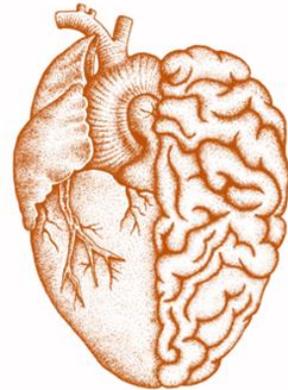


Module 3

Cardiovascular Medicine



Sex and Gender Differences in Heart Brain Interactions

Prof. Catherine Gebhard, MD, PhD

Program Director CAS Sex- and Gender-Specific Medicine

Center for Molecular Cardiology, University of Zurich

Department of Nuclear Medicine, University Hospital Zurich

Interventional Cardiology, Department of Internal Medicine, Kantonsspital Baden

gendermedizin@med.uzh.ch



Universität
Zürich ^{UZH}



Day 2 17 May 2022

Time	Subject	Lecturers
08:30 - 09:15	Sex and Gender Aspects in Cardiovascular Risk Factors and Lifestyle Interventions	Prof. Dr. med. Dr. sc. nat. Taulant Muka PD Dr. Marija Glisic Institute of Social and Preventive Medicine University of Bern
09:15 - 10:00		
10:00 - 10:30	<i>Coffee break</i>	
10:30 - 11:15	Sex and Gender Aspects in Cardiac Arrhythmias, Sudden Cardiac Death	Prof. Dr. med. Corinna Brunckhorst, University Heart Center, University Hospital Zurich
11:15 - 12:00		
12:00 - 13:30	<i>Lunch break</i>	
13:30 - 14:15	Sex and Gender Differences in Mental Stress and Heart Brain Interactions	Prof. Dr. med. Dr. sc. nat. Catherine Gebhard Department of Nuclear Medicine, University Hospital Zurich Center for Molecular Cardiology, University of Zurich
14:15 - 15:00	Diagnostic Strategies in Women	
15:00 - 15:30	<i>Coffee break</i>	
15:30 - 16:15	Gender Medicine Initiatives in the Medical Technology Industry	Katja Grünenfelder, National Sales Manager, Fumedica AG, Switzerland
16:15 - 17:00	Sum up	Prof. Dr. med. Dr. sc. nat. Catherine Gebhard Department of Nuclear Medicine, University Hospital Zurich Center for Molecular Cardiology, University of Zurich

Recommended Reading Material



ESC

European Society
of Cardiology

European Heart Journal (2022) **00**, 1–14
<https://doi.org/10.1093/eurheartj/ehac061>

STATE OF THE ART REVIEW

Ischaemic heart disease

Heart–brain interactions in cardiac and brain diseases: why sex matters

Alexia Rossi ^{1,2}, **Nidaa Mikail** ^{1,2}, **Susan Bengs** ^{1,2}, **Ahmed Haider**^{1,2,3},
Valerie Treyer ¹, **Ronny Ralf Buechel** ¹, **Susanne Wegener** ⁴, **Katrin Rauen**^{5,6},
Ahmed Tawakol ⁷, **C. Noel Bairey Merz**⁸, **Vera Regitz-Zagrosek** ^{9,10}, and
Catherine Gebhard ^{1,2*}

¹Department of Nuclear Medicine, University Hospital Zurich, Raemistrasse 100, 8091 Zurich, Switzerland; ²Center for Molecular Cardiology, University of Zurich, Schlieren, Switzerland; ³Division of Nuclear Medicine and Molecular Imaging, Department of Radiology, Massachusetts General Hospital, and Harvard Medical School, Boston, MA, USA; ⁴Department of Neurology, University Hospital Zurich and University of Zurich, Zurich, Switzerland; ⁵Department of Geriatric Psychiatry, Psychiatric Hospital, Zurich, Switzerland; ⁶Institute for Stroke and Dementia Research, University Hospital, Ludwig Maximilian University of Munich, Munich, Germany; ⁷Cardiovascular Imaging Research Center, Cardiology Division, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA; ⁸Barbra Streisand Women's Heart Center, Smidt Heart Institute, Cedars-Sinai Medical Center, Los Angeles, CA, United States; ⁹Charité, Universitätsmedizin Berlin, Berlin, Germany; and ¹⁰University of Zurich, Zurich, Switzerland

Received 1 September 2021; revised 24 January 2022; accepted 30 January 2022



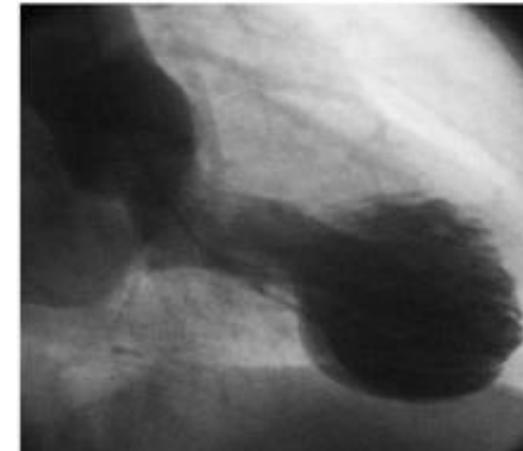
Universität
Zürich ^{UZH}

u^b

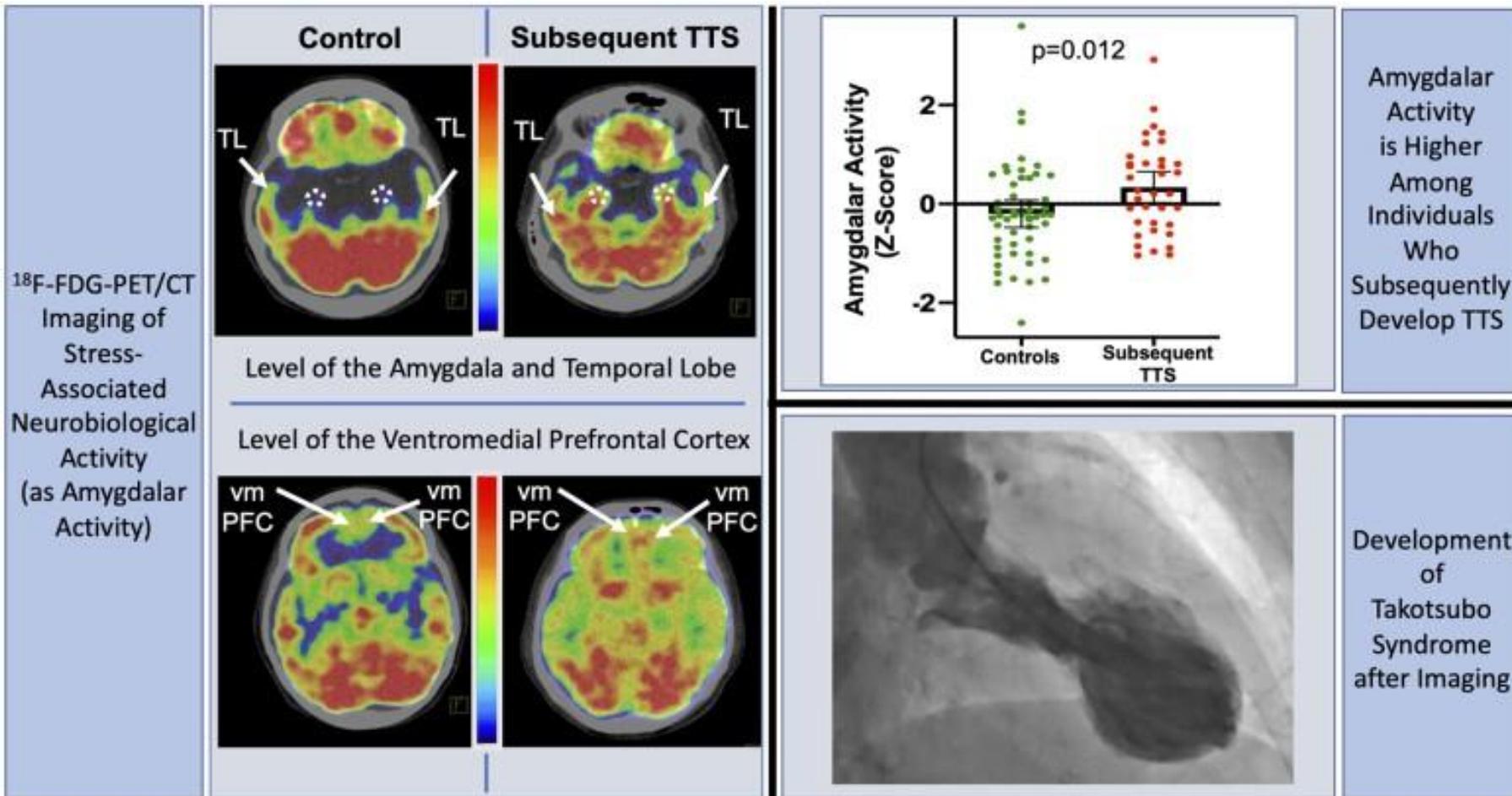
UNIVERSITÄT
BERN

Heart Diseases: Takotsubo syndrome

- Takotsubo syndrome: **Transient weakening of the left ventricle that is usually the result of a stressful life event.** The syndrome is named after the Japanese takotsubo which is a ceramic pot used to trap octopus
- **Takotsubo syndrome predominantly affects postmenopausal women**
- Evidence suggests an involvement of the limbic system (in particular the amygdala) and increased sympathetic activity in the pathophysiology of Takotsubo syndrome
- **Oestrogens** attenuate sympathetic responses to mental stress in perimenopausal women; **Oestrogens** attenuate catecholamine-mediated vasoconstriction and upregulate endothelial nitric oxide synthase activity
- The combination of enhanced baseline sympathetic tone and impaired vasomotor function may render postmenopausal women susceptible to **Takotsubo syndrome**
- Heightened sympathetic activity seems to be present years before disease onset and may represent a **promising prevention target!**

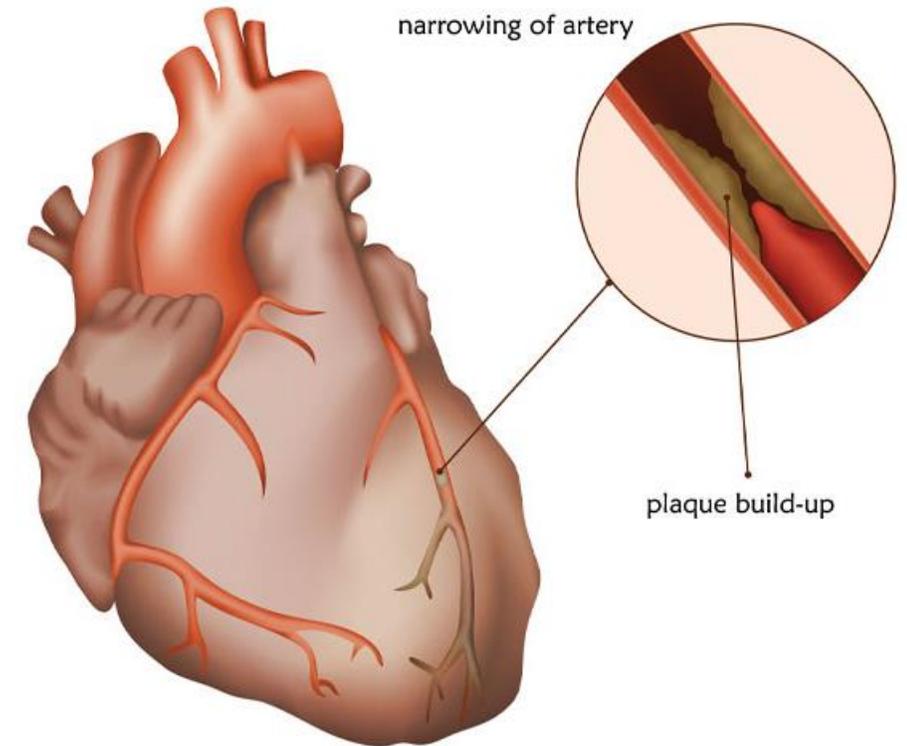


Heart Diseases: Takotsubo syndrome



Heart Diseases: Coronary Artery Disease

- Chronic psychological stress is a risk factor for incident coronary artery disease
- Endothelial dysfunction in response to cumulative mental stress has previously been described in women but less so in men
- Mental stress-induced myocardial ischaemia was more common in young women with previous myocardial infarction as compared to men



Heart Diseases: Coronary Artery Disease

Traditional, Non-traditional, and Sex-specific Cardiovascular Risk Factors in Women

Non-traditional RFs

High Prevalence in Women with CAD
 Depression
 Mental stress (Anxiety, Psychosocial stress)
 Low socioeconomic status
 Limited education

Strong Association with CAD/CV Events in Women
 Low socioeconomic status

Female Sex-specific RFs

Polycystic ovary syndrome
 Premature menopause
 Gestational diabetes
 Gestational hypertension
 History of pre-eclampsia
 Rheumatoid arthritis
 Systemic Lupus Erythematosus
 Radiation for breast cancer
 Chemotherapy for breast cancer
 Use of hormonal contraceptives*
 Menopausal hormone therapy *



Traditional RFs

High Prevalence in Women with CAD
 Diabetes
 Metabolic Syndrome
 Hypertension
 Abdominal obesity
 Chronic kidney disease**
 Smoking

Strong Association with CAD/CV Events in Young Women
 Diabetes (Type 1 and 2)
 Metabolic Syndrome
 Smoking
 Hypertension
 High Apolipoprotein B/A level
 Family history of MI in mothers and/or sisters
 Family history of CAD

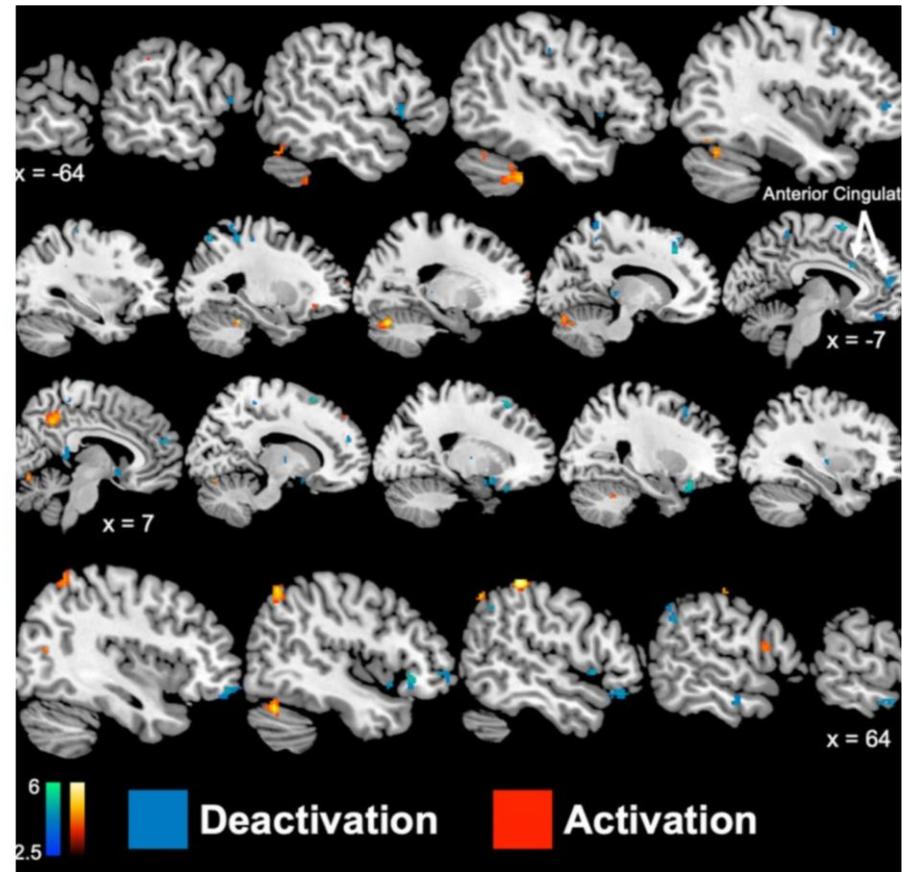
Protective Factors

Association with Risk Reduction in Women
 Exercise
 Fruit and vegetable intake
 Moderate alcohol consumption



