

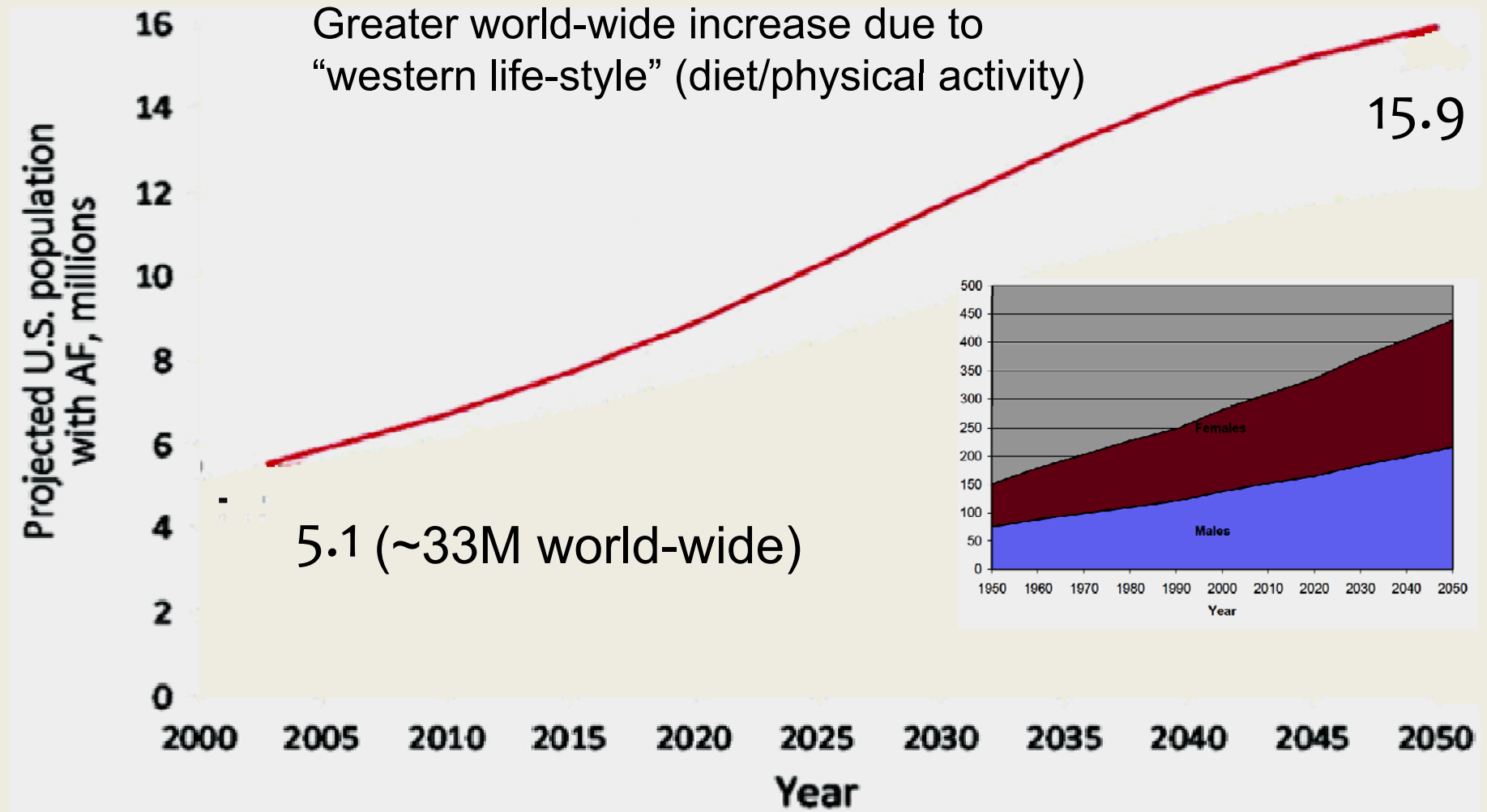
Basic Science Insights into Exercise, Lifestyle, Obesity Primary Prevention of Atrial Fibrillation

