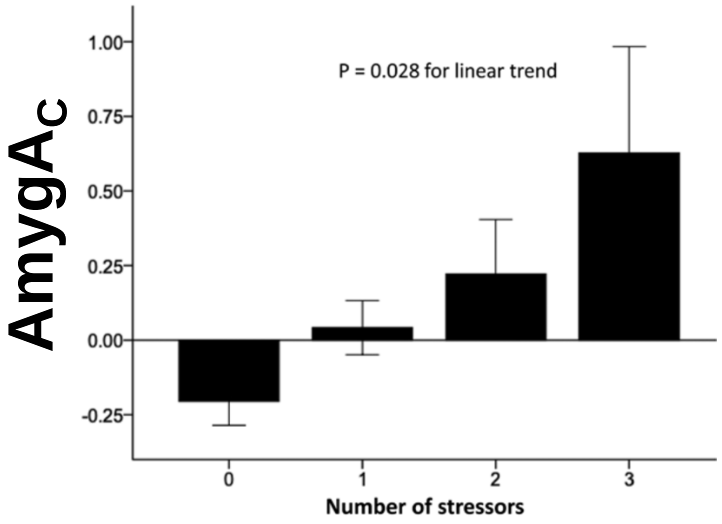
Is it the stressor…
or the stress response that causes disease?

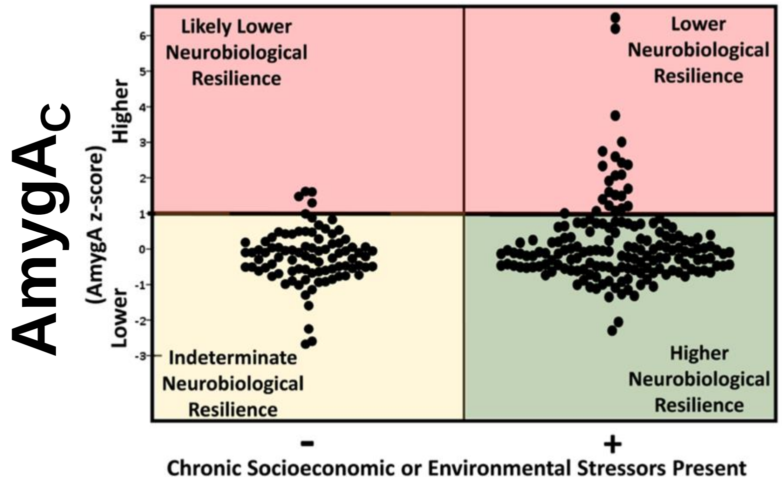


<u>Stressors:</u>
- Income
- crime
- noise

Dar et al
Circ Imaging
2020

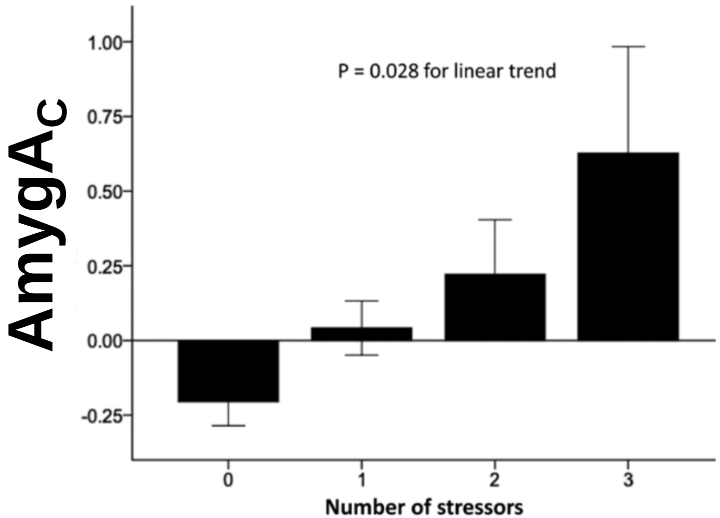
Neurobiological Resilience

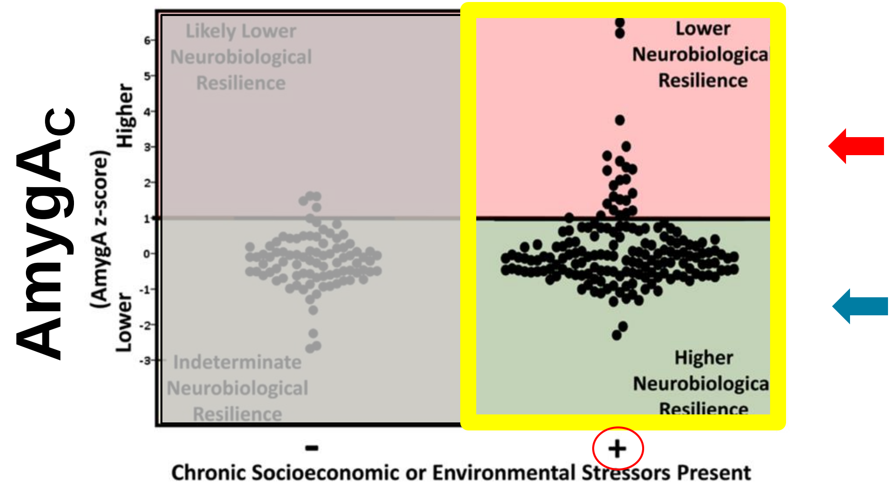




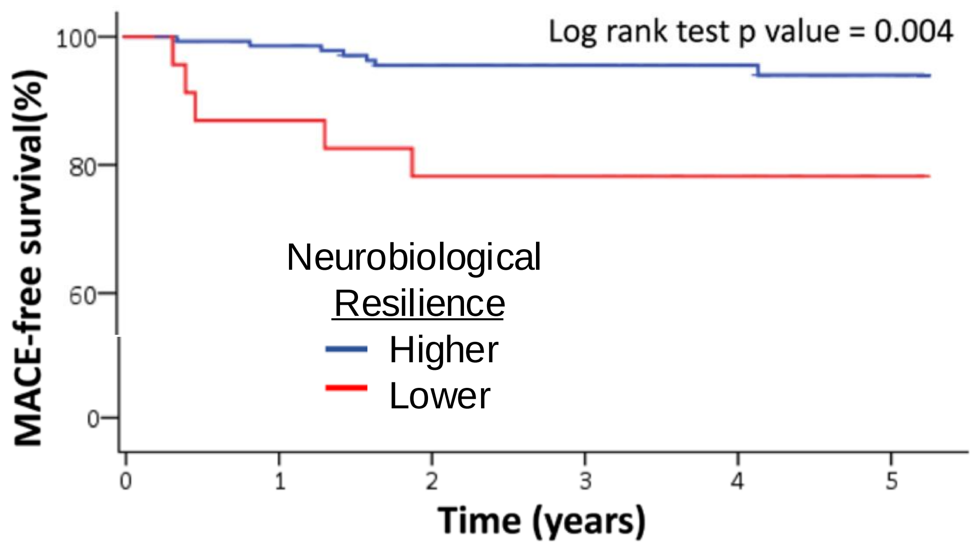
Dar el al Circ Imaging 2020

Neurobiological Resilience





Neurobiological Resilience Determines Outcomes among Stress-Exposed



Dar el al Circ Imaging 2020

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Could **neurobiological resilience** influence risk for having CVD events that are triggered by **acute** stress?

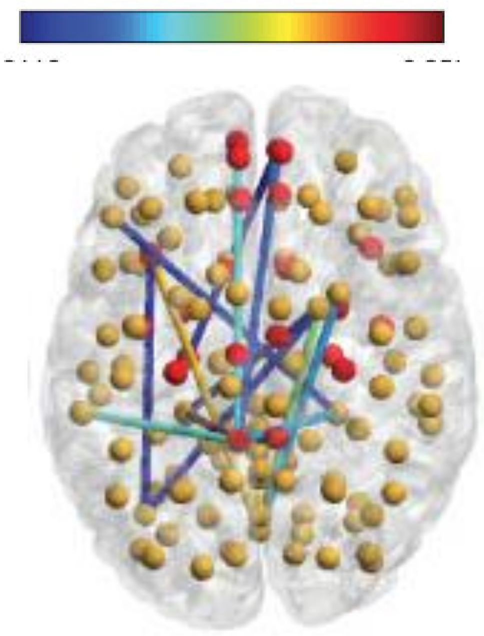
MASSACHUSETTS GENERAL HOSPITAL

CORRIGAN MINEHAN HEART CENTER

Classic Stress-Associated CVD Syndrome: Takotsubo Syndrome (TTS)

- Acute, usually reversible heart failure syndrome
- Often triggered by acute emotional or physical stressor.
- Pathogenesis remains incompletely delineated.
- Link between the brain and heart has long been proposed as a factor.