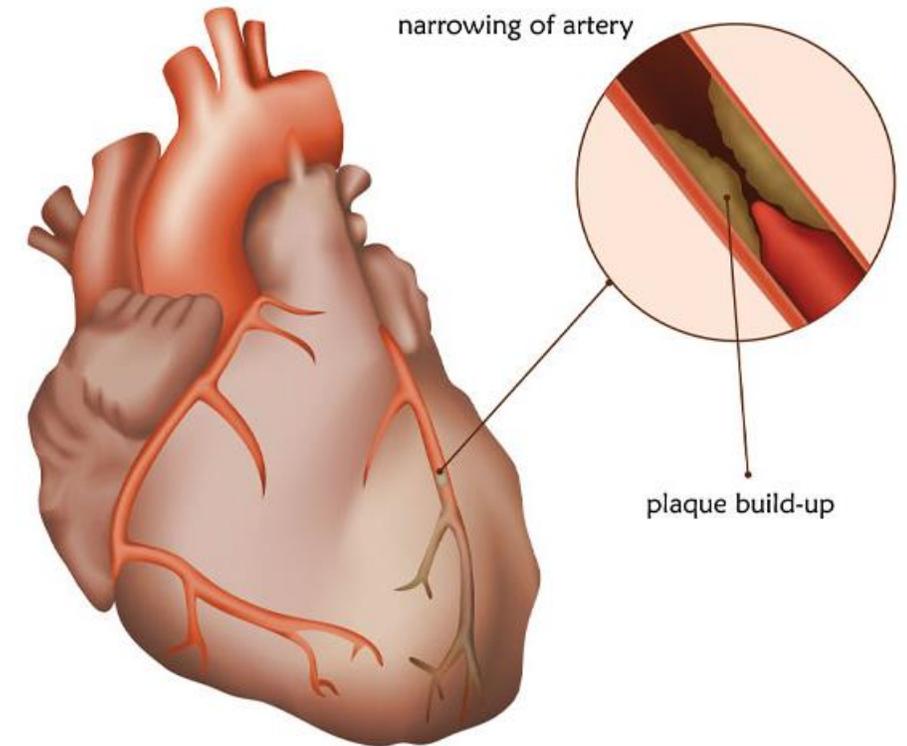
Heart Diseases: Coronary Artery Disease

- Chronic psychological stress is a risk factor for incident coronary artery disease
- Endothelial dysfunction in response to cumulative mental stress has previously been described in women but less so in men
- Mental stress-induced myocardial ischaemia was more common in young women with previous myocardial infarction as compared to men
- Men and women with coronary artery disease show different responses to acute mental stress in brain limbic areas



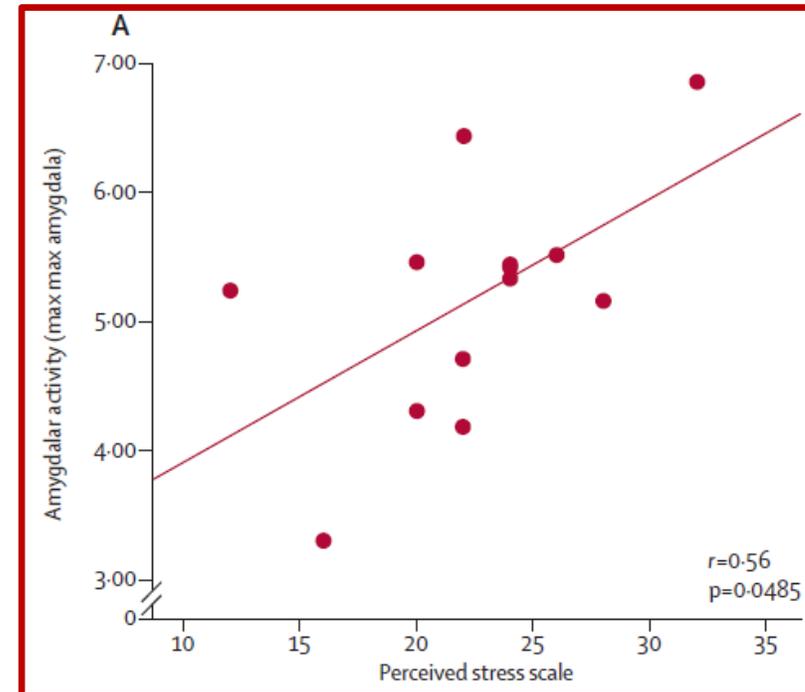
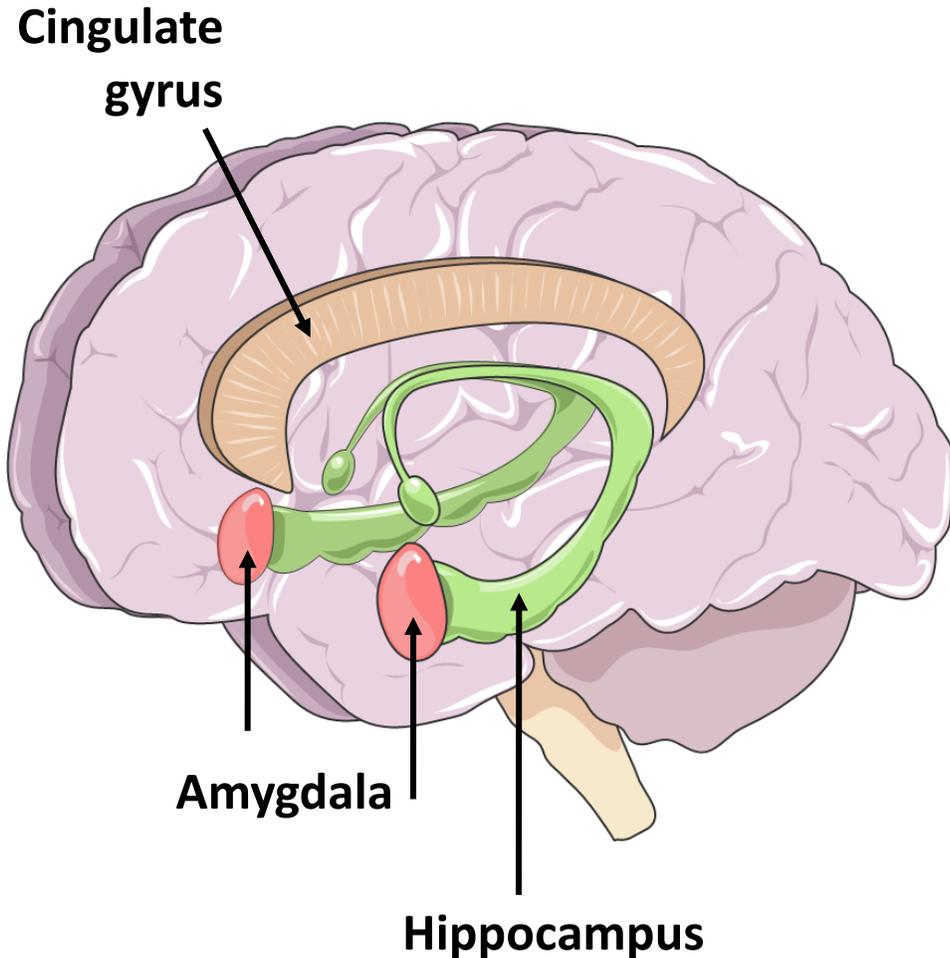
Heart Diseases: Coronary Artery Disease

- Chronic psychological stress is a risk factor for incident coronary artery disease
- Endothelial dysfunction in response to cumulative mental stress has previously been described in women but less so in men
- Mental stress-induced myocardial ischaemia was more common in young women with previous myocardial infarction as compared to men
- Men and women with coronary artery disease show different responses to acute mental stress in brain limbic areas
- Increased metabolic activity of the **amygdala** is an independent predictor of future major adverse cardiovascular events



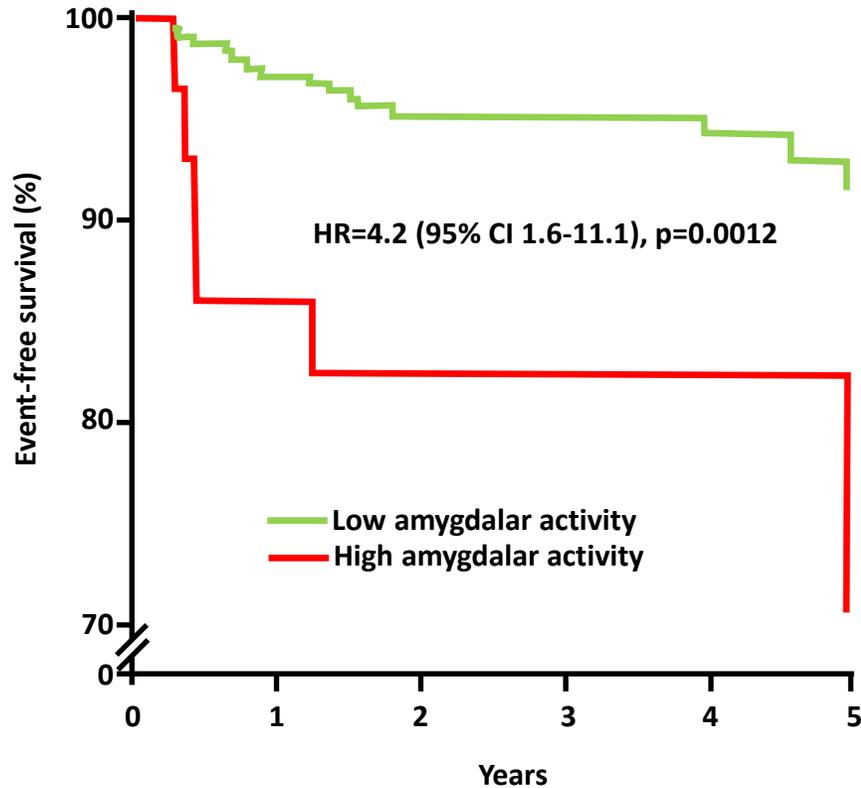
The Amygdala

Amygdala: part of the limbic system, plays an important role in the processing of emotional responses (fear, anxiety, aggression)



Tawakol A et al. Lancet. 2017

The Amygdala



Number at risk

Low activity	263	246	224	183	102	64
High activity	29	24	23	18	13	6



Relation between resting amygdalar activity and cardiovascular events: a longitudinal and cohort study

Ahmed Tawakol*, Amorina Ishai*, Richard AP Takx, Amparo L Figueroa, Abdelrahman Ali, Yannick Kaiser, Quynh A Truong, Chloe JE Solomon, Claudia Calcagno, Venkatesh Mani, Cheuk Y Tang, Willem JM Mulder, James W Murrrough, Udo Hoffmann, Matthias Nahrendorf, Lisa M Shin, Zahi A Fayad†, Roger K Pitman†



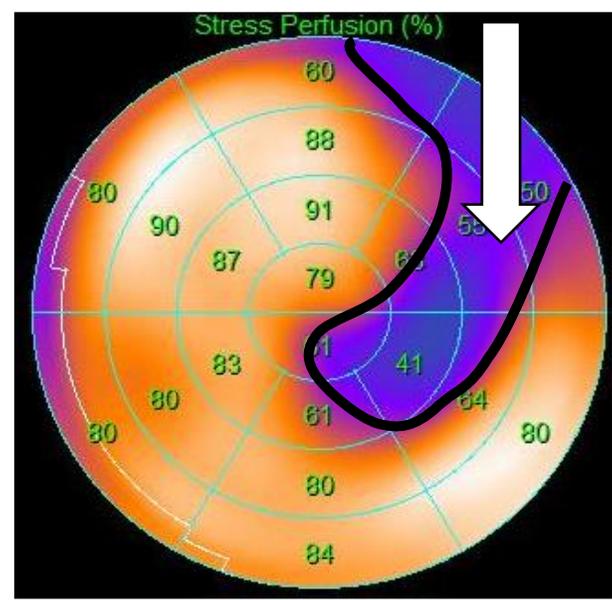
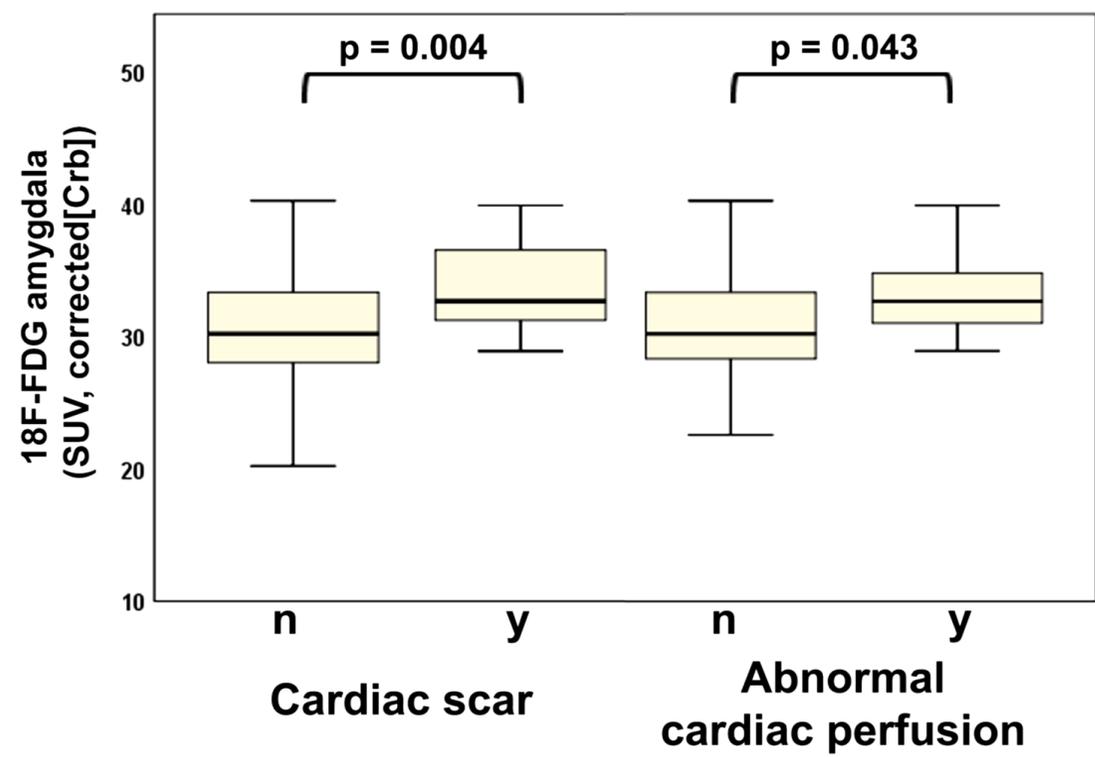
Universität
Zürich UZH