Peter Backx

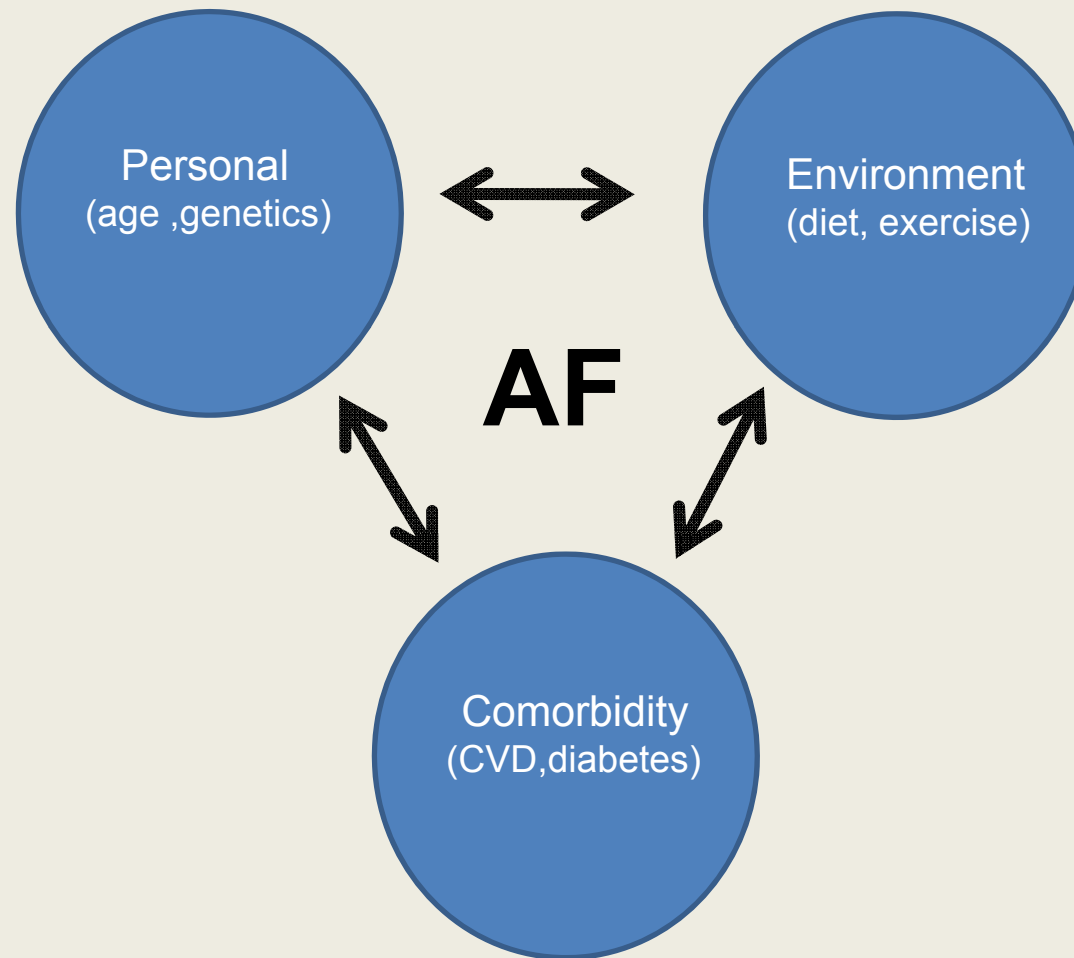
**Departments of Biology, York University
Cardiology, University Health Network**