Classic Stress-Associated CVD Syndrome: Takotsubo Syndrome (TTS)



- fMRI study
- 15 patients w TTS vs. 39 controls

- **TTS assoc w impaired cortico-limbic connectivity**
  - **notably involving the amygdala and prefrontal cortex**

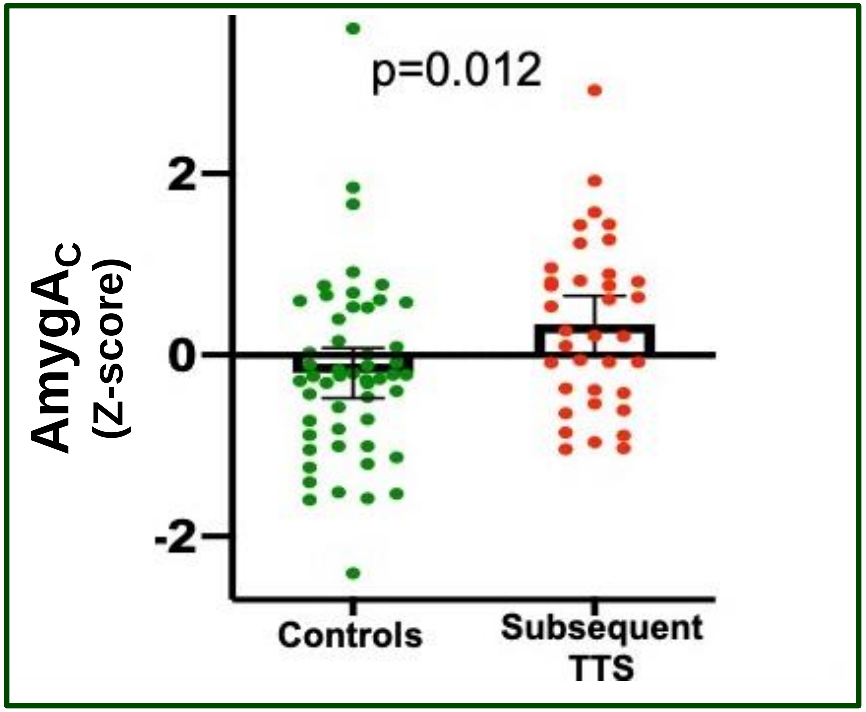
"unknown whether [fMRI] changes observed in TTS patients were present before the onset of the disease …."

Templin et al EHJ 2019

MASSACHUSETTS GENERAL HOSPITAL
CORRIGAN MINEHAN HEART CENTER

AmygA$_C$ vs. Risk of Takotsubo Syndrome (TTS)

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



A Radfar, et al European Heart Journal 2021

AmygA$_C$ vs. Risk of Takotsubo Syndrome (TTS)

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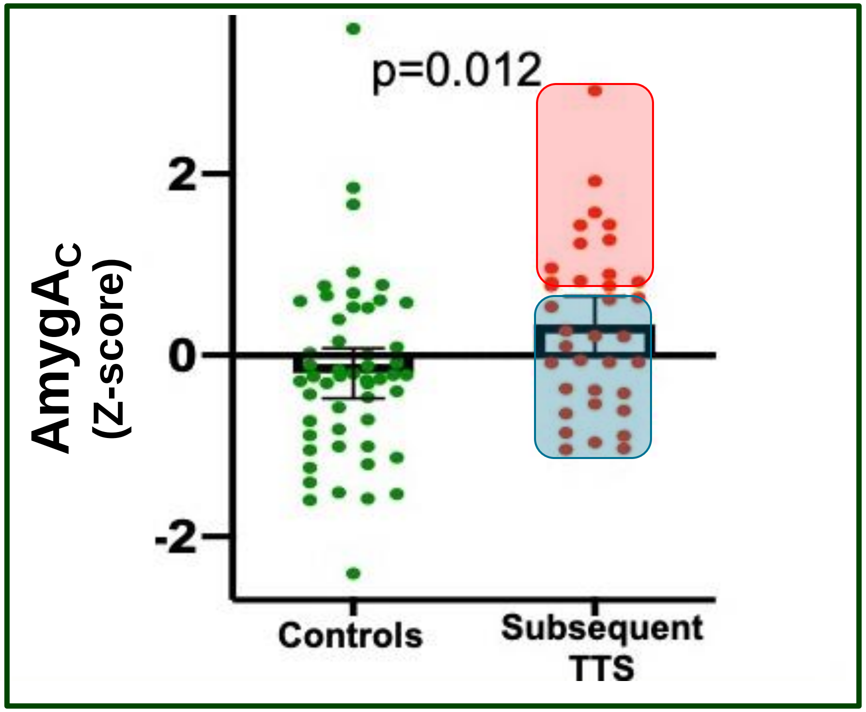
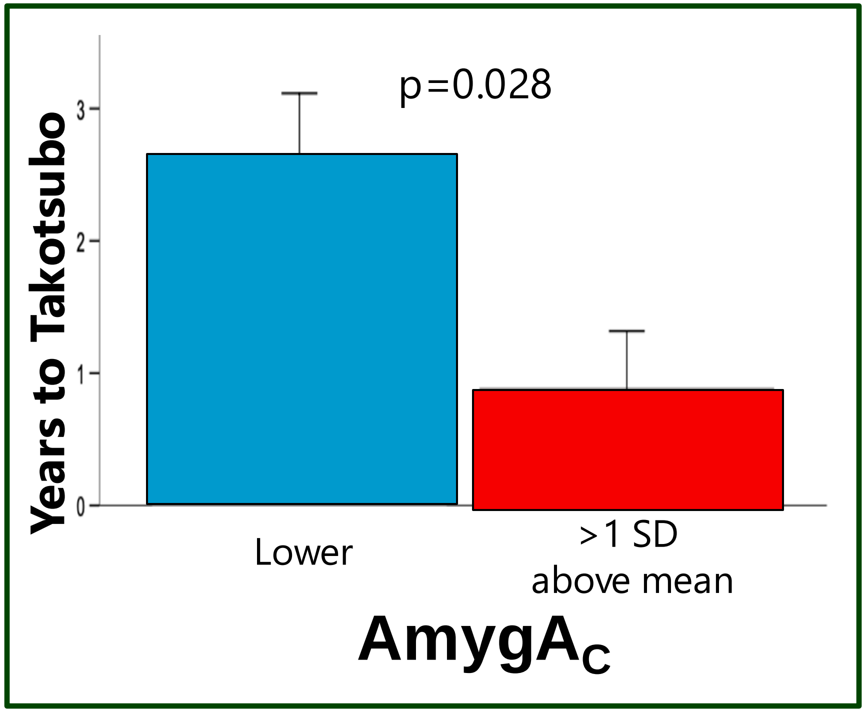


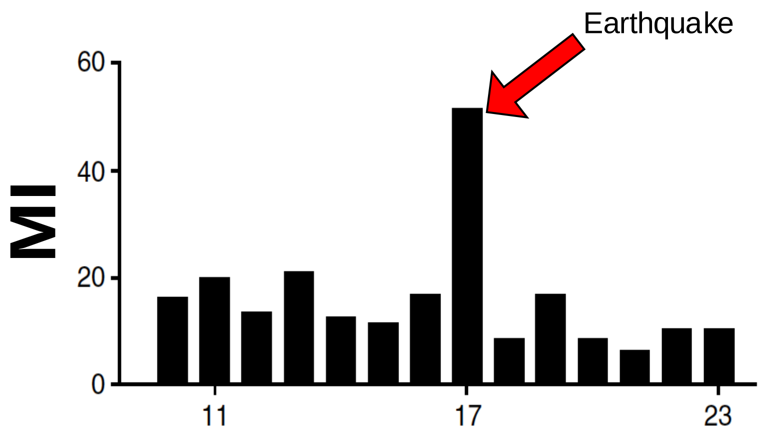


A Radfar, et al European Heart Journal 2021

Acute Stress and CVD

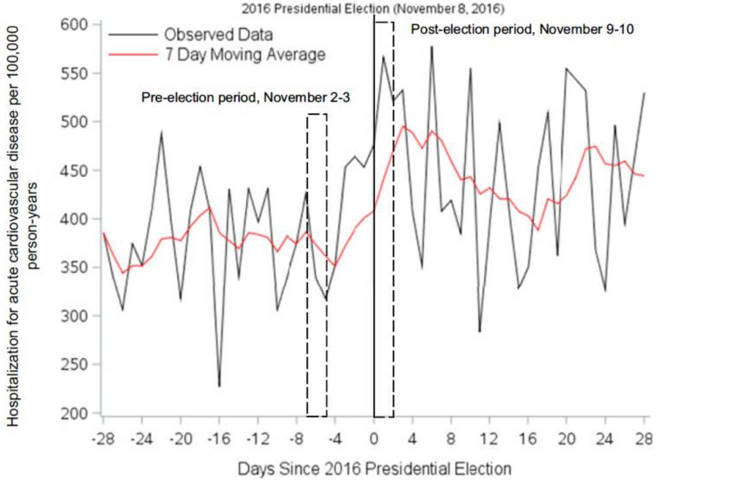
Surges in Cardiovascular Events during Stressful Periods