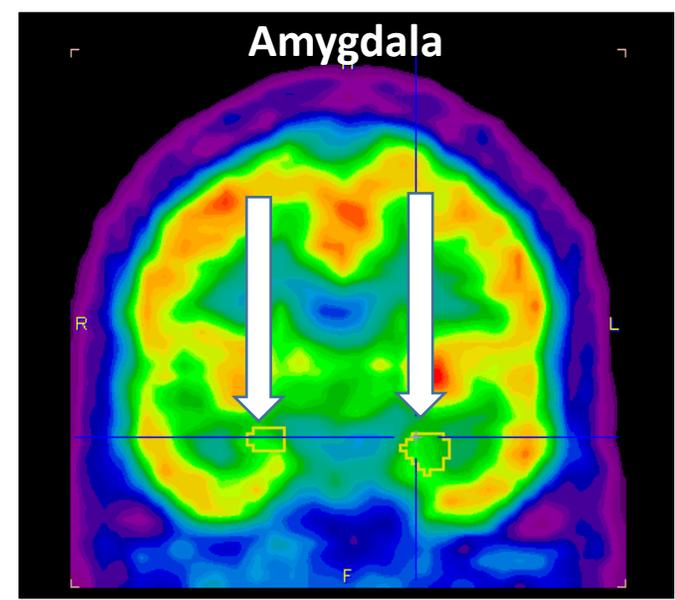
UNIVERSITÄT
BERN

Sex and Gender Differences in Neuronal Stress Responses

Association Between Neuronal Stress Responses and Myocardial Injury in Women, but not in Men – ¹⁸F-FDG-PET



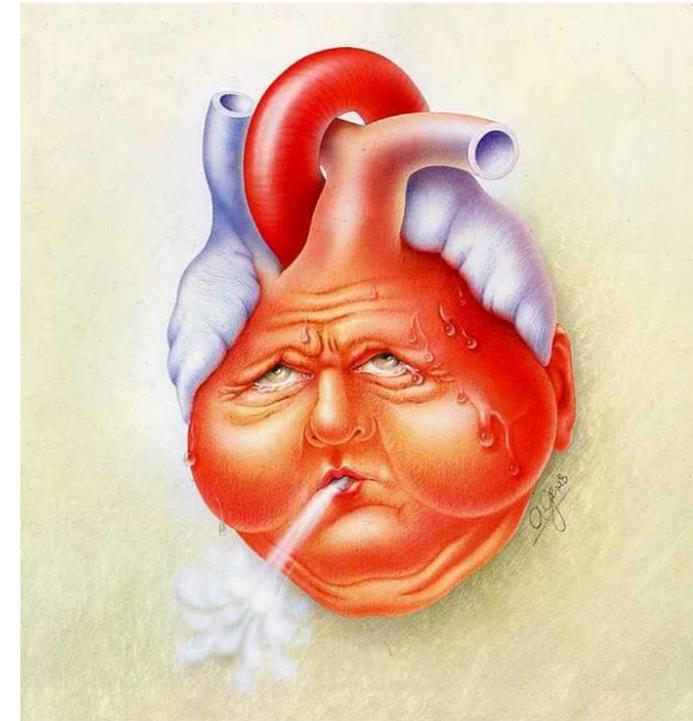
Myocardial perfusion defect



Increased amygdalar metabolic activity_b

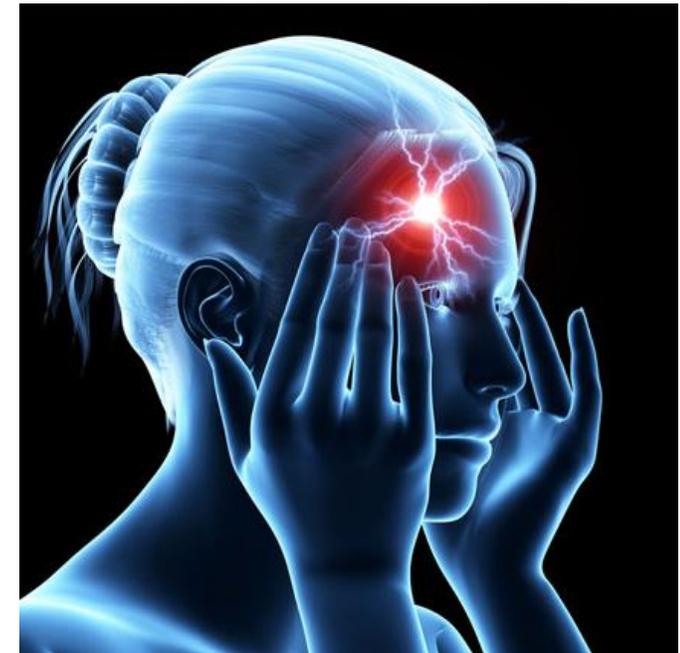
Heart Diseases: Heart Failure

- **Hyperactivation of the sympathetic** nervous system is a critical mechanism in the development of heart failure
- Both the heart and the brain have an intrinsic **renin-angiotensin-aldosterone system (RAAS)** that is activated in heart failure
- Women with HF are usually older than men and have a better prognosis. Women are more commonly affected by **HFpEF**, while **HFrEF** is more prevalent in men
- There are sex differences in inflammation, RAAS activation, and sympathetic hyperactivity in heart failure which seem to modify treatment responses (e.g. sacubitril-valsartan in PARAGON-HF)



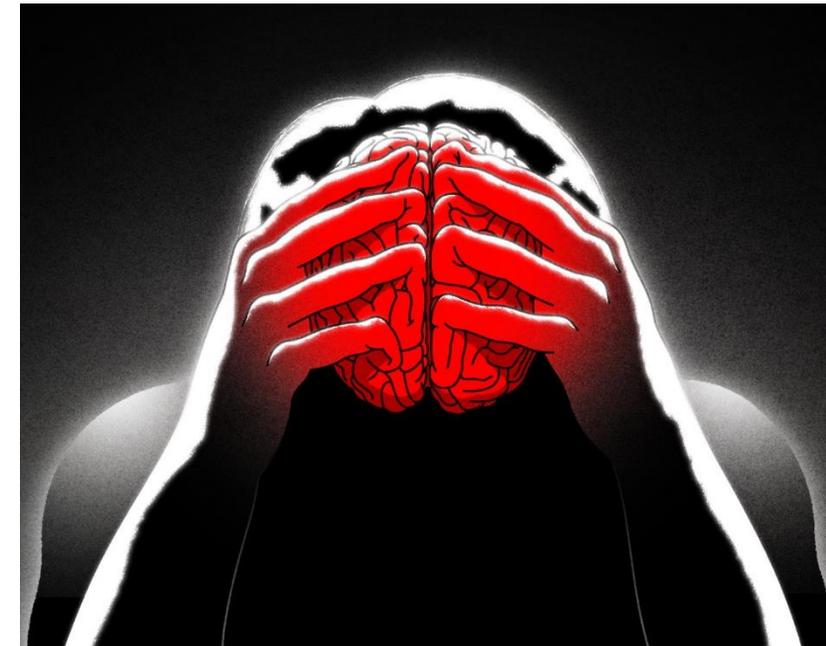
Brain Diseases: Stroke

- The absolute risk of incident stroke is lower in women, but the incidence of cardiovascular morbidity and mortality after stroke is higher in women as compared to men
- Ischaemic stroke is caused by ischemic heart disease in about 20% of cases. Stroke due to atrial fibrillation is more common in women as compared with men, particularly at an older age
- Heart failure induces a state of hypercoagulability (decreased blood flow velocity, endothelial dysfunction, enhanced platelet aggregation, reduced fibrinolysis) all of which increase stroke risk
- Cardiac complications represent the second leading cause of mortality after stroke (stroke–heart syndrome: elevation of cardiac biomarkers, cardiac dysfunction, arrhythmia, and myocardial infarction)



Brain Diseases: Depression

- Female-male ratio 2:1
- The prevalence of cardiac comorbidities among patients with depression is 3-fold greater than in the general population
- The presence of depressive symptoms is associated with higher cardiac morbidity and mortality after myocardial infarction
- Anti-depressant medication is an effective therapeutic strategy to improve long-term cardiovascular outcomes in both sexes -> **Depression is a modifiable cardiovascular risk factor!**
- The prevalence of depression after myocardial infarction is higher in women than men

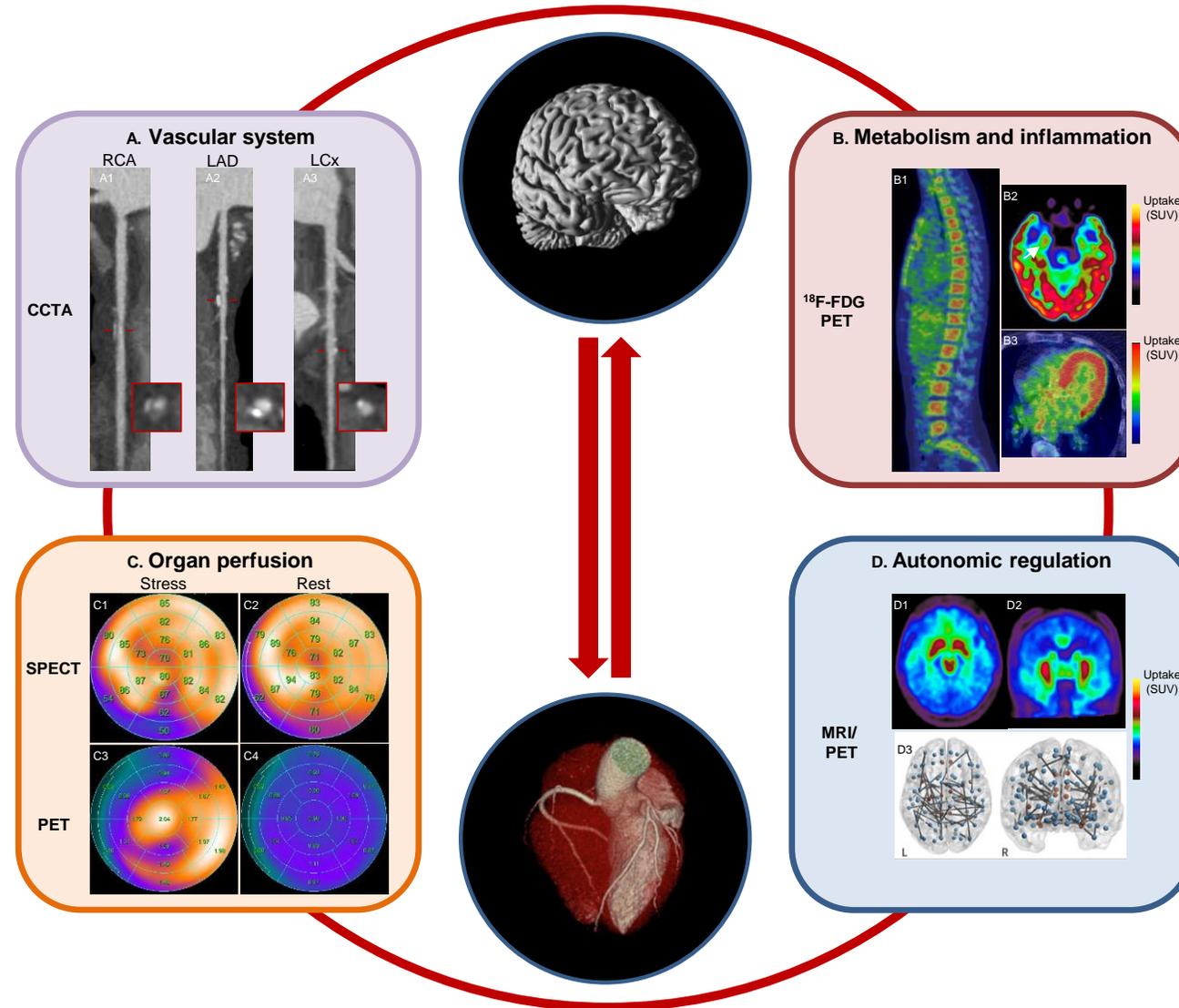


Brain Diseases: Dementia

- Female-male ratio 2:1
- Cognitive impairment is more common in patients with previous myocardial infarction and chronic heart failure (mechanism: **regional cerebral hypoperfusion** and **enhanced inflammation**)
- Atherosclerosis is a risk factor for Alzheimer's disease through endothelial dysfunction and impaired microcirculation
- Hypertension is associated with dementia through impairment of cerebral blood supply and neuroinflammation
- Hypertensive postmenopausal women have worse cognitive performance than normotensive women

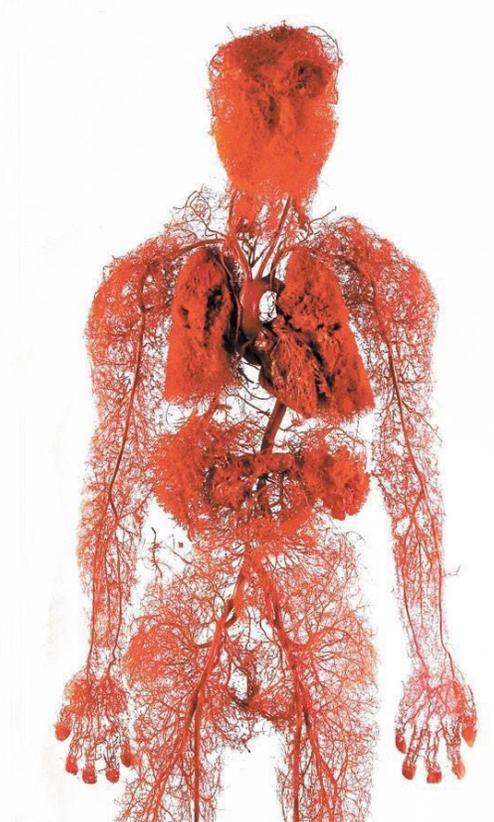


Heart-Brain Connections – Potential Mechanisms

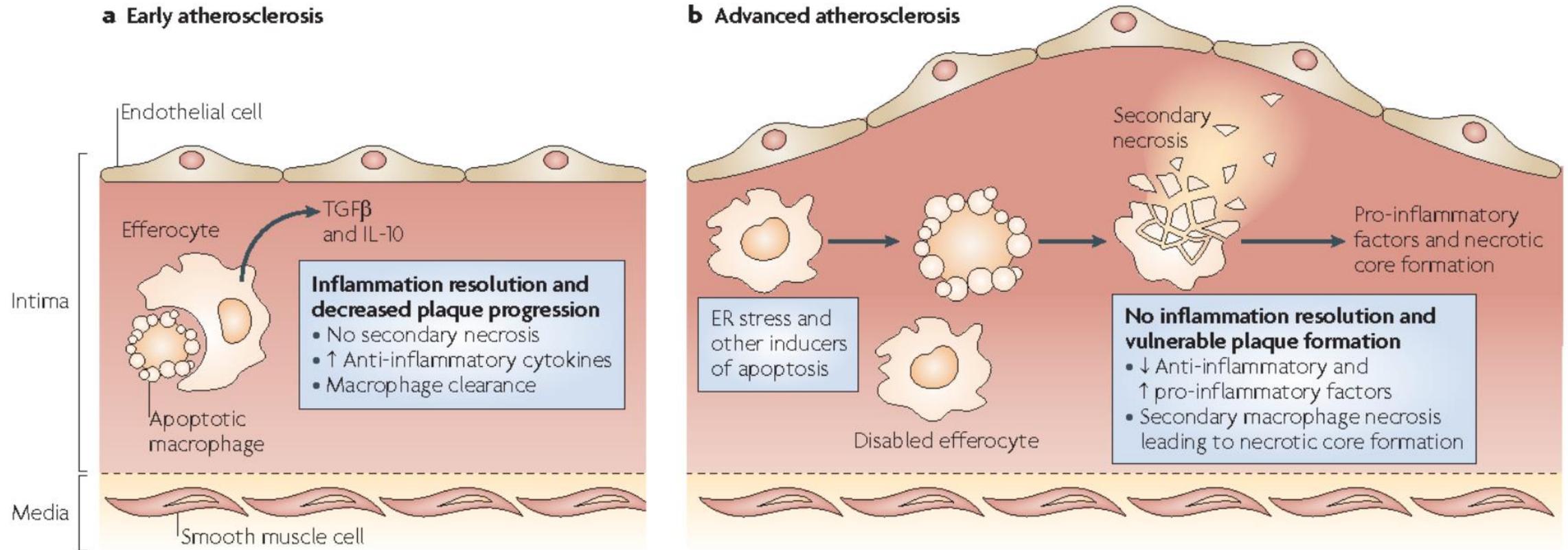


Heart-Brain Connections – Vascular and Immune System

- **Atherosclerosis is the systemic process identified as the culprit for causing both acute myocardial infarction and stroke**
- Women have less often obstructive coronary artery disease and lower plaque burden, yet with worse clinical outcomes. The risk of stroke is lower in women, but the incidence of cardiovascular morbidity and mortality after stroke is higher in women as compared to men
- Women have a higher global and regional blood flow than men in both heart and brain
- **Atherosclerosis is an inflammatory disease** (endothelial dysfunction -> increased vascular permeability -> release of pro-inflammatory mediators -> state of hypercoagulability -> increased risk of cardio – and neurovascular events and long-term cognitive impairment)