**Ottawa Heart Research Conference
June 2, 2016**

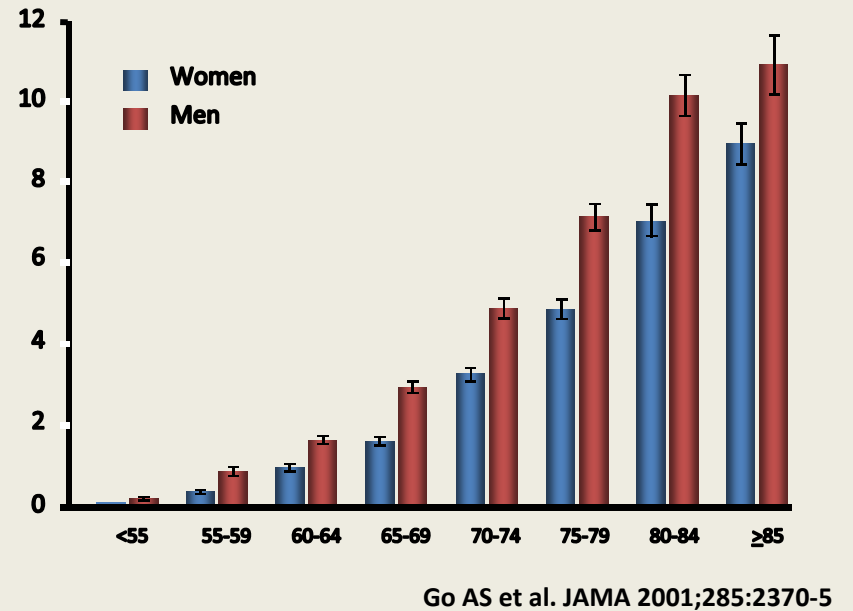
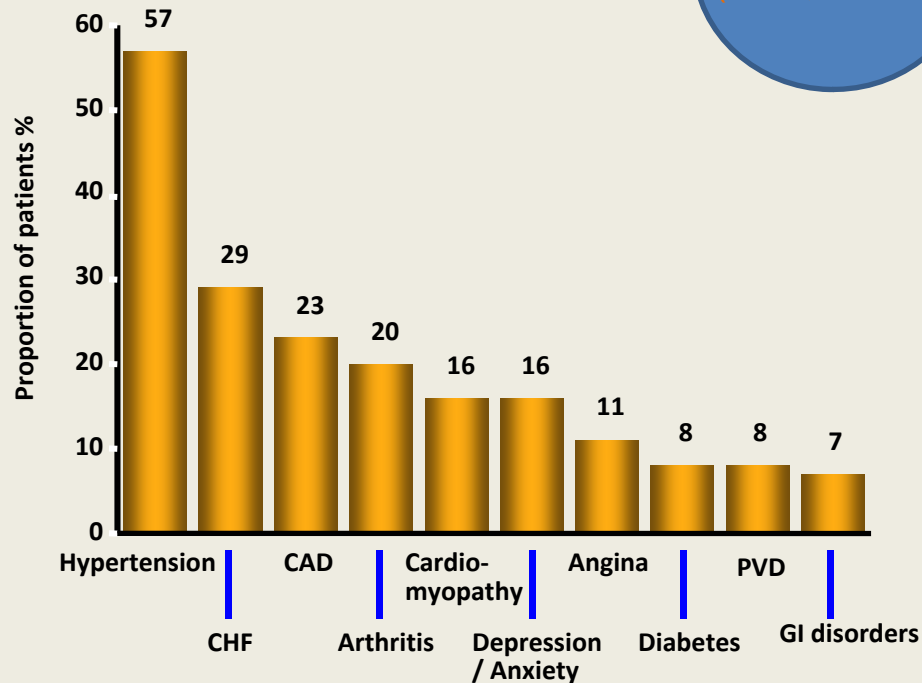
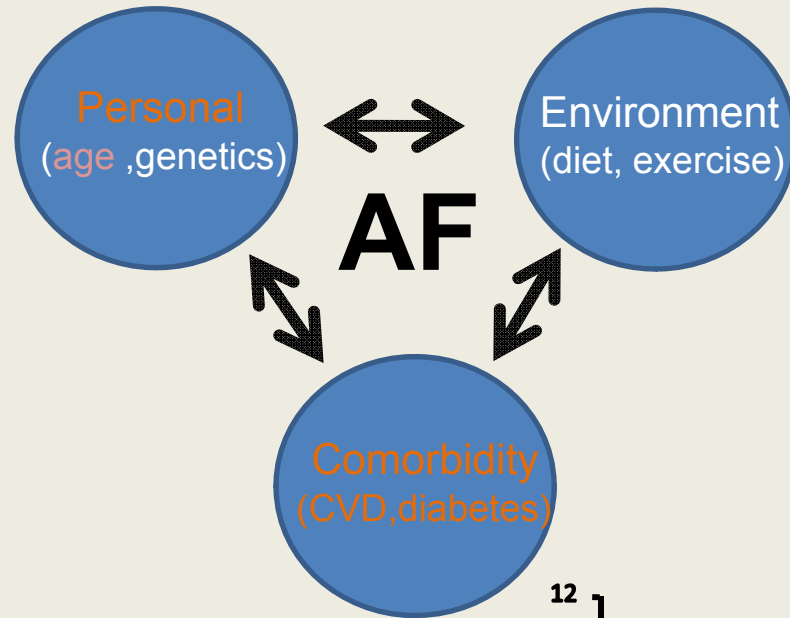
Growing Burden of Atrial Fibrillation (AF)



Factor That Influence Vulnerability to Atrial Fibrillation (AF)