Natural Disasters



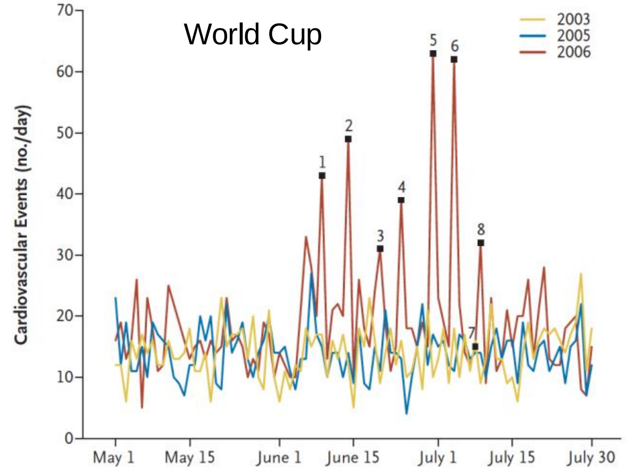
Leore, et al NEJM 1996

Elections

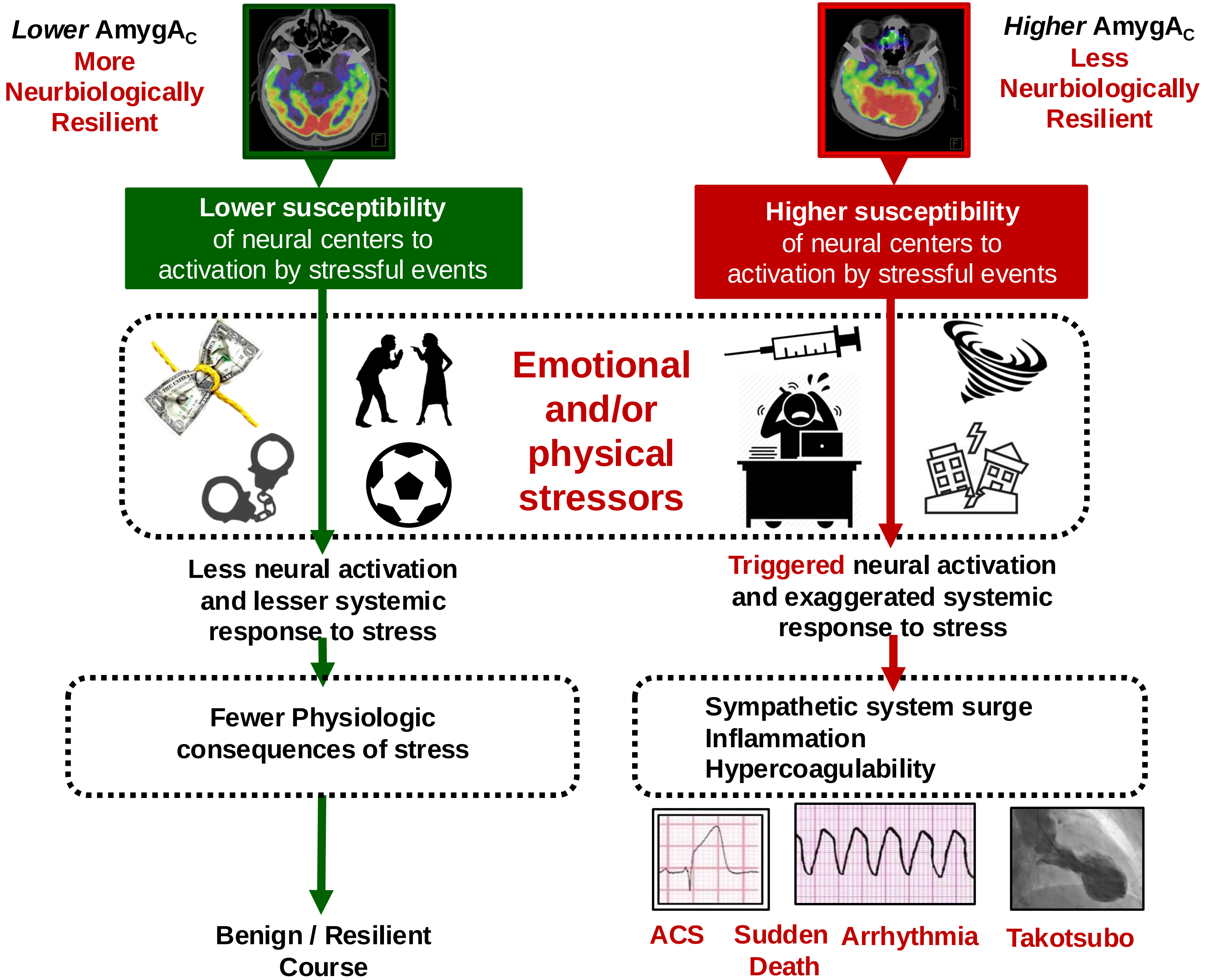


Mefford, et al JAMA NO 2022

Championship Sporting Events



Wilbert-Lampen et al NEJM 2008

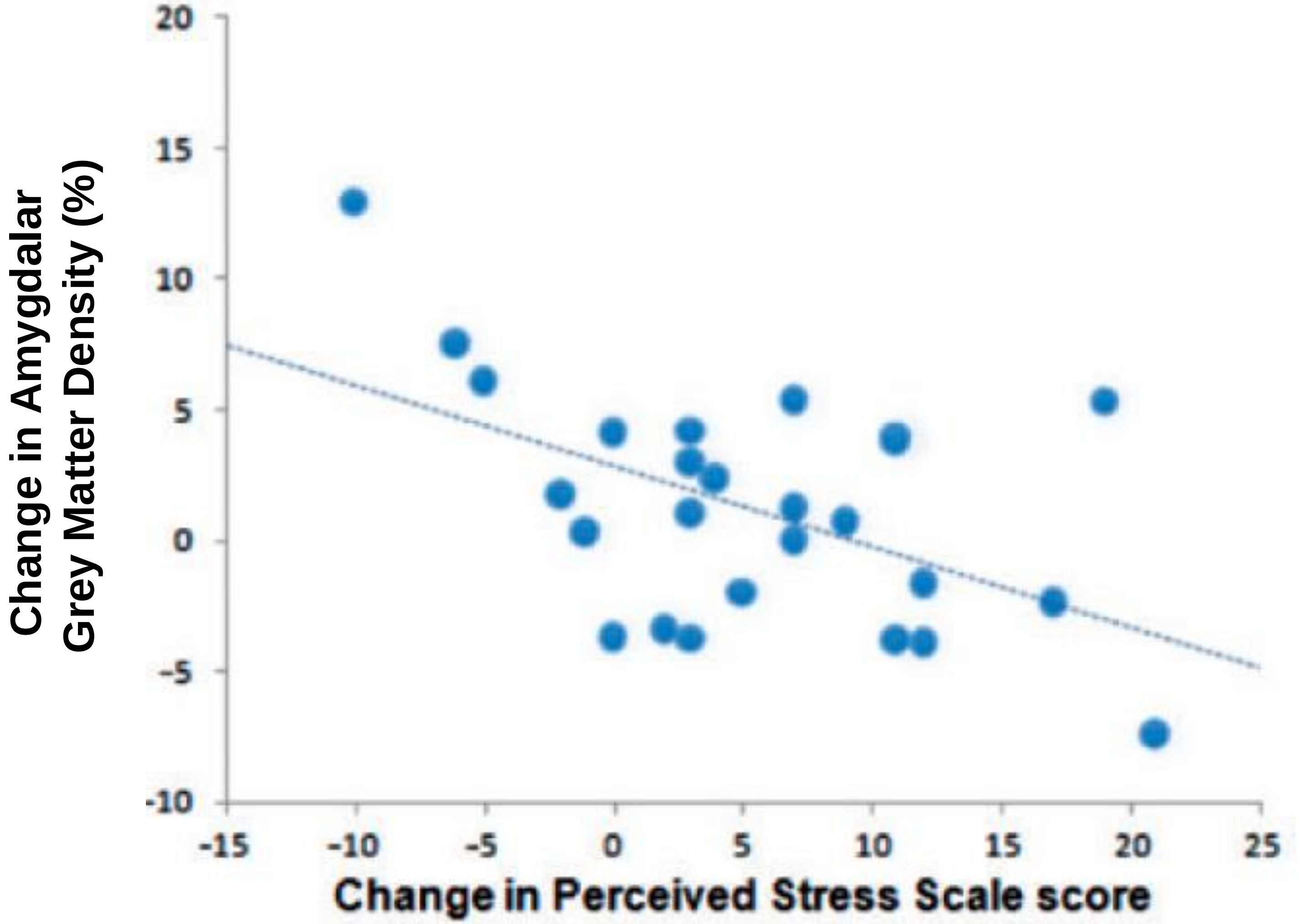

Lower AmygA$_C$
More Neurbiologically Resilient
Higher AmygA$_C$
Less Neurbiologically Resilient
Lower susceptibility
of neural centers to activation by stressful events
Higher susceptibility
of neural centers to activation by stressful events
Emotional and/or physical stressors
Less neural activation 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
TEACHING HOSPITAL

Modifying Stress Neural Activity and Neurobiological Resiliance

MASSACHUSETTS GENERAL HOSPITAL
CORRIGAN MINEHAN HEART CENTER

Stress reduction intervention alters amygdalar grey mater density



Holzel et al SCAN 2010

Stress Reduction may Impart CVD Benefits