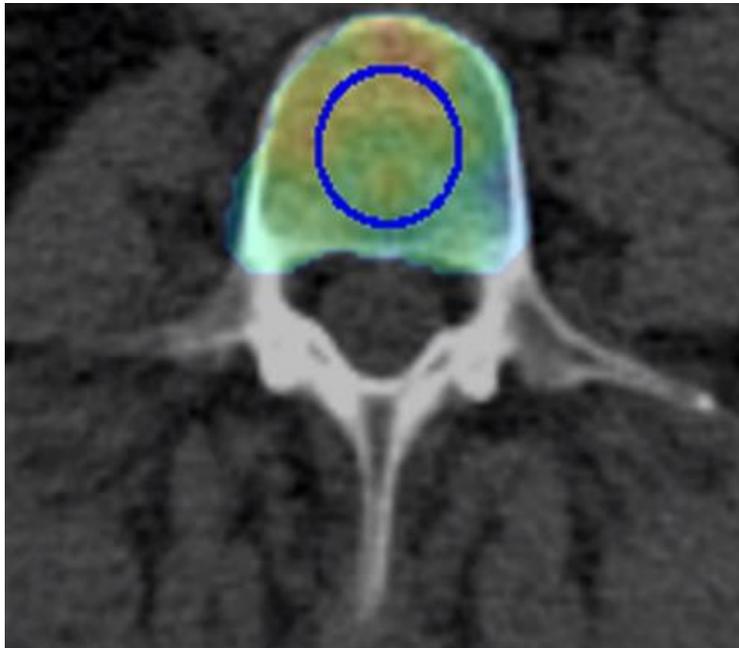


Atherosclerosis is an Inflammatory Disease

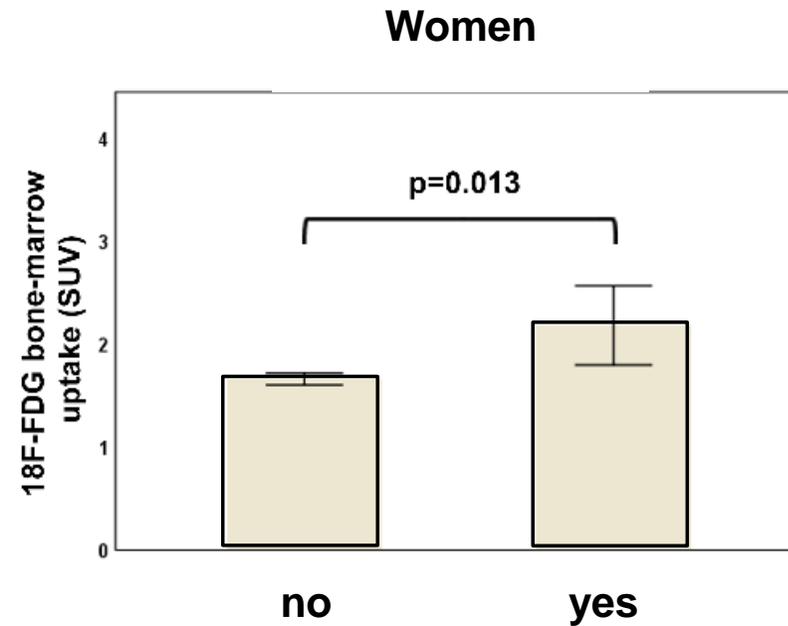


Atherosclerosis: Sex and Gender Differences in Inflammation

Association Between Inflammation and Ischemic Heart Disease



Increased progenitor cell
release from bone marrow

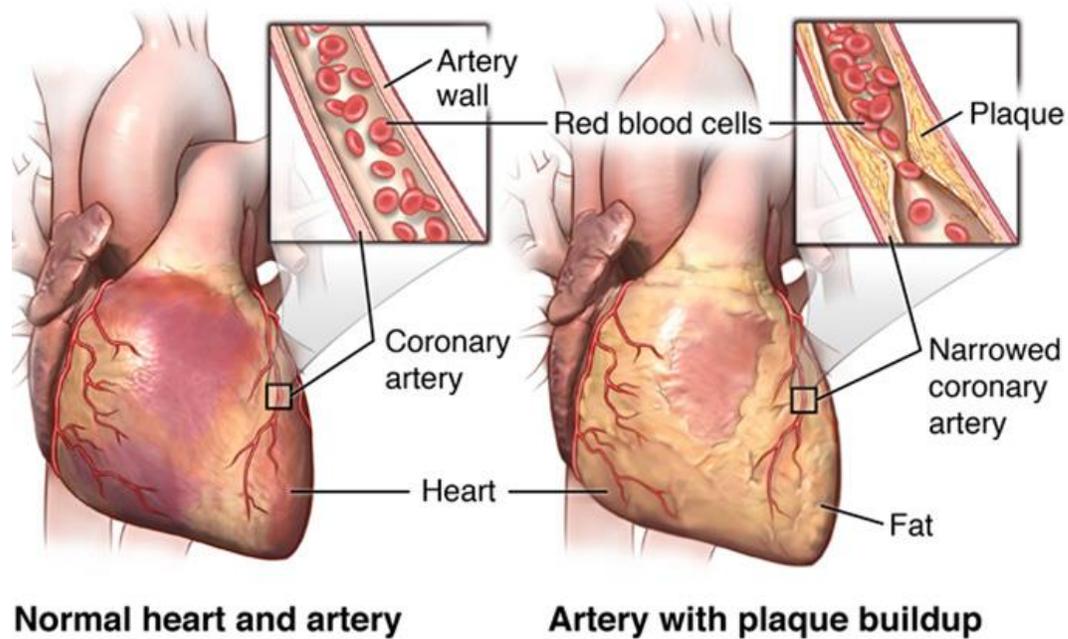


Ischemic heart disease

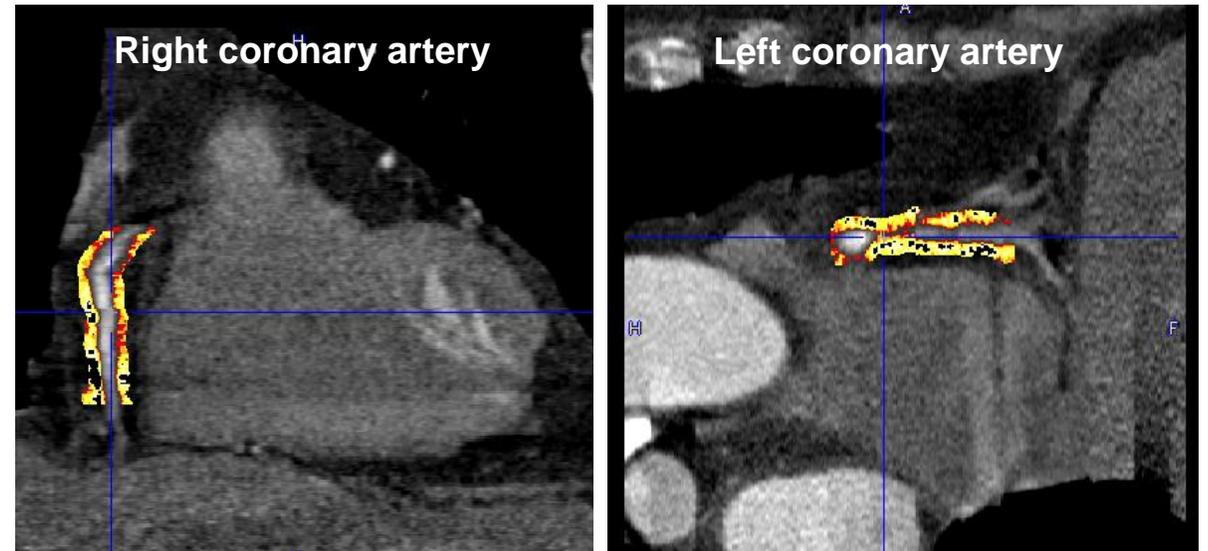


Ischemic heart disease

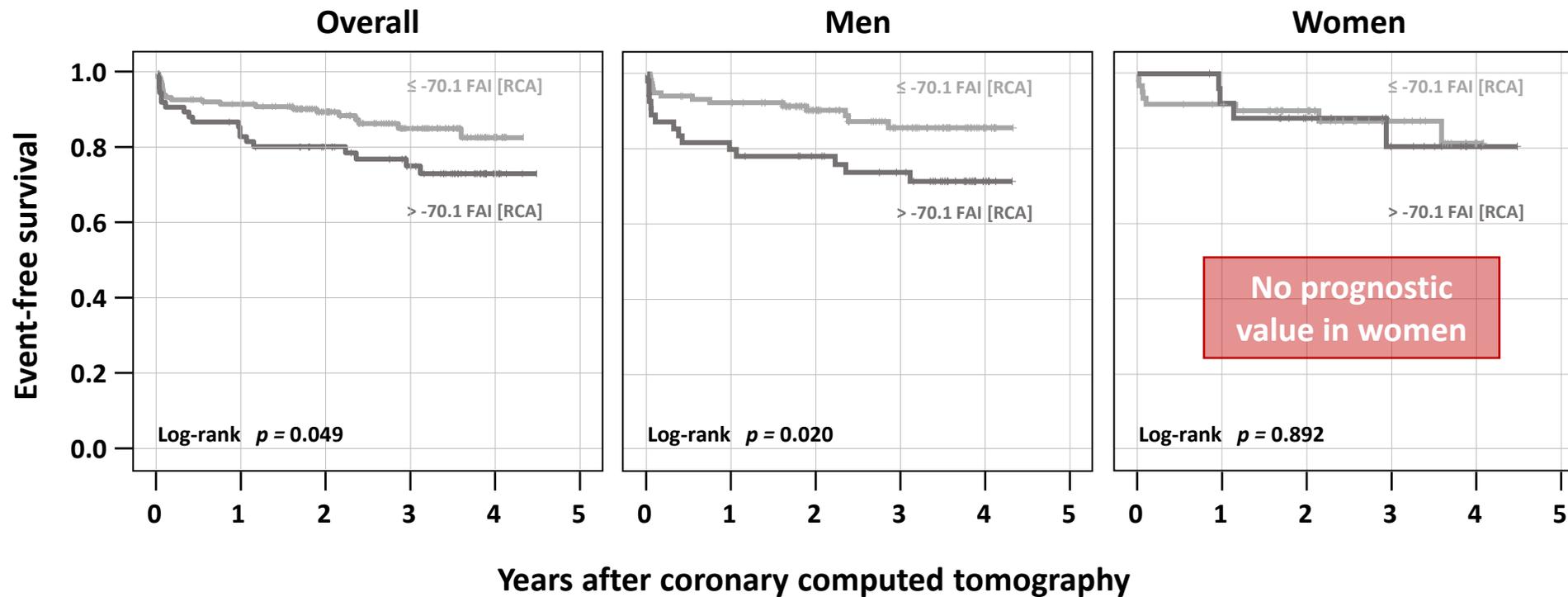
Sex and Gender Differences in Inflammation: Clinical Implications



Fat attenuation index (FAI): Perivascular coronary inflammation assessed by computed tomography



Sex and Gender Differences in Inflammation: Clinical Implications



The Bias: Clinical Trials on Anti-inflammatory Drugs

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Colchicine in Patients with Chronic Coronary Disease

S.M. Nidorf, A.T.L. Fiolet, A. Mosterd, J.W. Eikelboom, A. Schut, T.S.J. Opstal, S.H.K. The, X.-F. Xu, M.A. Ireland, T. Lenderink, D. Latchem, P. Hoogslag, A. Jerzewski, P. Nierop, A. Whelan, R. Hendriks, H. Swart, J. Schaap, A.F.M. Kuijper, M.W.J. van Hessen, P. Saklani, I. Tan, A.G. Thompson, A. Morton, C. Judkins, W.A. Bax, M. Dirksen, M. Alings, G.J. Hankey, C.A. Budgeon, J.G.P. Tijssen, J.H. Cornel, and P.L. Thompson, for the LoDoCo2 Trial Investigators*

- Sex differences in inflammation/immune responses are known
- 15% women, 85% men
- No benefit in women (supplementary information)