Understanding Atrial Fibrillation (AF): CV disease and age are key risk factors



Understanding Atrial Fibrillation (AF): cumulative effects of risk factors

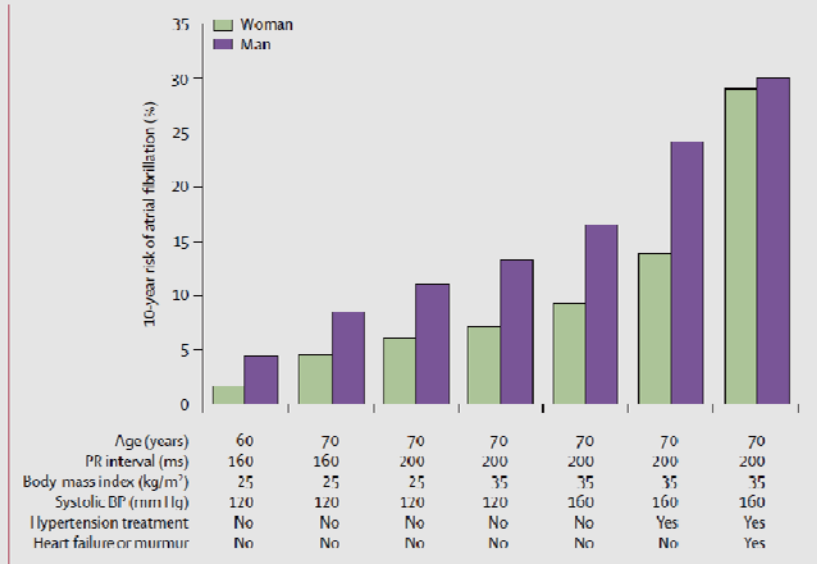
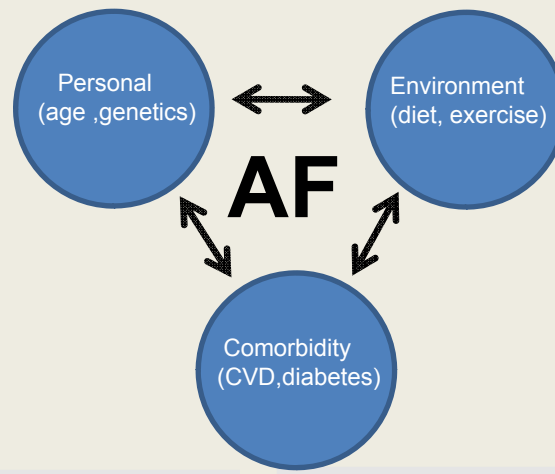
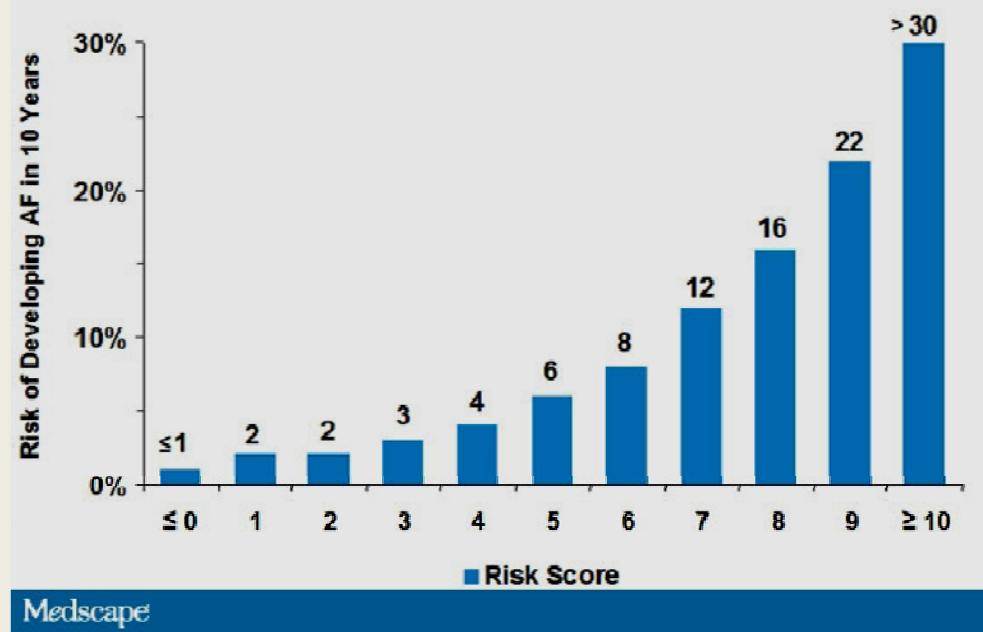
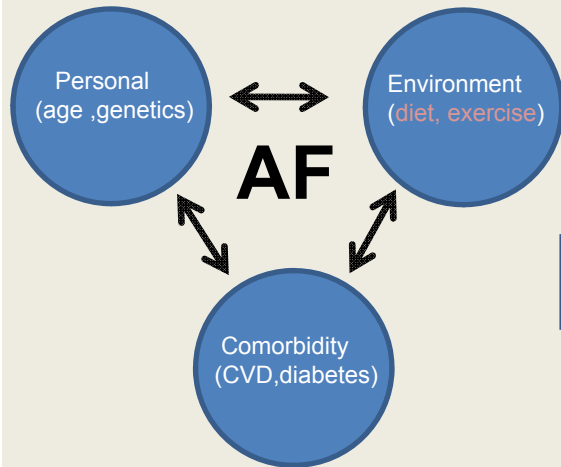


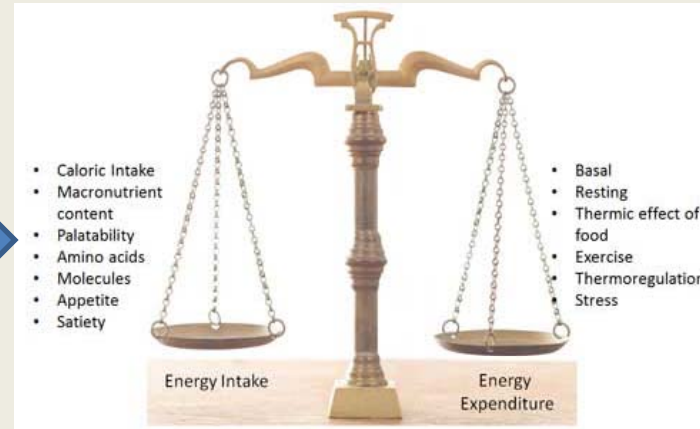
Figure 1: Comparison of the risk of atrial fibrillation in 10 years by sex calculated from associated risk factors with the risk equation