Eligible Subjects:

- Recent ACS
- Recent coronary revascularization

Non-Randomized

Randomized

75 Subjects

- No Cardiac Rehab

75 Subjects

- Standard Cardiac Rehab

76 Subjects

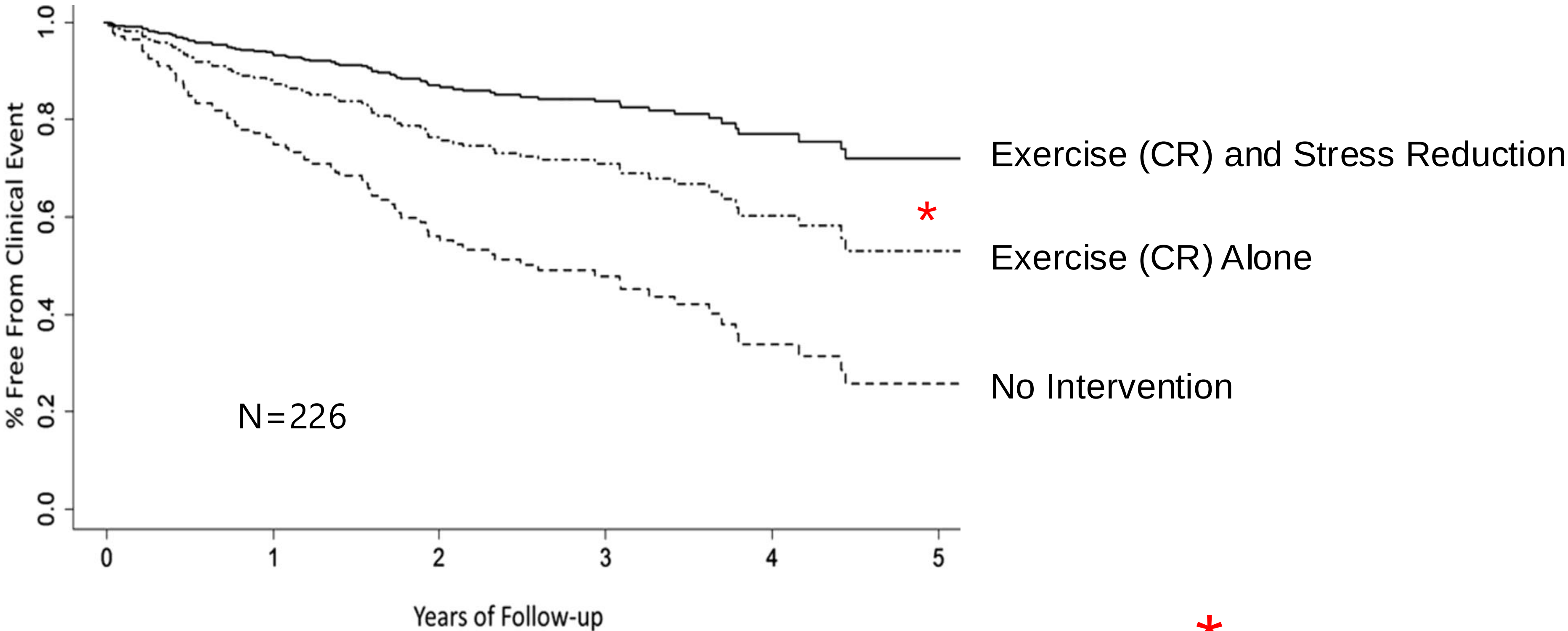
- Cardiac Rehab +
- Stress Reduction

5-yr Follow-up for CVD Events

Blumenthal et al Circulation 2016

Stress Reduction may Impart CVD Benefits

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



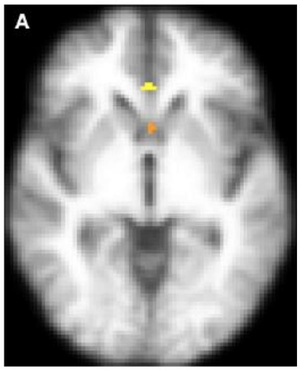
* P=0.025

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

Blumenthal et al Circulation 2016

Stress Neural Network Changes Associated with Tai Chi and Qigong

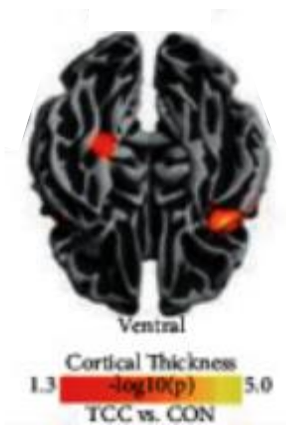
Tai Chi In Osteoarthritis Study



Improvements in amygdala-mPFC connectivity

Shen et al Frontiers in Med 2022

Brain Imaging in Tai Chi vs Controls

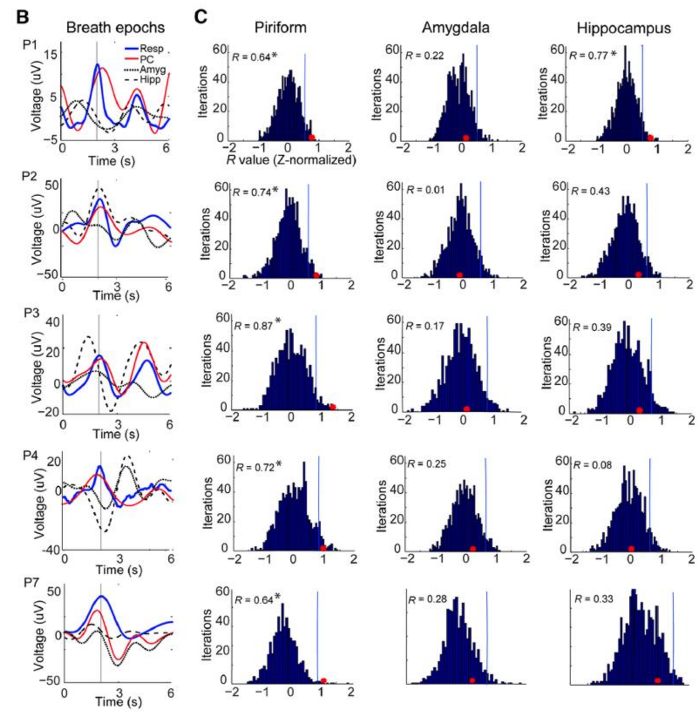


Tai Chi vs Controls:

- **thicker cortical regions**

Yao et al EBC Alt Med. 2021

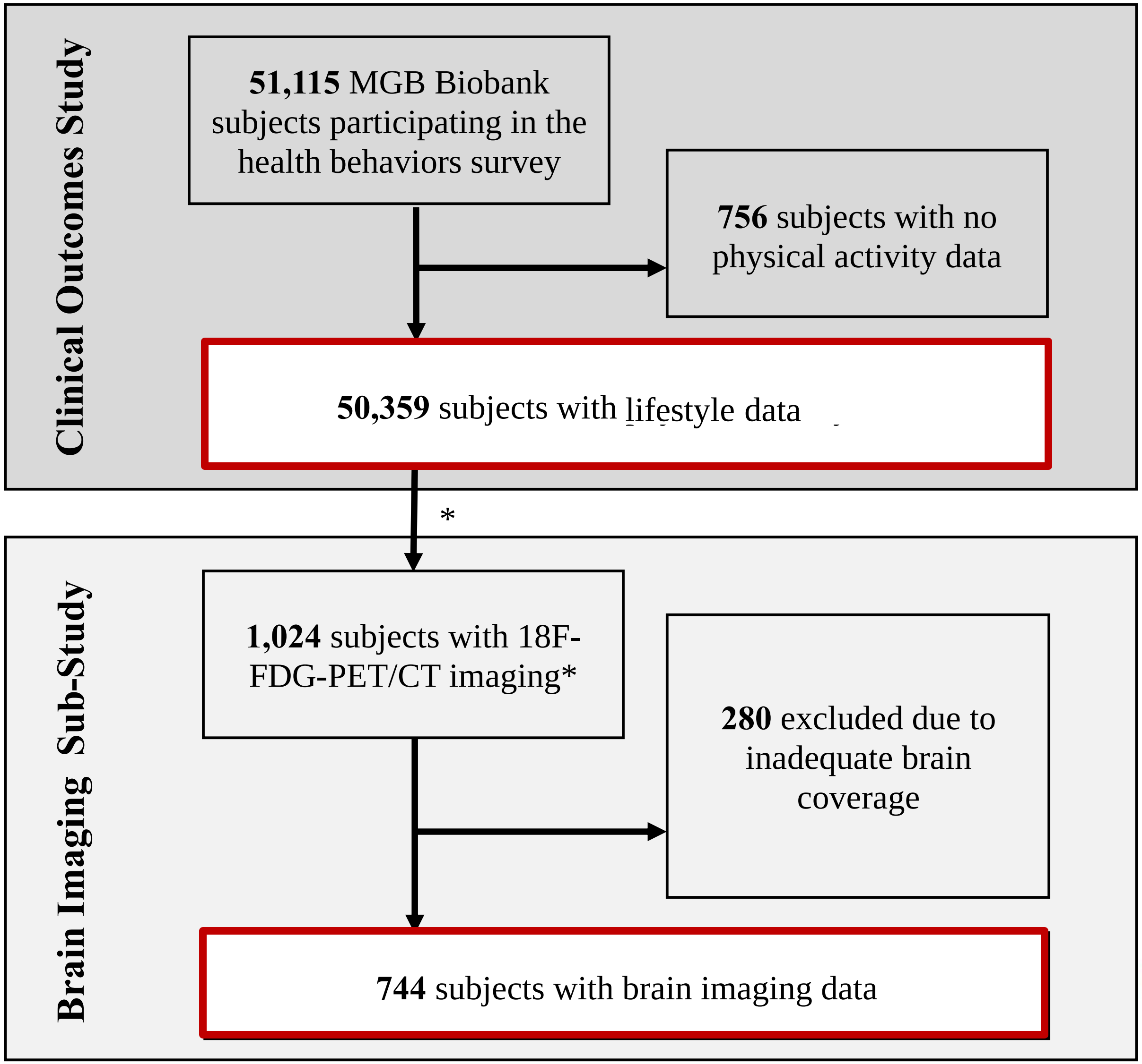
Respiration vs. Amygdalar Oscillations



Respiratory entrainment results in **changes in field potential activity within the amygdala**

Zelano et al J Neuroscience 2016

Evaluation of Lifestyle Factors : MGB Biobank Heart-Mind Study



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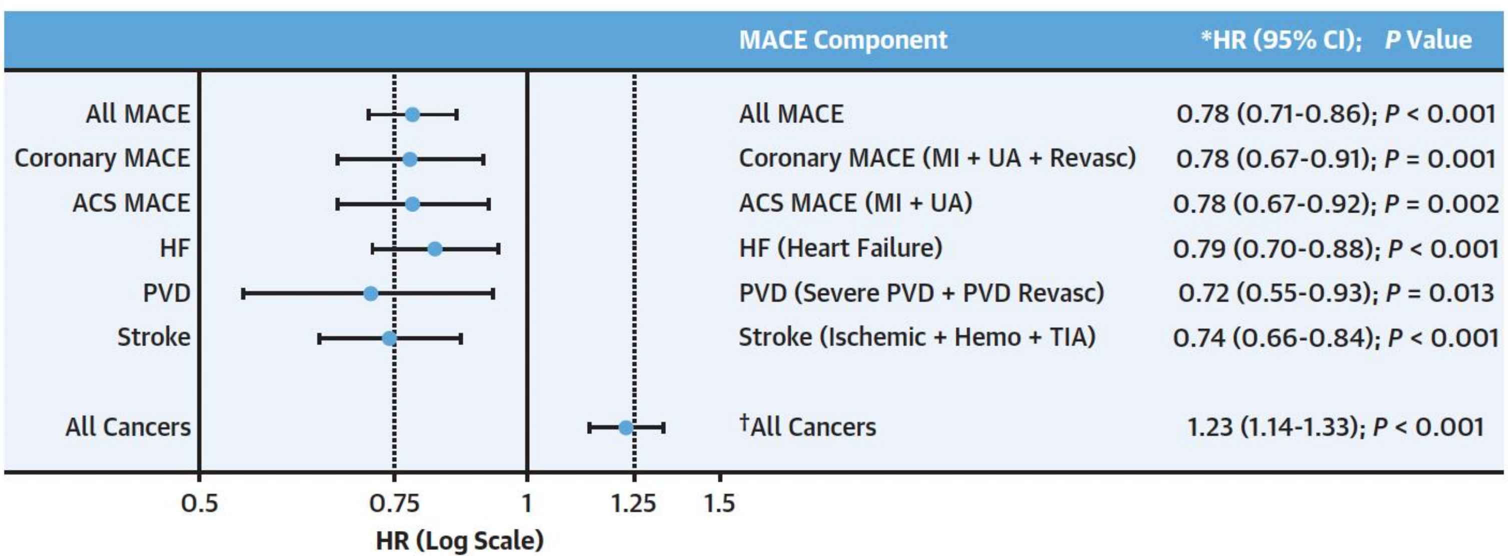
CORRIGAN MINEHAN HEART CENTER