The Bias: Clinical Trials on Anti-inflammatory Drugs



The NEW ENGLAND
JOURNAL of MEDICINE

CORRESPONDENCE

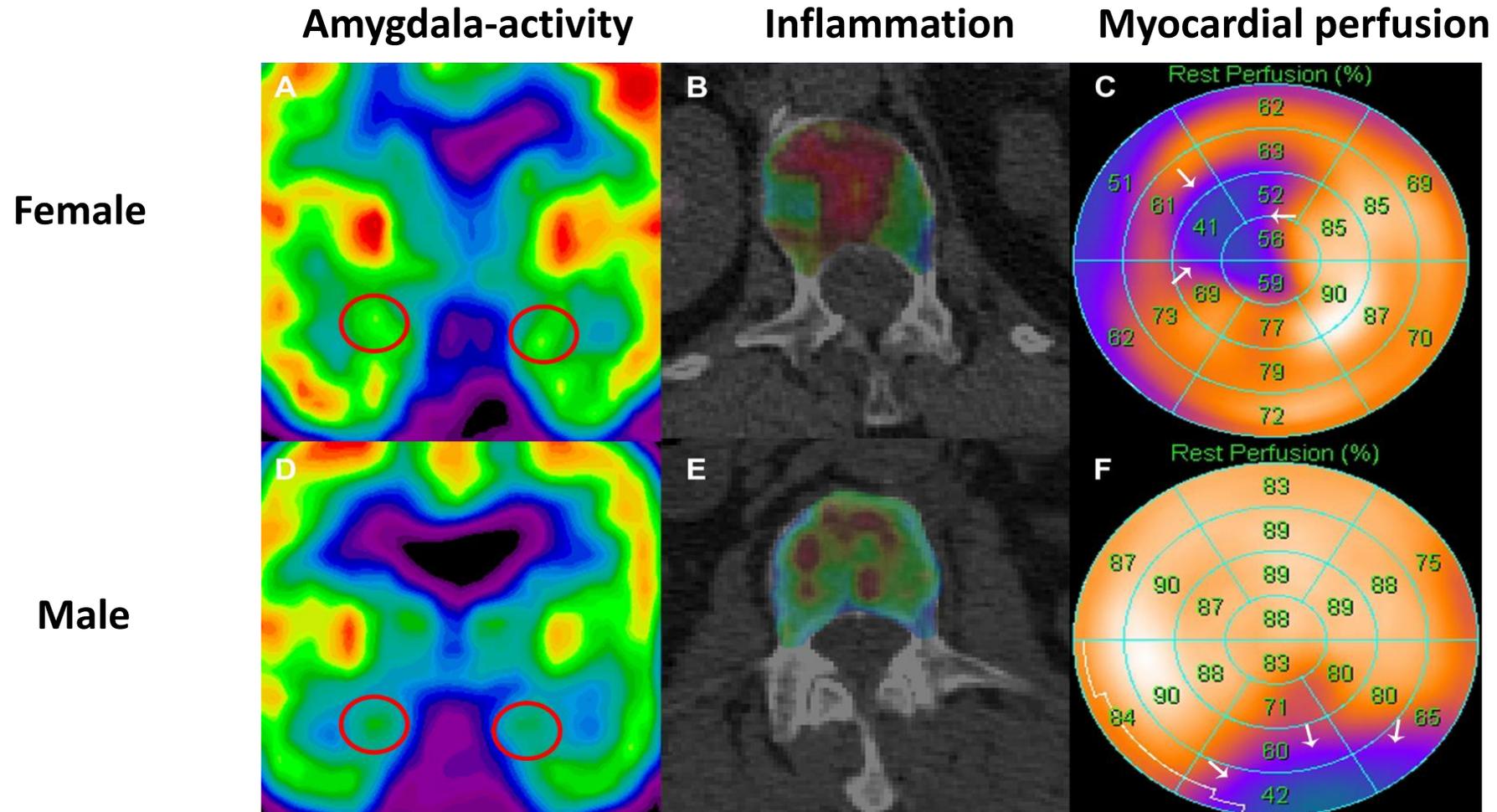
Colchicine in Patients with Chronic Coronary Disease

TO THE EDITOR

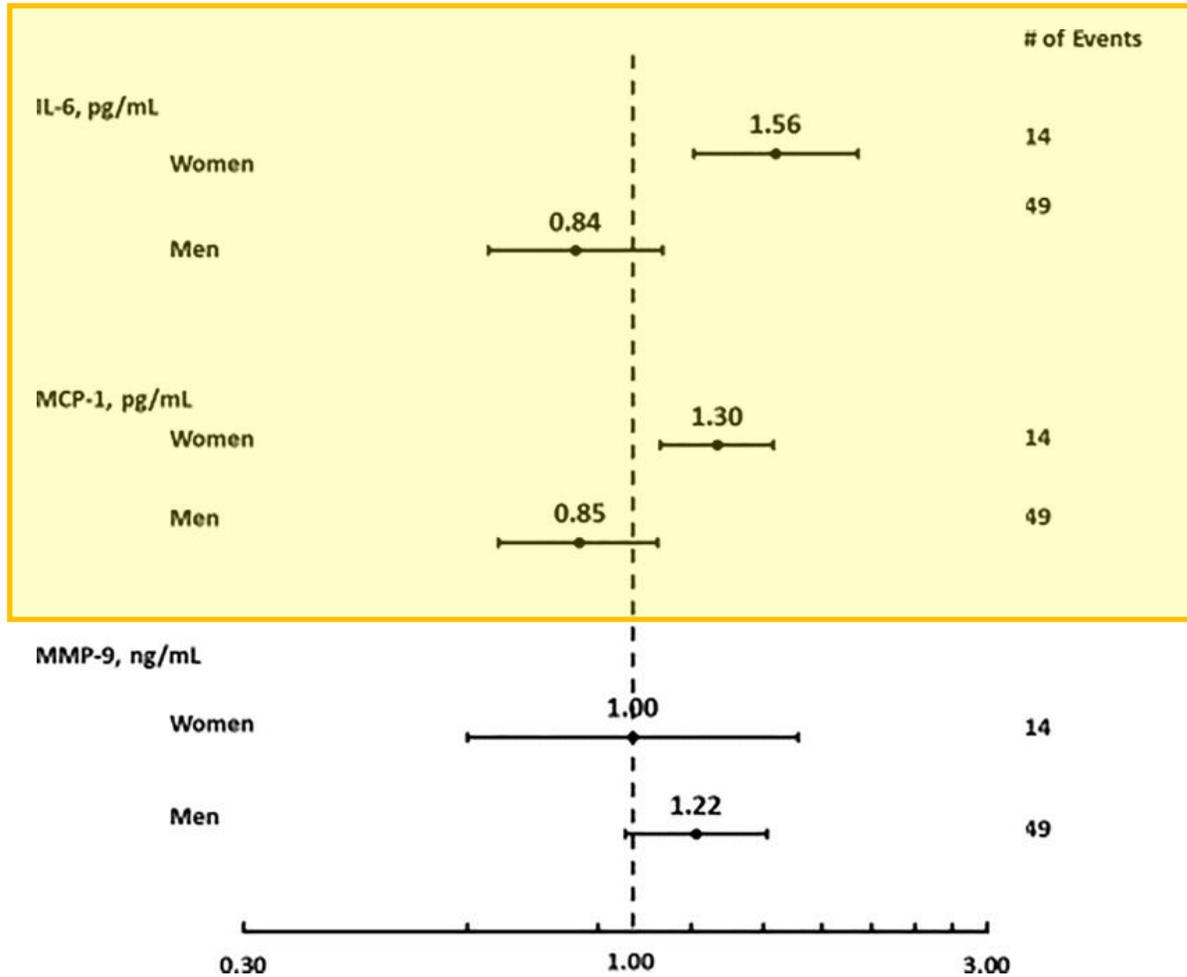
- **No statistically significant effect in women**
- **Adverse effects in women not reported**
- **Despite similar disease prevalence and higher case fatality rate in women**



Association Between Inflammation, Neuronal Stress Responses and Abnormal Myocardial Perfusion

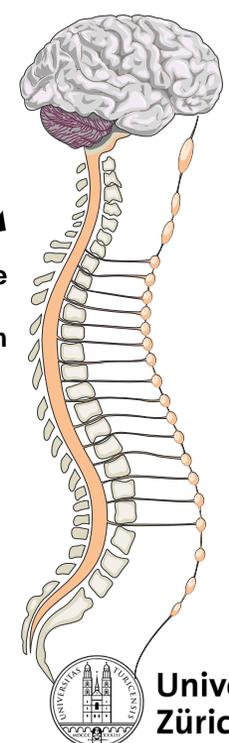
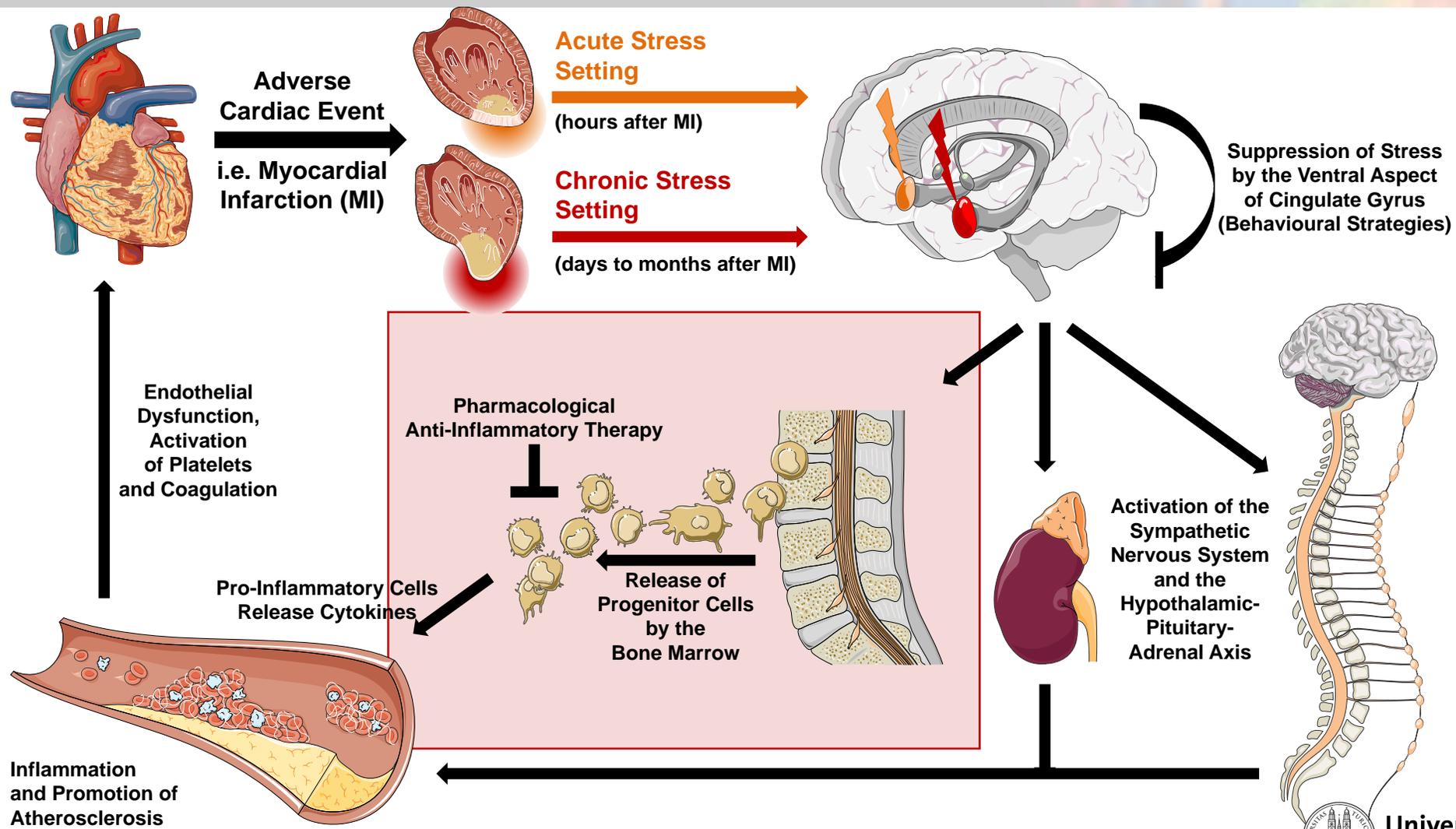


Association Between Stress, Inflammation and Cardiovascular Events



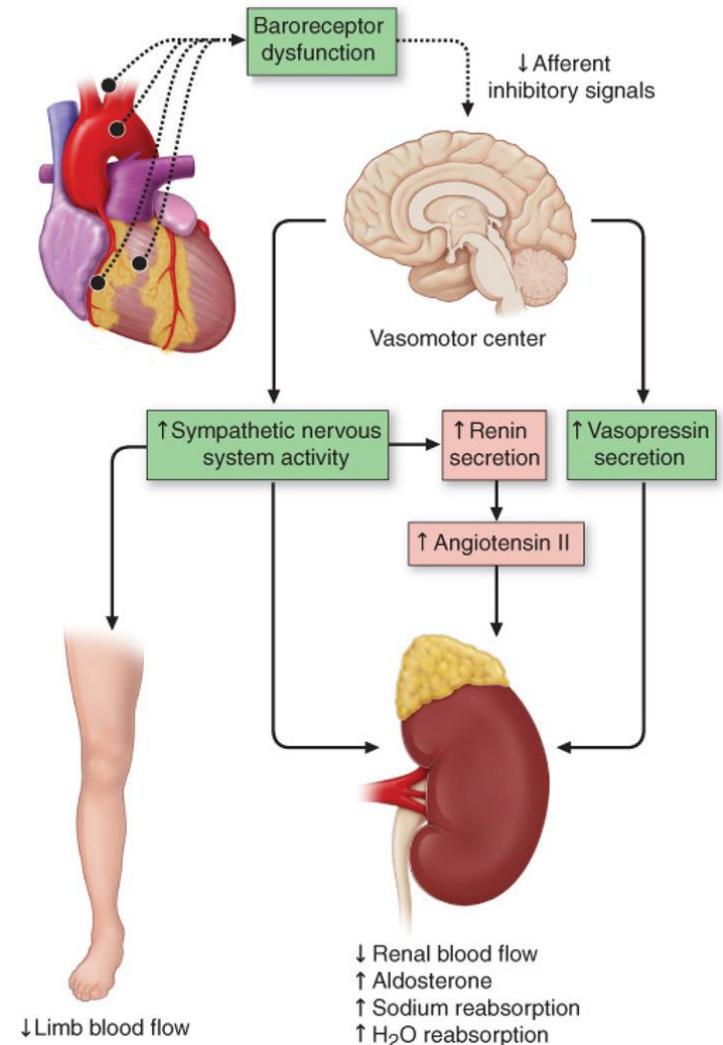
- **Stress-induced** interleukin 6 (IL-6) and monocyte chemoattractant protein-1 (MCP-1) have been identified as predictors of future cardiovascular events in women with existing cardiovascular disease
- This association was not observed in men