Understanding Atrial Fibrillation (AF): Interdependence of exercise and obesity

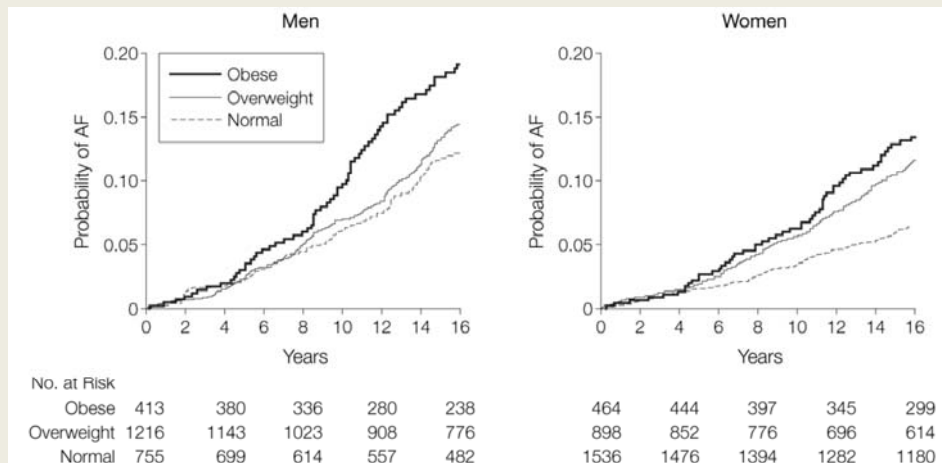


Diet/Excessive
Calories



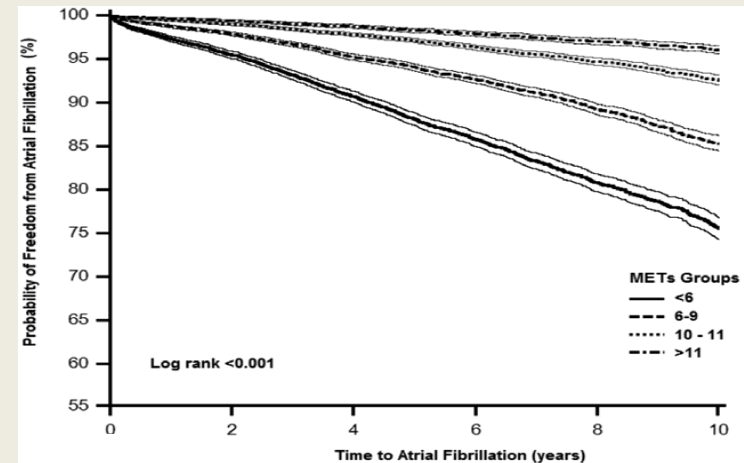
Exercise
Physical activity

4% increase in AF risk for each BMI unit



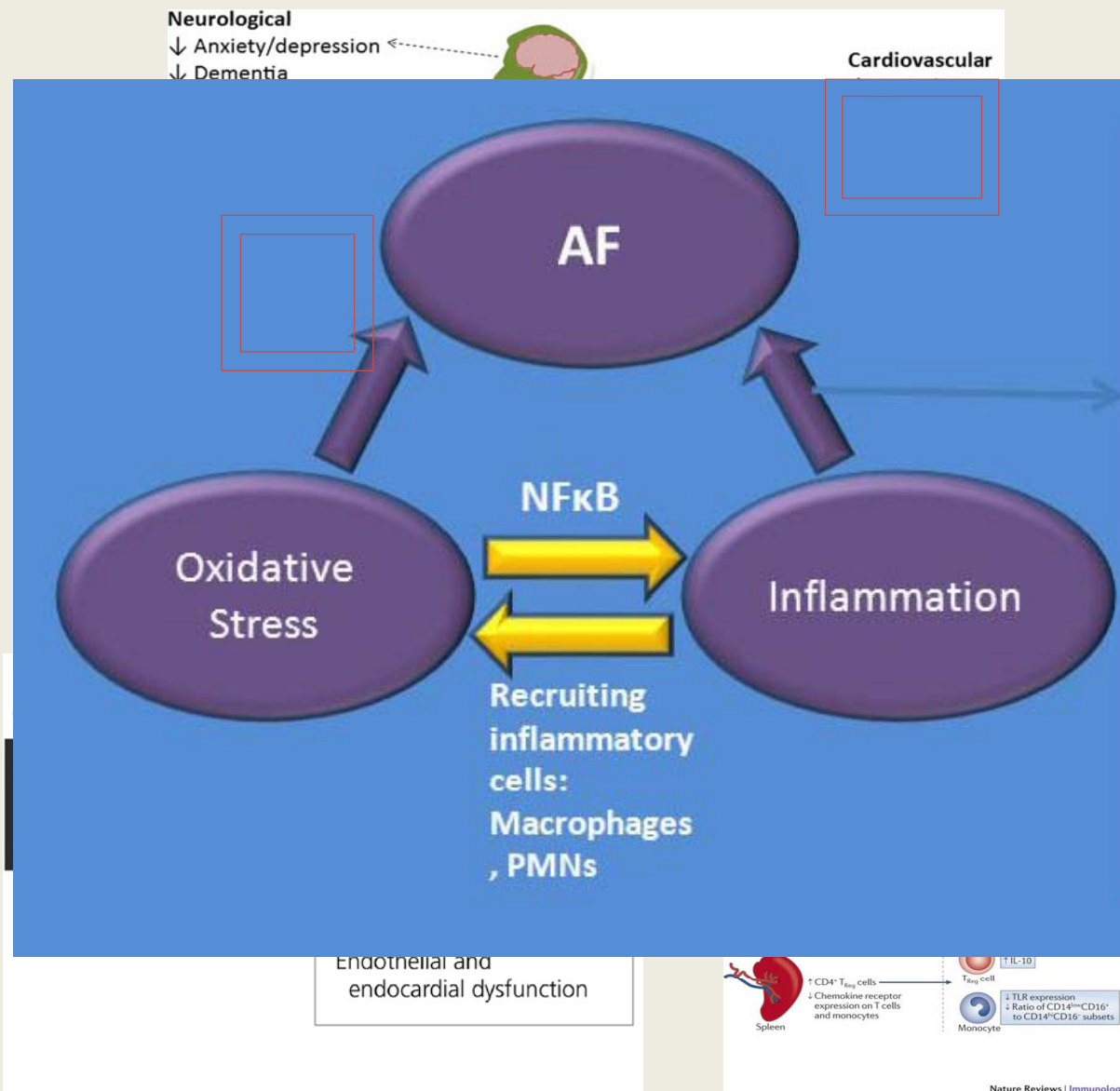
Wang et al JAMA. 2004

10% reduction in AF for each MET unit



Qureshi et al, Circulation, 2015

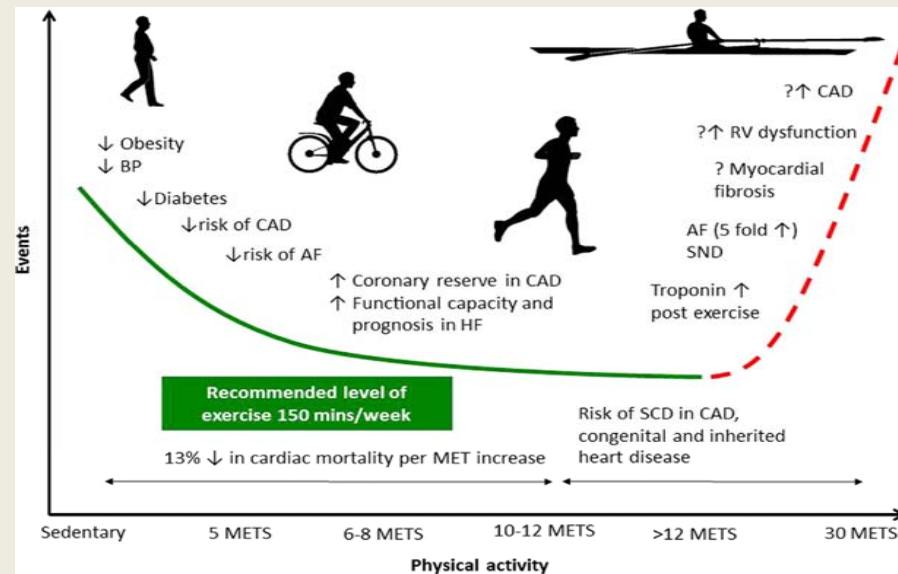