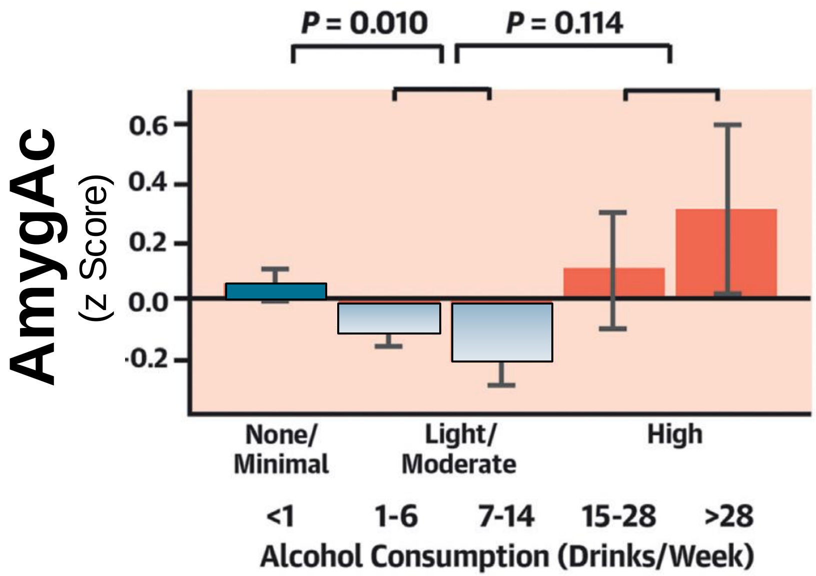
Light/Mod Alcohol vs MACE

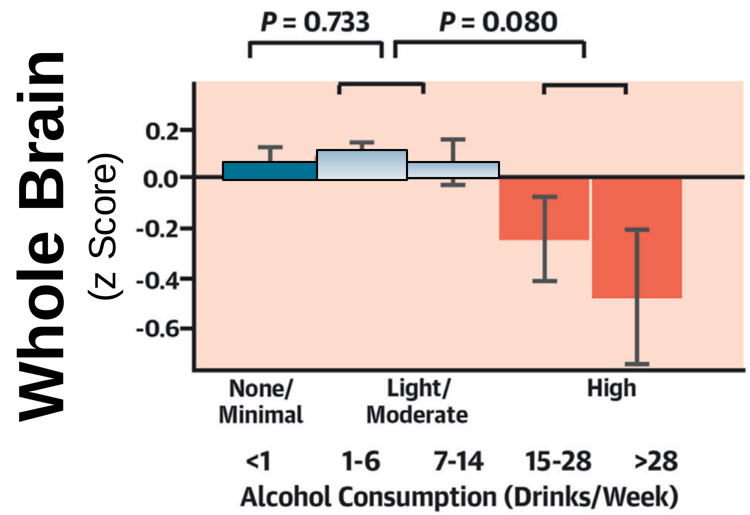
	Covariable Themes	Covariables	10-year MACE	P-Value
Light/moderate vs Low Alcohol consumption	+ CVD risk factors (primary analysis)	Age, sex, HTN, DM, HLD, smoking	0.81 (0.75-0.88)	**P<0.001**
	+ Health behaviors	Exercise, Sleep disorders	0.83 (0.77-0.90)	**P<0.001**
	+ Socioeconomic factors	Employment, 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**

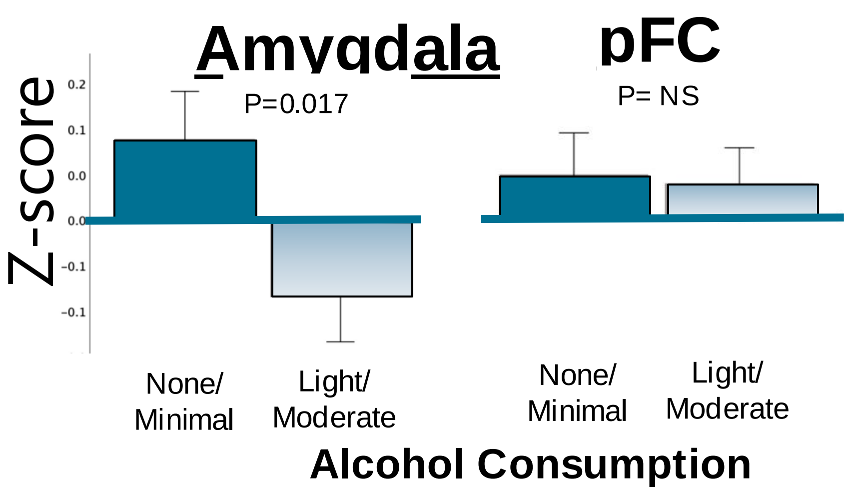
Mezue et al JACC 2023

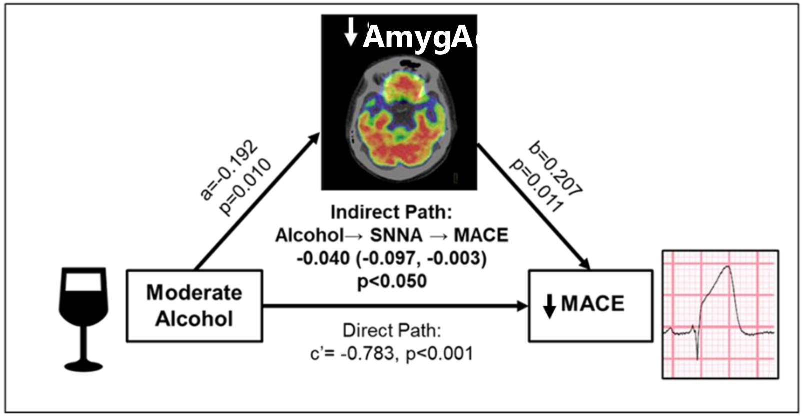


Light/Mod Alcohol vs. Stress-Associated Neural Activity









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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

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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.

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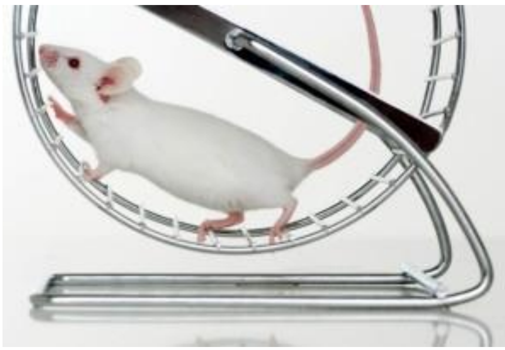
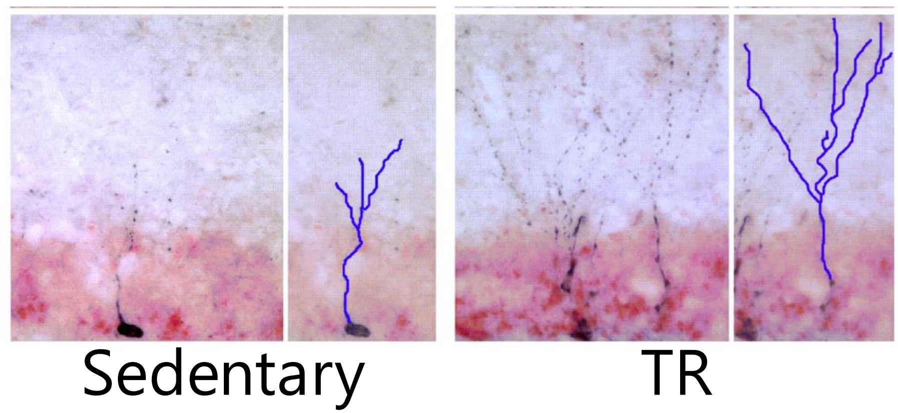
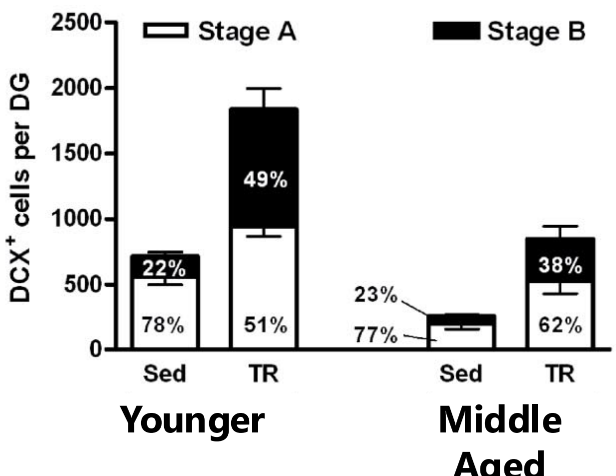
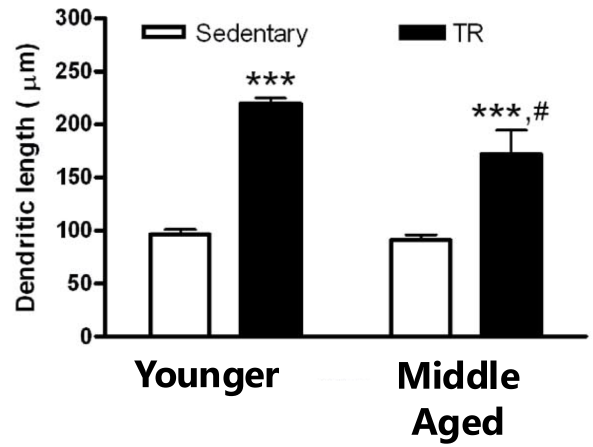
Physical Activity and Stress:
It's not all about endorphins