Potential Impact of Statins on Neuronal Stress Responses

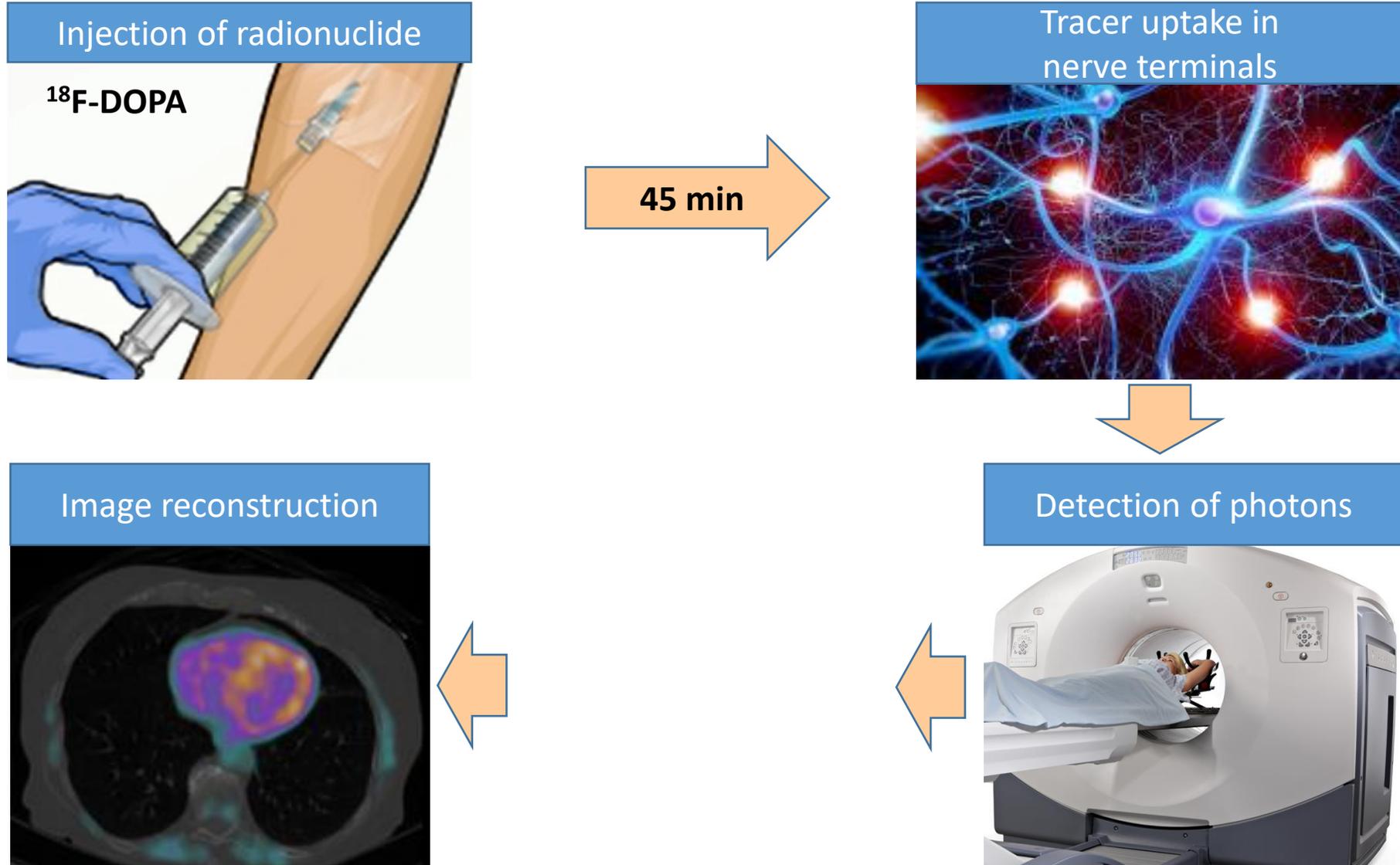


Heart-Brain Connections – Neurohumoral System

- The autonomic nervous system, the limbic network, and the renin–angiotensin–aldosterone system (RAAS) are all important variables affecting the heart–brain axis
- The central autonomic network regulates cardiac contraction, heart rate, and blood flow during rest and stress.
- Cerebral areas which modulate sympathetic activity are the prefrontal cortex, anterior cingulate, left amygdala, as well as the right anterior and left posterior insular cortices
- There is sex dimorphism in sympatho-vagal balance

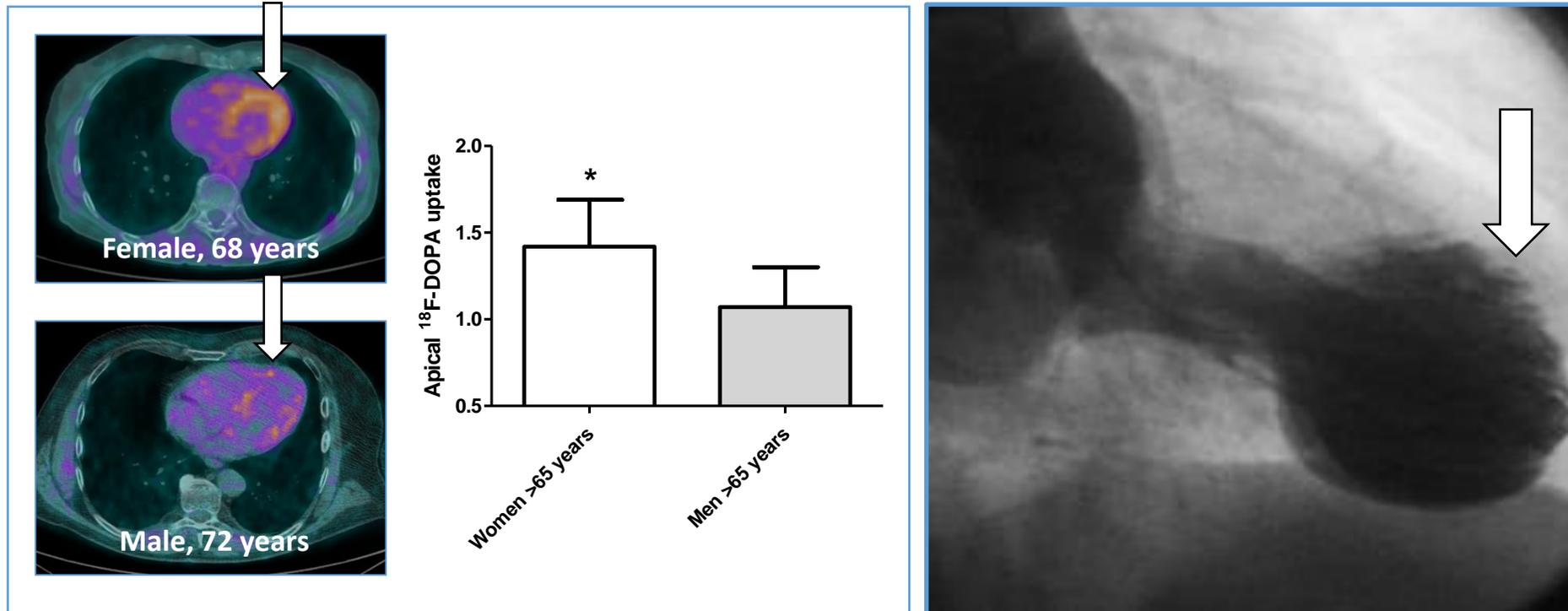


Imaging of cardiac sympathetic activity by positron emission tomography



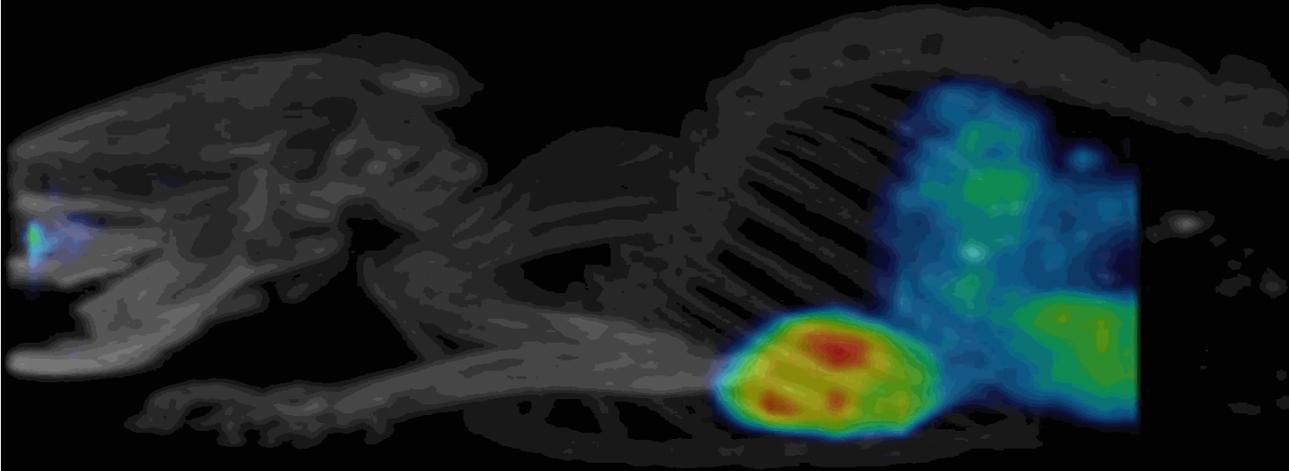
Sex Dimorphism in Sympatho-Vagal Balance

Enhanced cardiac sympathetic activity in healthy postmenopausal women



Sex Dimorphism in Sympatho-Vagal Balance

High-resolution PET-imaging (^{11}C -mHED)



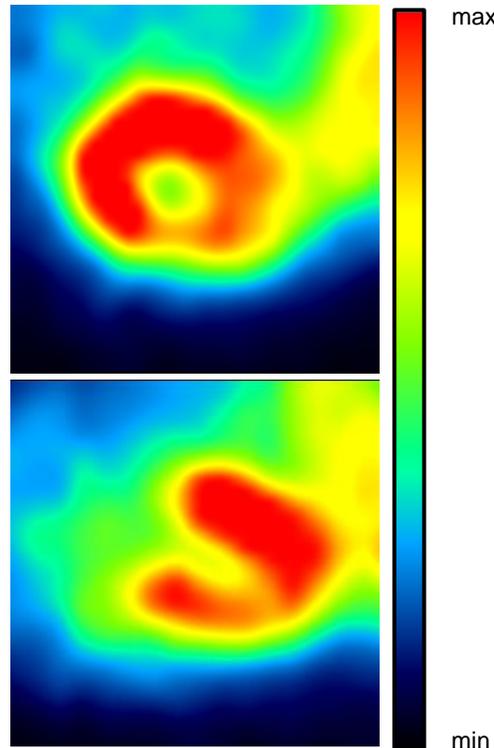
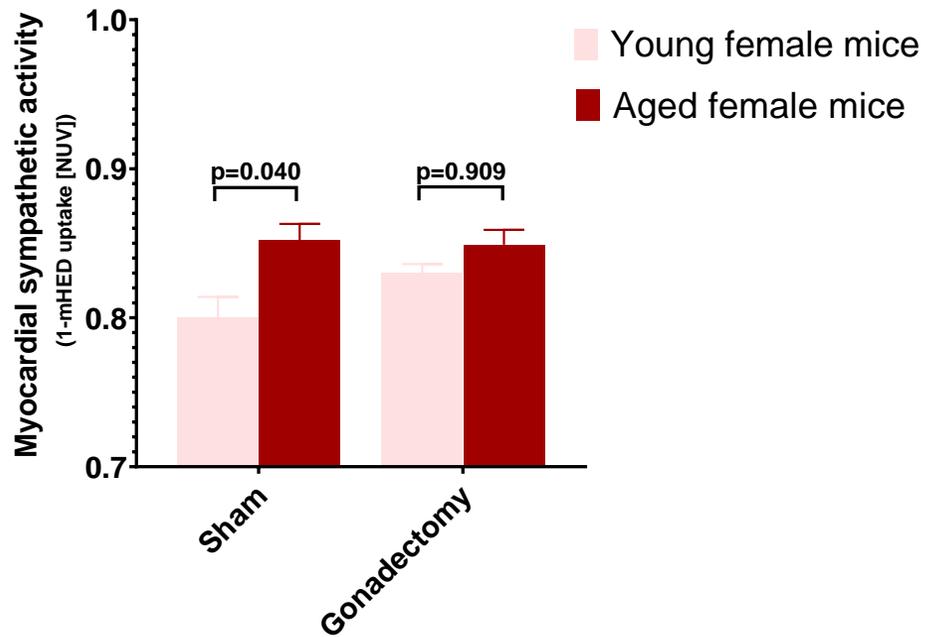
Female mouse, 25g

Imaging of Cardiac
Sympathetic Activity
in Mice

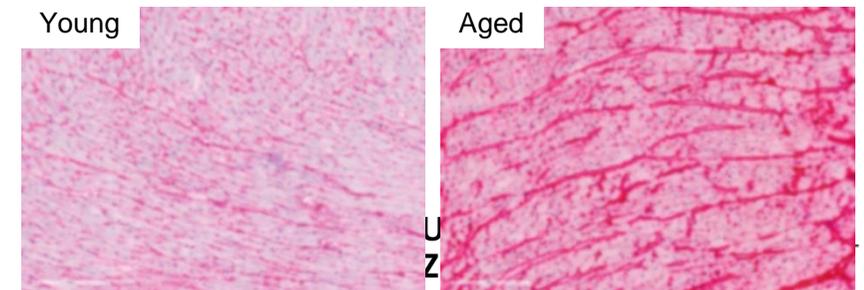
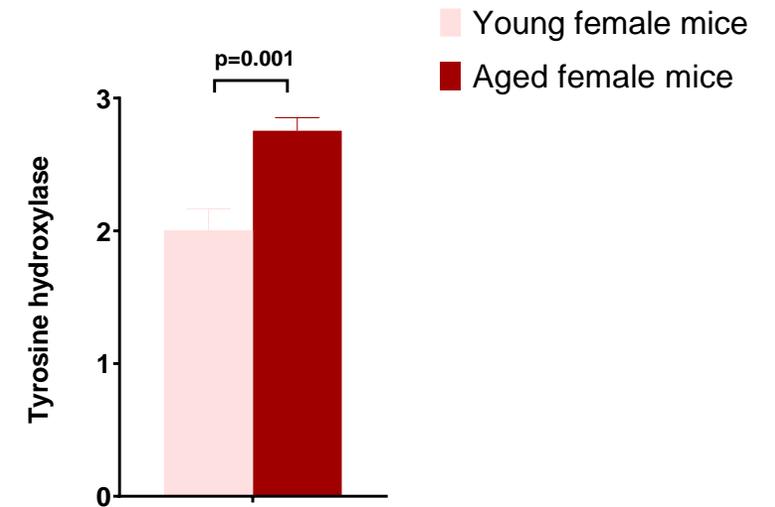
Sex Dimorphism in Sympatho-Vagal Balance