Obesity and exercise affect many physiological and molecular processes in many tissues with inflammation playing a dominant role in obesity



Hajhosseiny et al, Heart Rhythm 2015

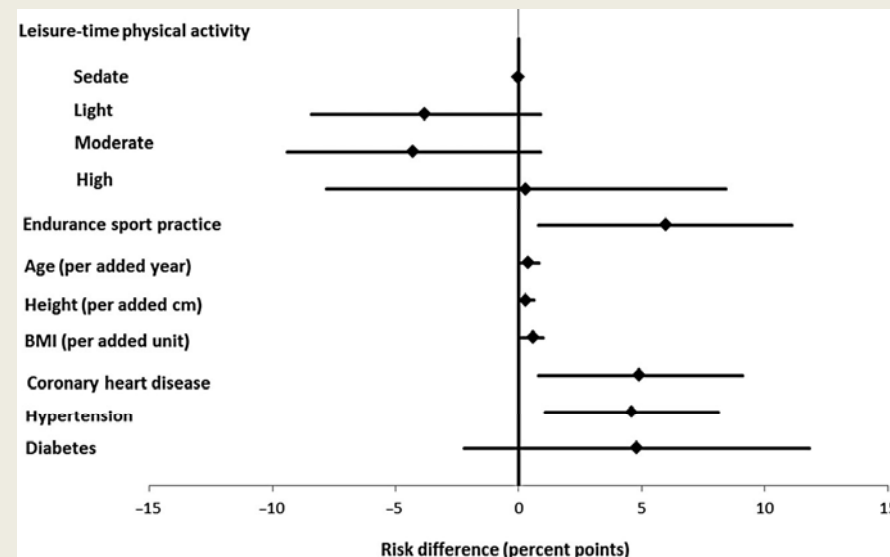
Gleeson Nature Reviews 2011

But the benefits of exercise are U-shape



Merghani et al, J Cardiovasc Med, 2015

Fig. 2 – The U-shaped curve; moderate exercise is better than no exercise, but extreme exercise may be harmful. CAD = coronary heart disease, BP = blood pressure, AF = atrial fibrillation, SND = sinus node disease, RV = right ventricular.