Mandatory Treadmill Running (TR)
Enhances Dendritic Arborization



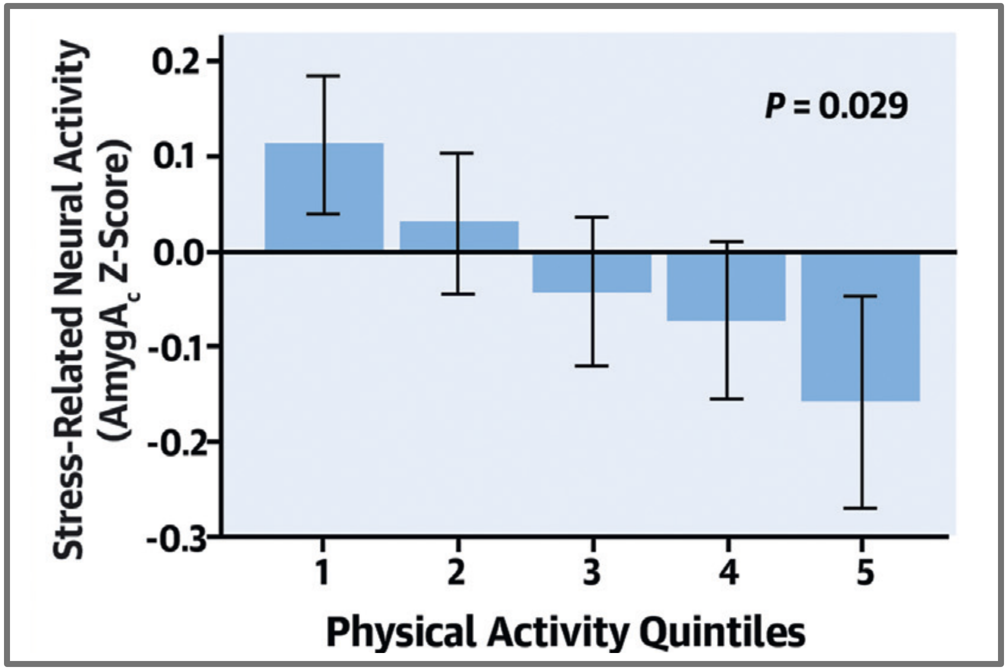


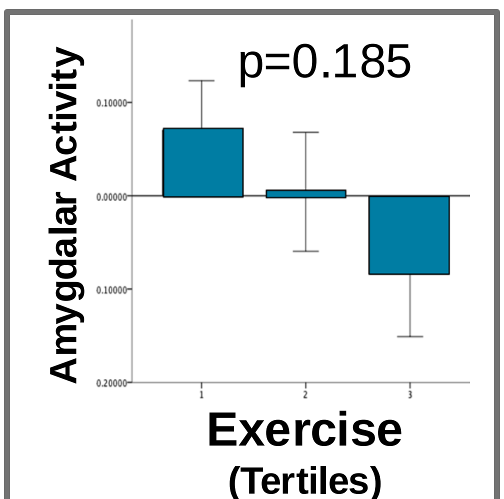


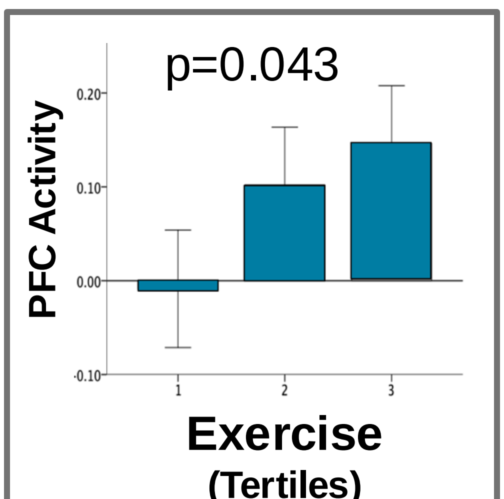


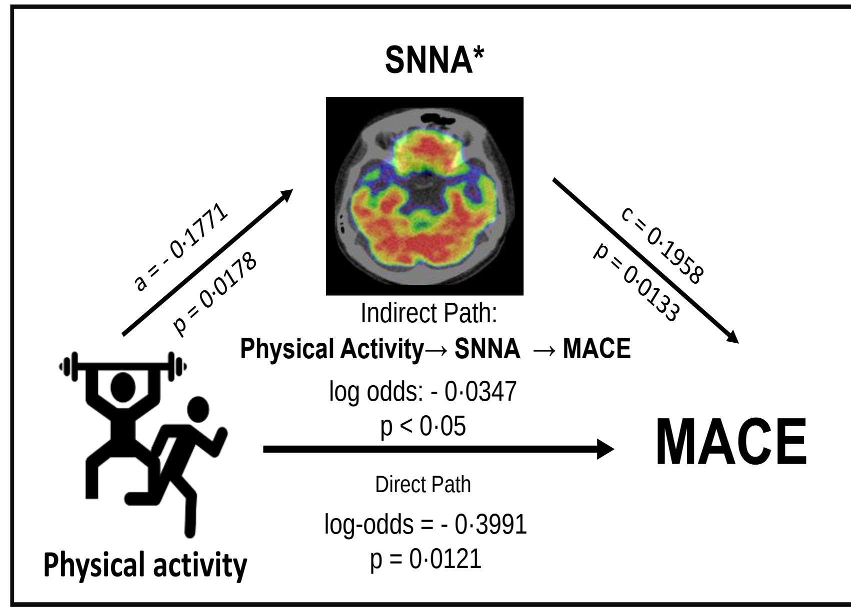
Wu et al J Appl Physiol 2008

Relationship between Exercise and Stress-Associated Neural Activity









Zureigat et al
JACC 2024

Hypothesis

If exercise reduces MACE in part by attenuating stress-associated mechanisms…

…then exercise should have a larger impact on MACE risk among individuals with chronically heightened $AmygA_c$ (e.g. those w depression)

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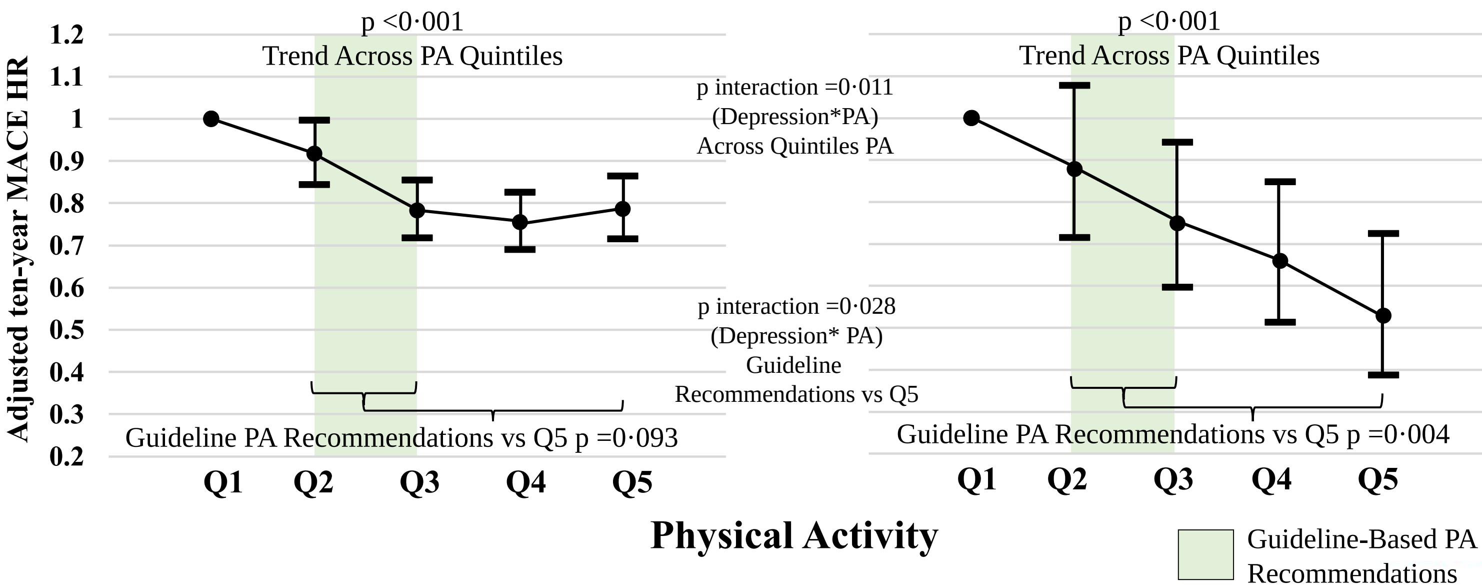
Physical Activity vs Cardiac Events: Greater Impact in those w Depression