Increase in Cardiac Sympathetic Activity in Female Aged Mice

¹¹C-mHED uptake

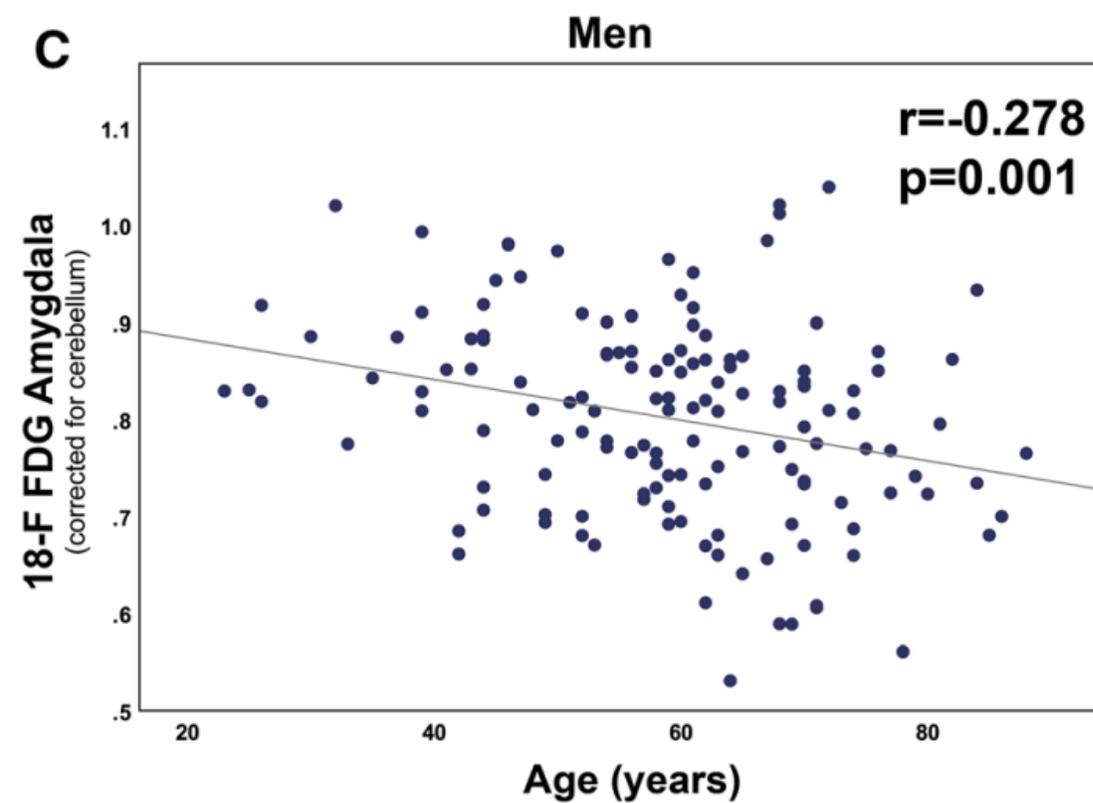
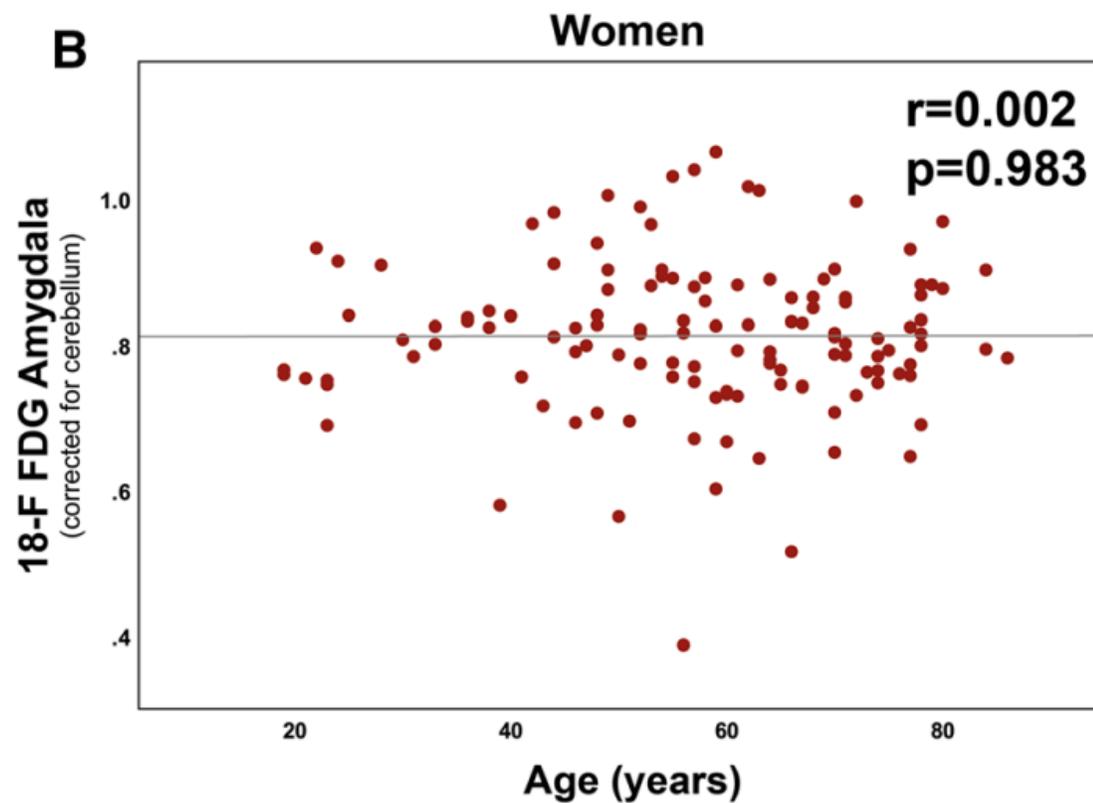


Tyrosine hydroxylase expression



Sex Differences in Cerebral Areas Modulating Sympathetic Activity

Age- and sex-dependent changes of resting amygdalar activity in individuals free of clinical cardiovascular disease



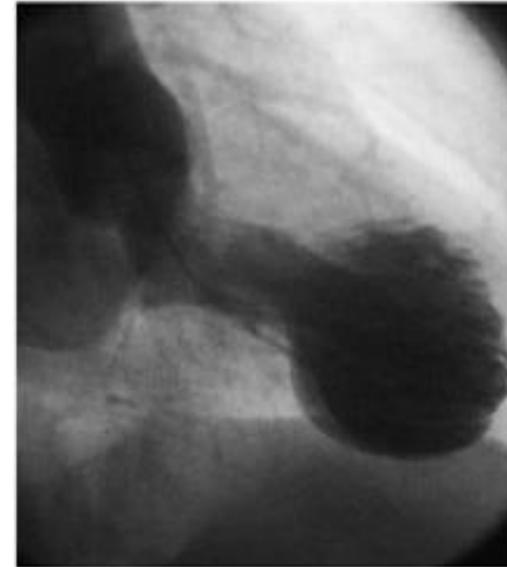
Sex and Gender Differences in Neuronal Stress Responses

Health | Mon Feb 9, 2015 4:57pm EST

After heart attack, women more stressed than men

BY KATHRYN DOYLE

- Greater mental stress in women presenting with an acute myocardial infarction
- High sympathetic activity persists for months after an acute coronary syndrome in women and is associated with an unfavourable prognosis
- Takotsubo syndrome predominantly affects women
- Microvascular dysfunction predominantly affects women and is associated with increased cardiac sympathetic activation



Sex and Gender Differences in Neuronal Stress Responses: Clinical Implications



European Heart Journal - Cardiovascular Imaging (2019) **20**, 633–635
doi:10.1093/ehjci/jez086

EDITORIAL

Adverse cardiovascular outcomes in women: blame the amygdala?

Puja K. Mehta  ^{1,2*}, **Bruno B. Lima**^{2,3}, **Michael D. Nelson**⁴, and
C. Noel Bairey Merz⁵



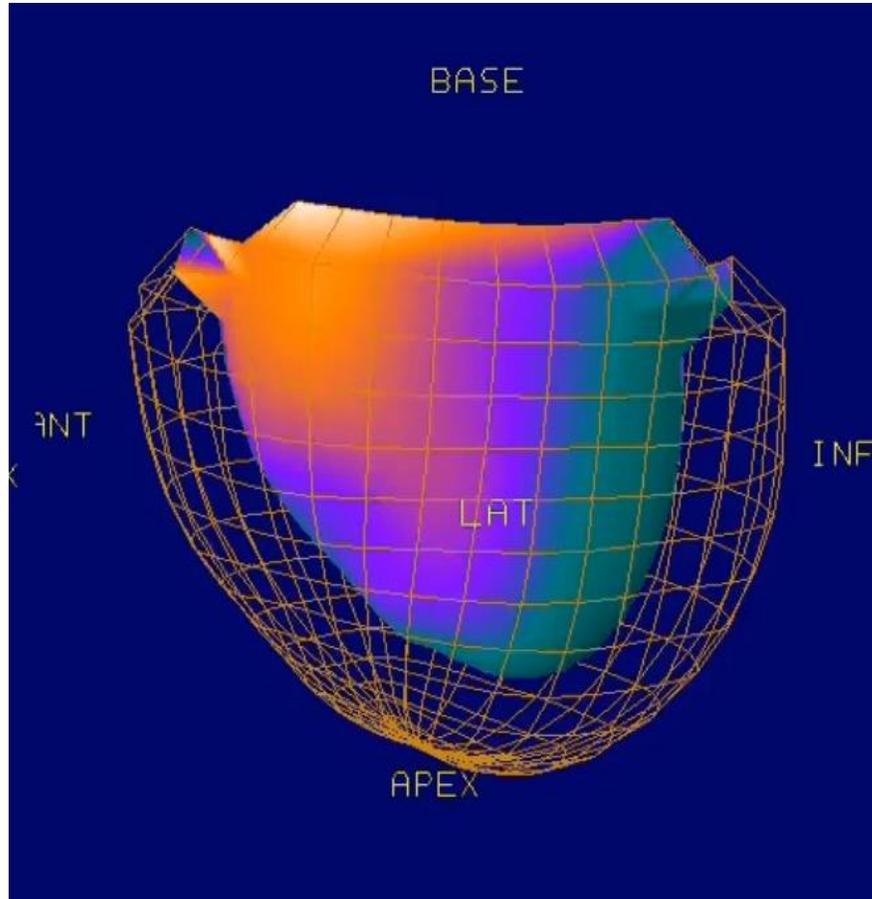
Universität
Zürich ^{UZH}

u^b

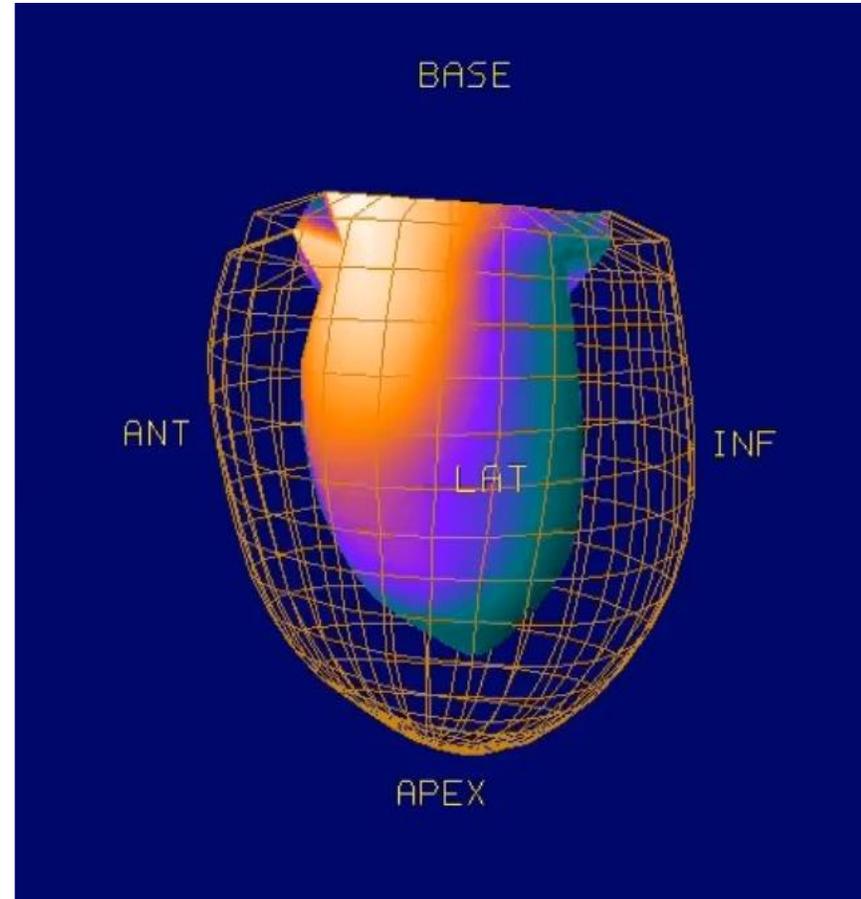
UNIVERSITÄT
BERN

Sex and Gender Differences in Neuronal Stress Responses: Potential Mechanisms

Does heart size matter?



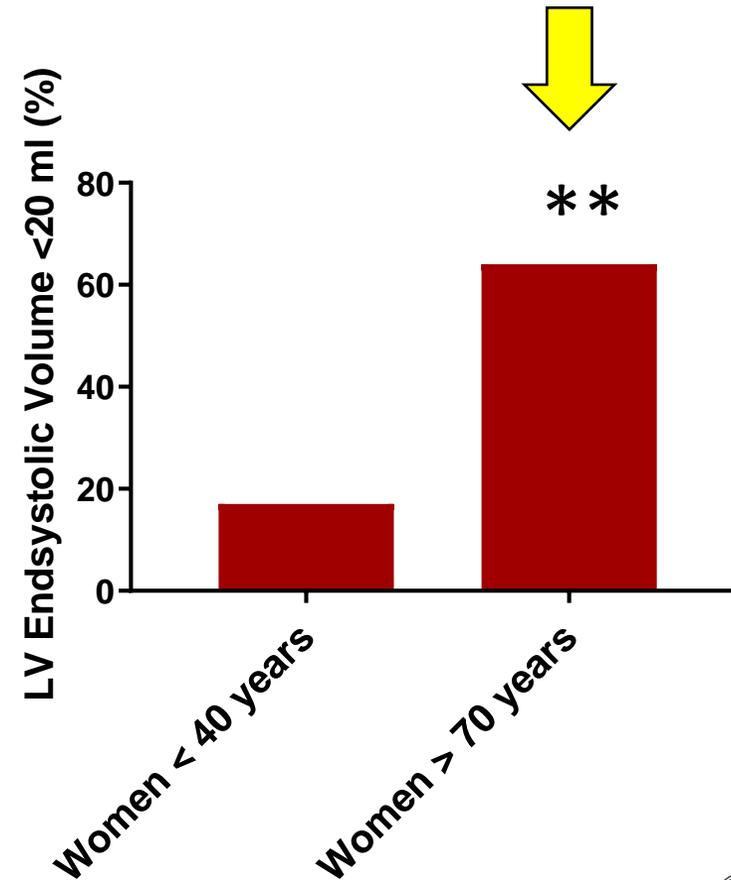
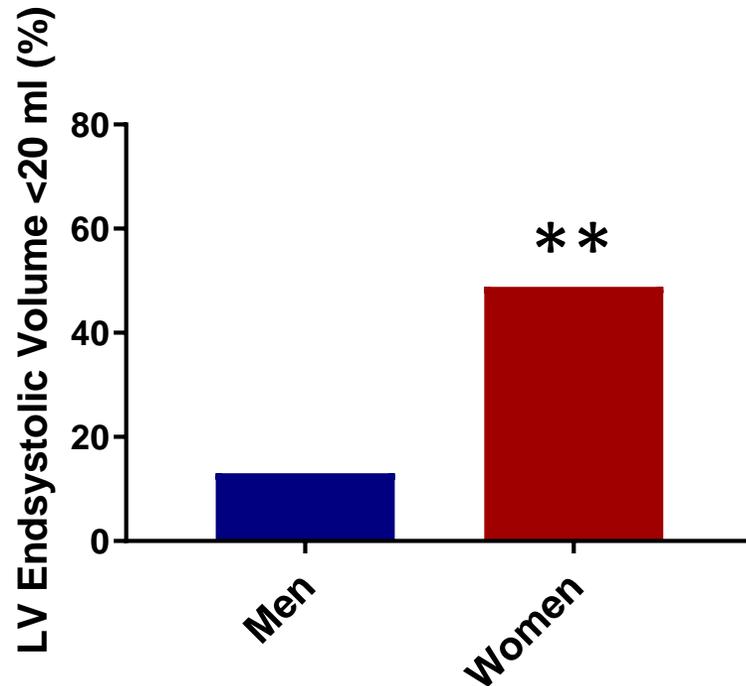
Healthy male patient, 72 years