Myrstad et al, Scand J Med Sci Sport, 2014

Fig. 2. Studied risk factors for atrial fibrillation. Estimated atrial fibrillation risk differences with 95% confidence intervals by selected covariates. Both study populations analyzed together, men 65–90 years old.

Objective:

**Develop mouse models of
exercise and test for
connection with AF**

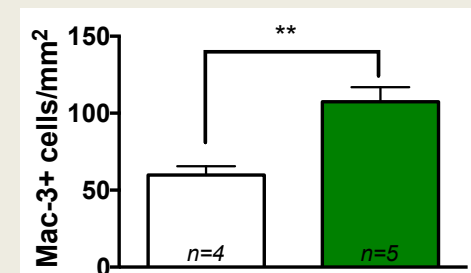
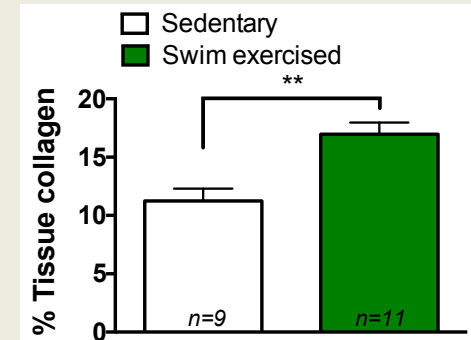
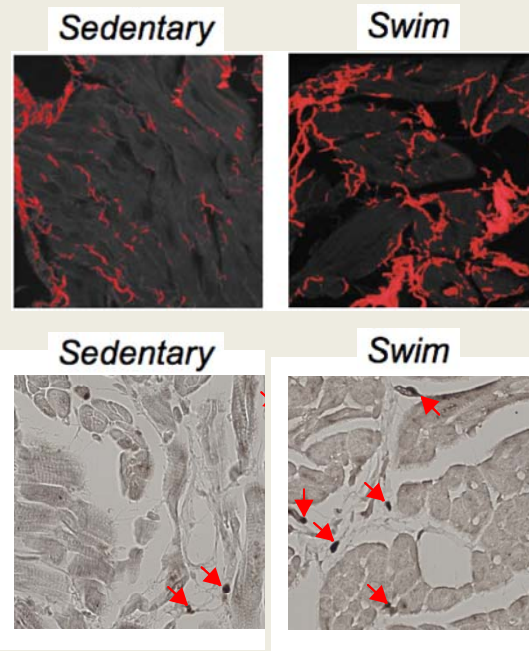
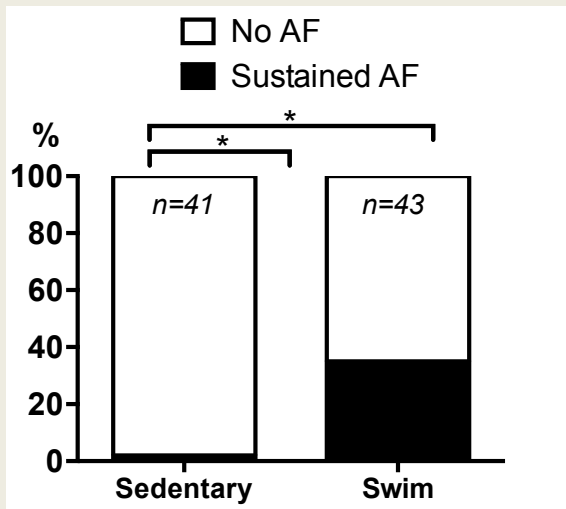
Exercise Mouse Models



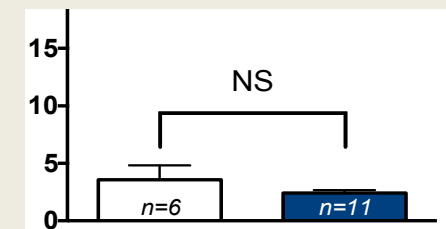
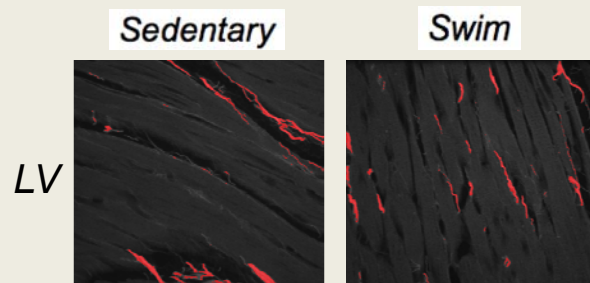
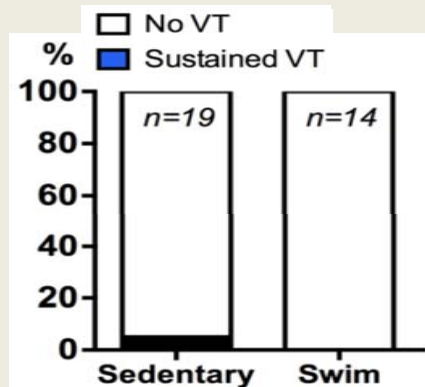
Sedentary versus exercised