More than double the CVD risk reduction among those with 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]		



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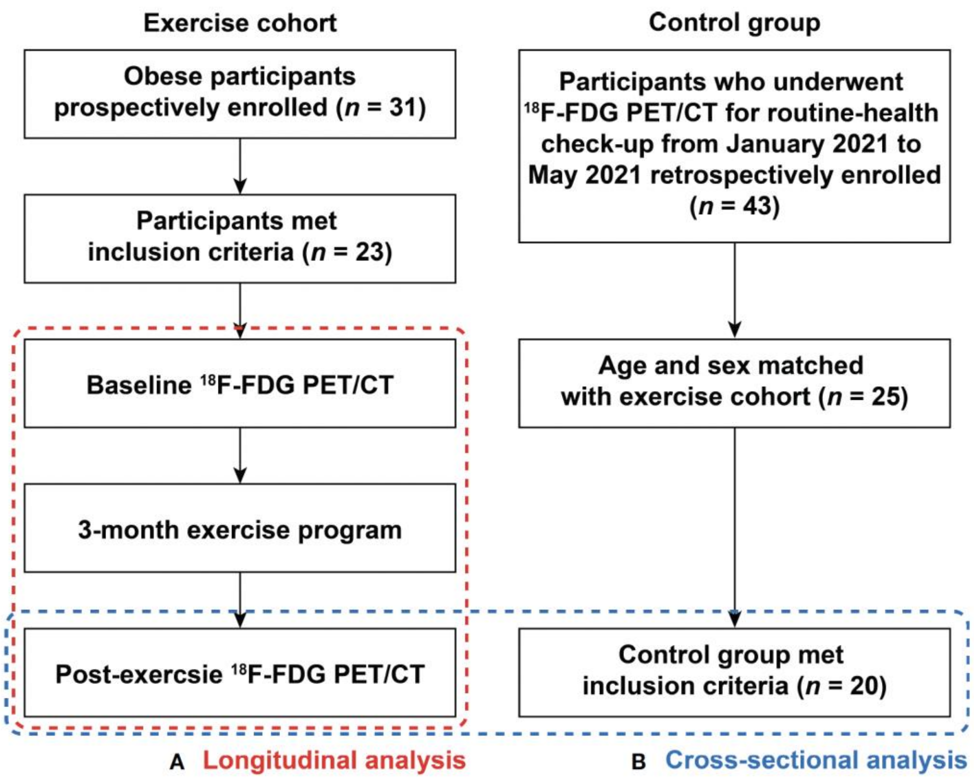
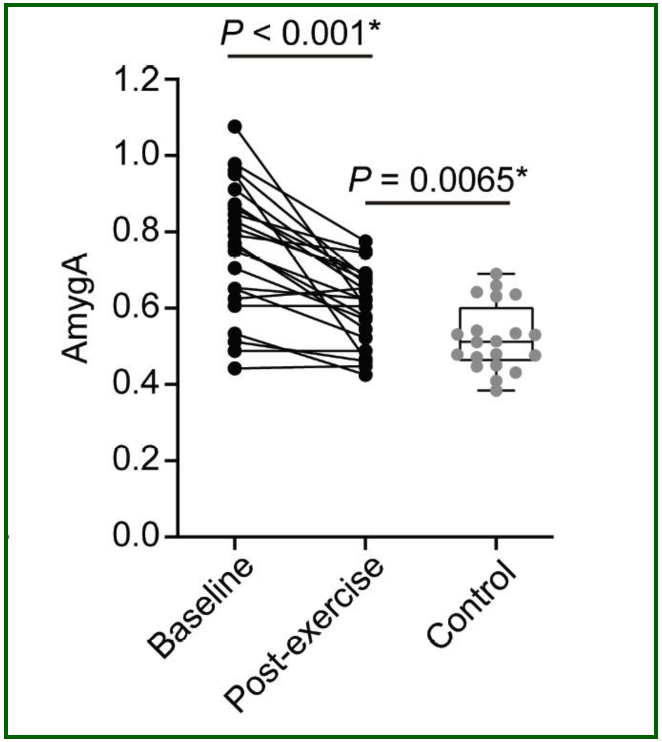
Small Prospective Study Evaluating Exercise





Pahk et al Frontiers in Endocrinology 2023

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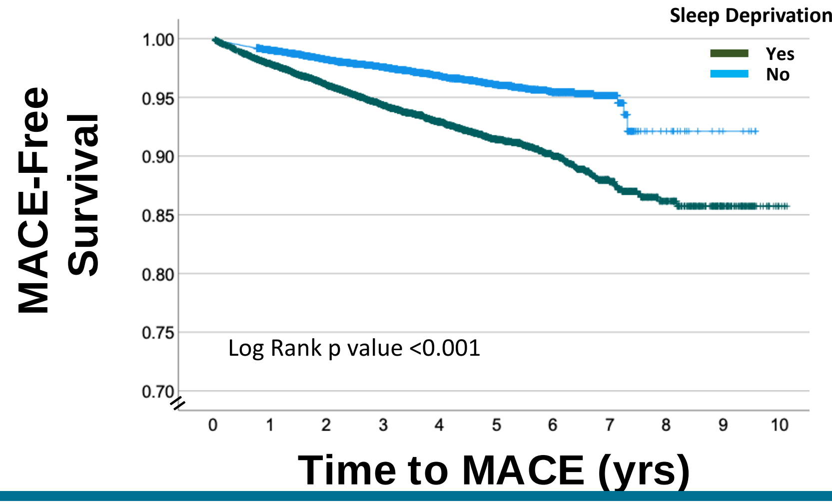
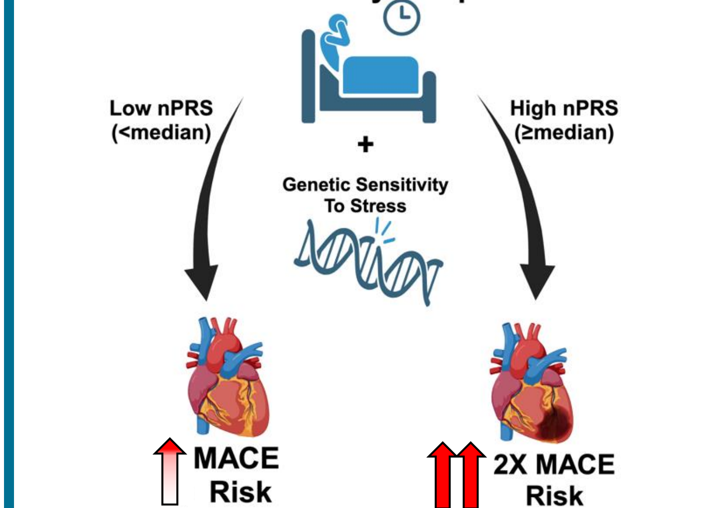
Sleep, Stress Sensitivity, and CVD Risk

Unhealthy Sleep vs MACE





Interaction between Genetics of Stress, Sleep and MACE Risk

nPRS Subgroup	Sleep Deprivation	MACE OR (95% CI)		MACE p-value*	Percentage of Additional MACE risk	Interaction p-value*
nPRS < Median	Yes	1.632 (1.390, 1.917)	↑63%	<0.001	103%	0.010
	No	1.00 (reference 1)		NA		
nPRS ≥ Median	Yes	2.283 (1.929, 2.703)	↑128%	<0.001		
	No	1.00 (reference 2)		NA		

1 1.5 2 2.5

Odds Ratio

Abohashem et al, AHA 2023

Key Points

- Stress and Stress-related Disorders:
  - Common, important risk factors for CVD
  - Attributable risk on par with HTN, smoking, DM
- Associate with:
  - higher stress-associated neural activity
  - leukopoietic activity & systemic inflammation
  - arterial inflammation and noncalcified plaque
  - thrombosis
  - CVD events
- Their CVD impacts might be modifiable
- Large trials are needed in order to:
  - Prove causation and
  - Determine efficacy of interventions

Key Points

For individuals with higher atherosclerotic risks and higher stress, would recommend :

- Stress reduction approaches
- Exercise
- Healthy sleep

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