Healthy female patient, 68 years

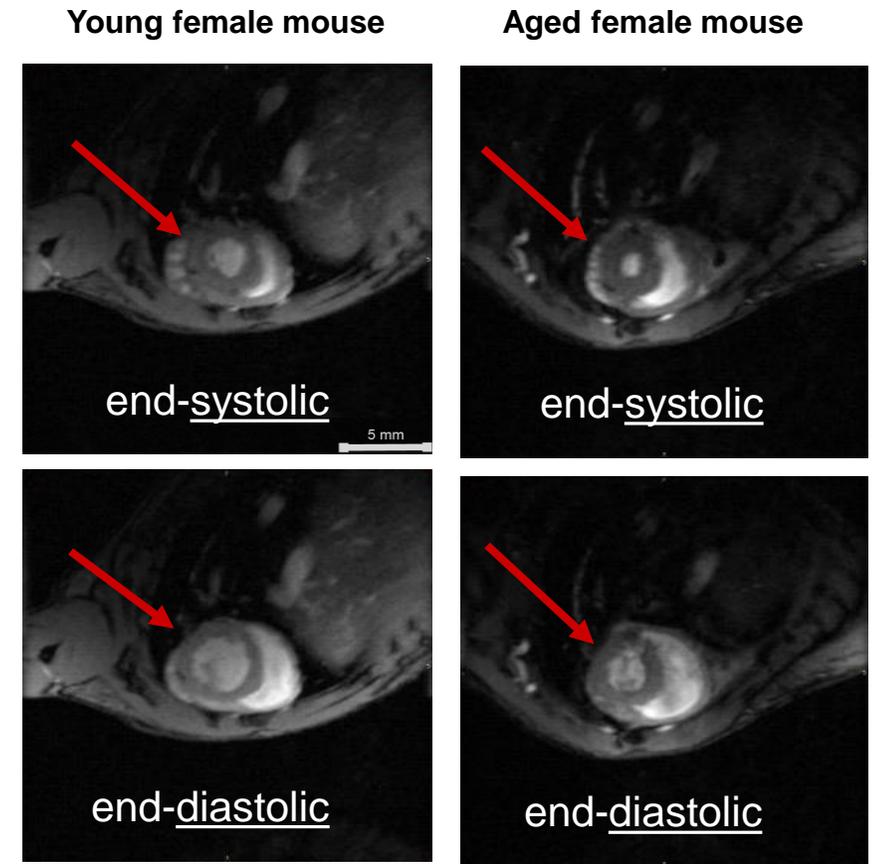
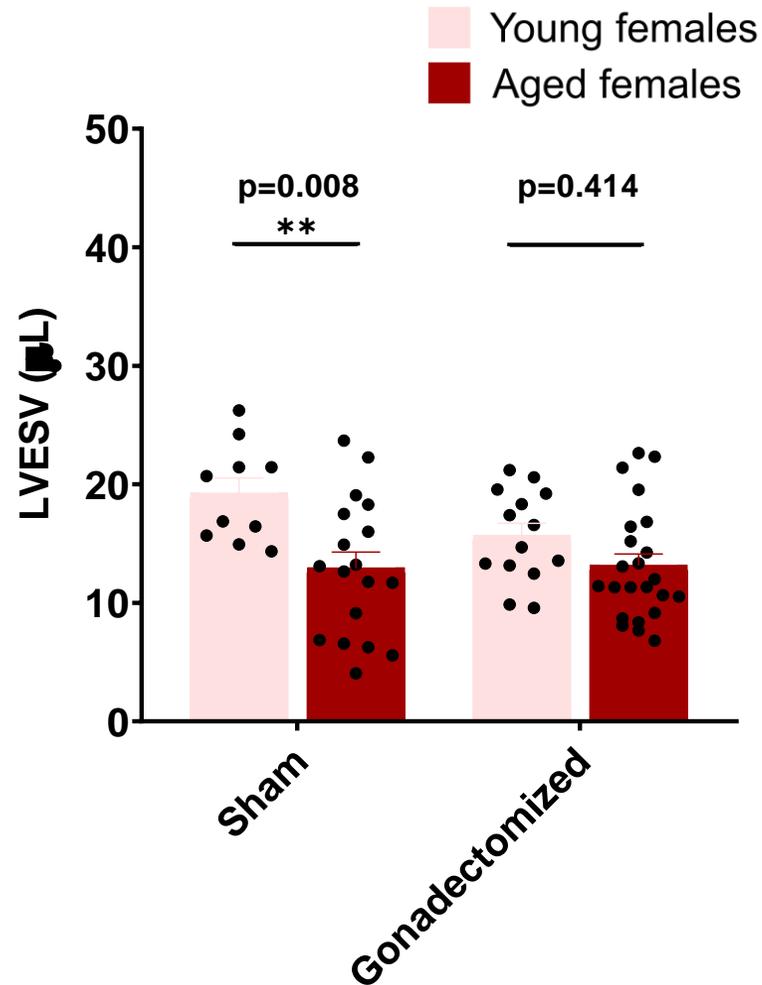
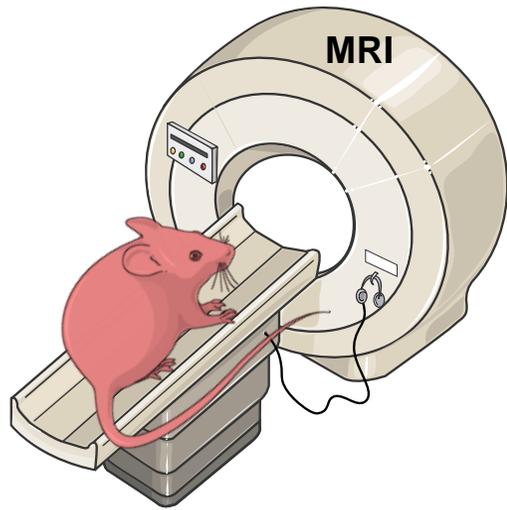
Sex and Gender Differences in Neuronal Stress Responses: Potential Mechanisms

Percentage of 'Small Hearts' increases with age in women



Sex and Gender Differences in Neuronal Stress Responses: Potential Mechanisms

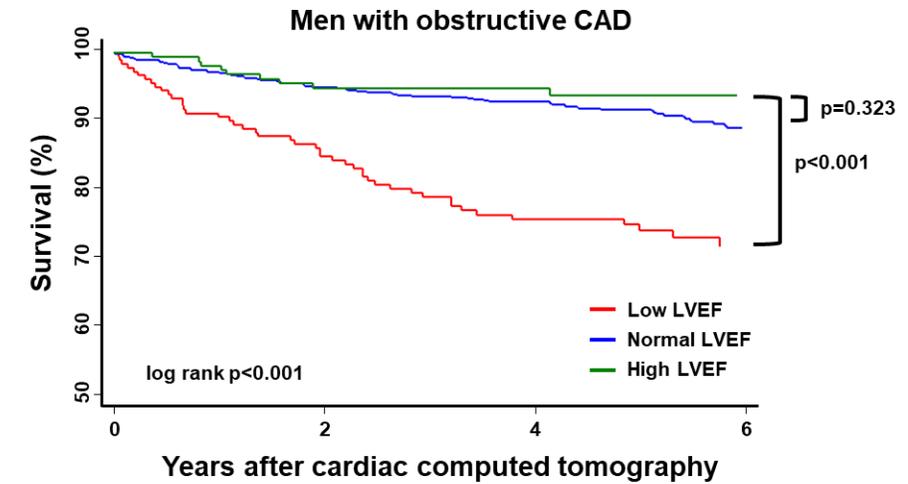
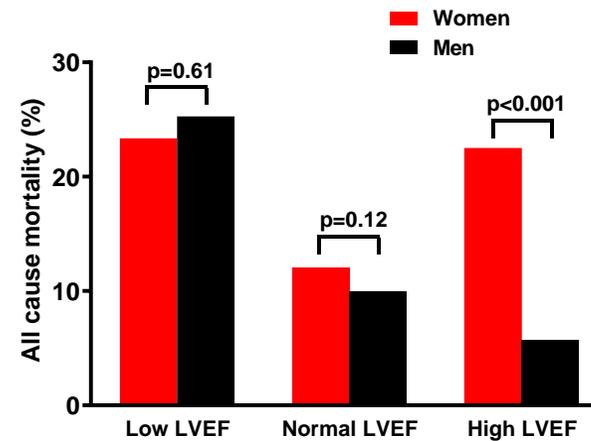
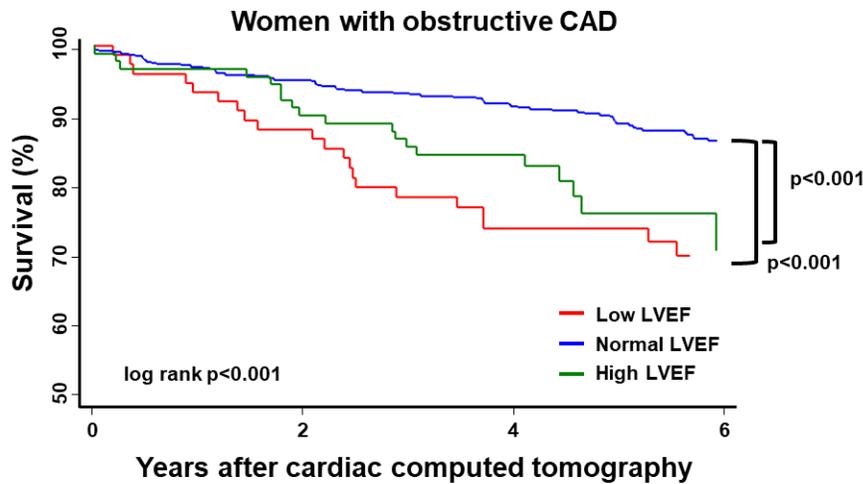
The 'Shrinking' Female Heart



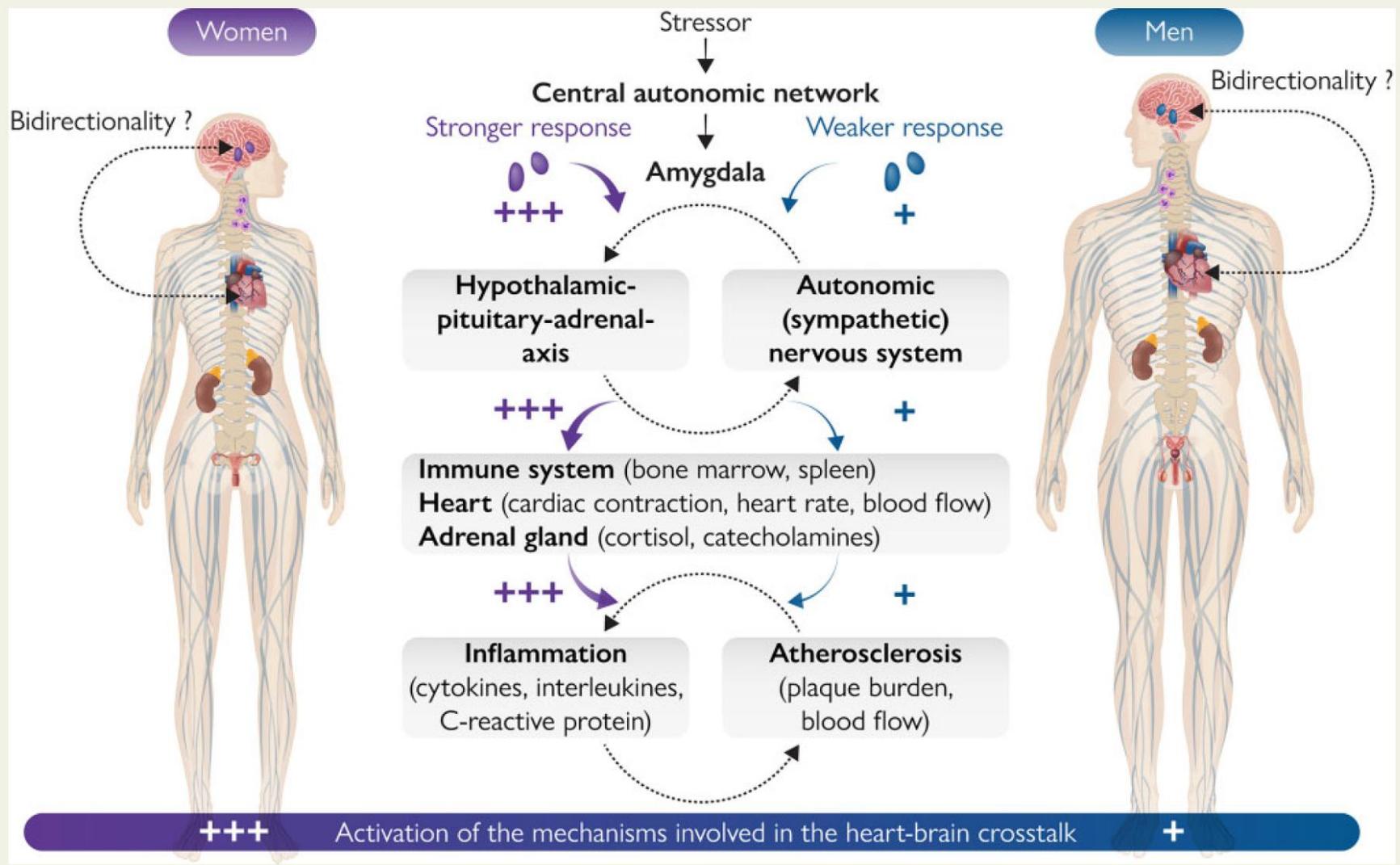
LVESV: Left ventricular end-systolic volume

The 'Hyperdynamic' Female Heart: Higher Mortality

The 'hyperdynamic' female heart: worse outcomes

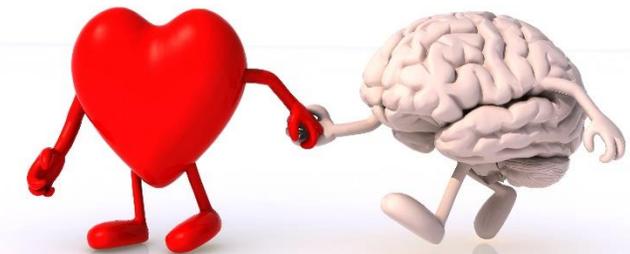


Summary



Conclusion and Outlook

- The neural stress response to cardiovascular illness differs between men and women
- A stronger reaction is being observed in women suggesting that women are disproportionately vulnerable to the adverse mental effects of chronic cardiovascular disease
- Enhanced inflammation and sympathetic activity might be a promising pathway to target stress responses following cardiac injury
- **Current knowledge gaps are:**
 - Directionality (or bidirectionality) of heart–brain interactions (chicken vs egg)
 - Effects of socio-cultural gender on heart–brain interactions
 - Treatments for specific heart and brain diseases and their interactions (approaches vs pharmacological targets)
 - Role of sex hormones in heart–brain interactions
 - Clinical role of brain imaging in cardiovascular risk stratification



Conclusion and Outlook

“If I were to start over today, I would choose a career in neuroscience, because the next 40 or 50 years are going to be all about the nervous system, just as the last half century has been about the circulation.”

Eugene Braunwald, MD, MACC

(Escaping Death and Prolonging Lives, Circulation Research, 2010)