Consequences of exercise (6 weeks) in mice

Atria

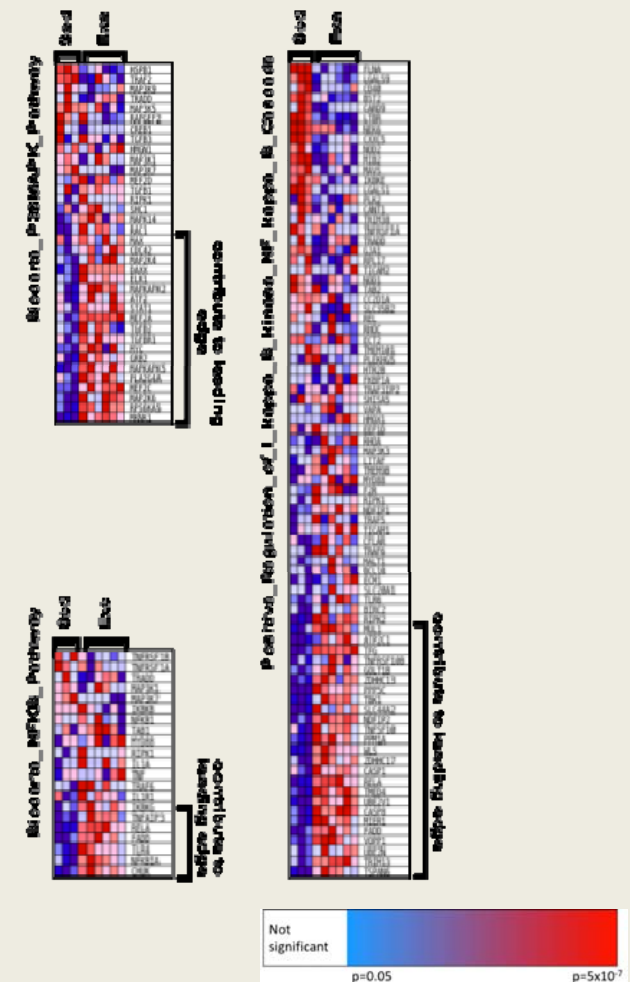
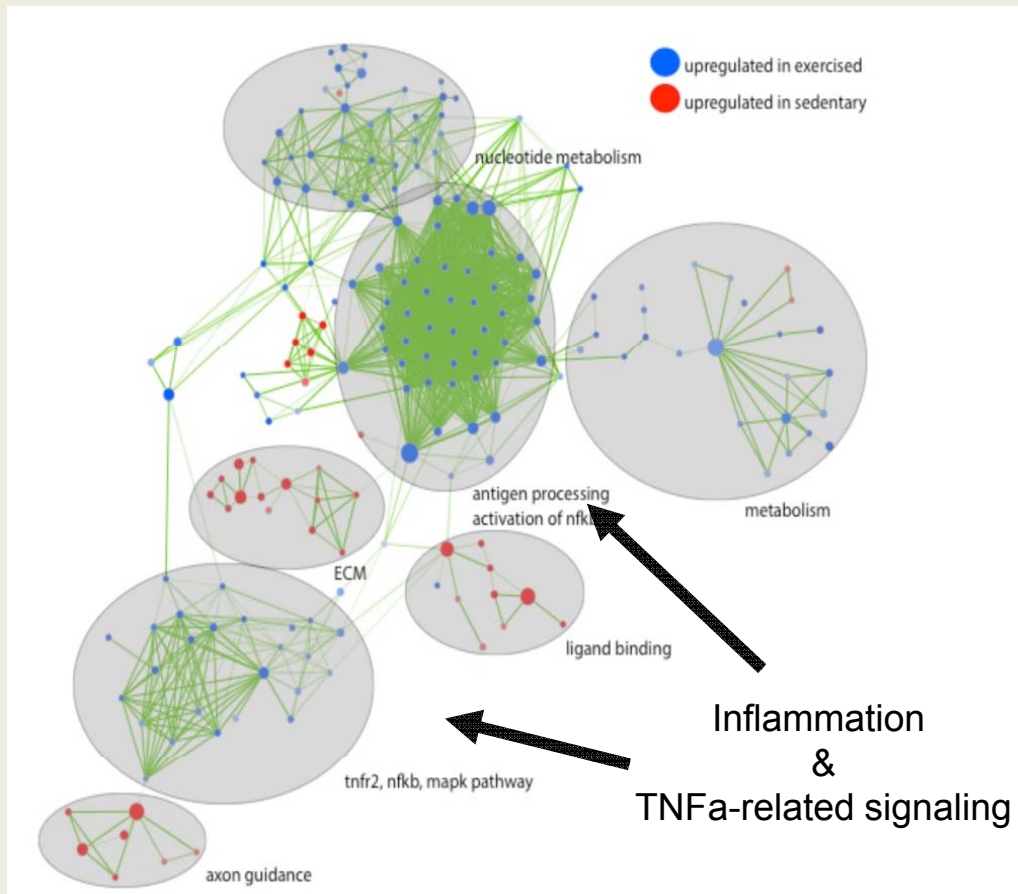


Ventricles



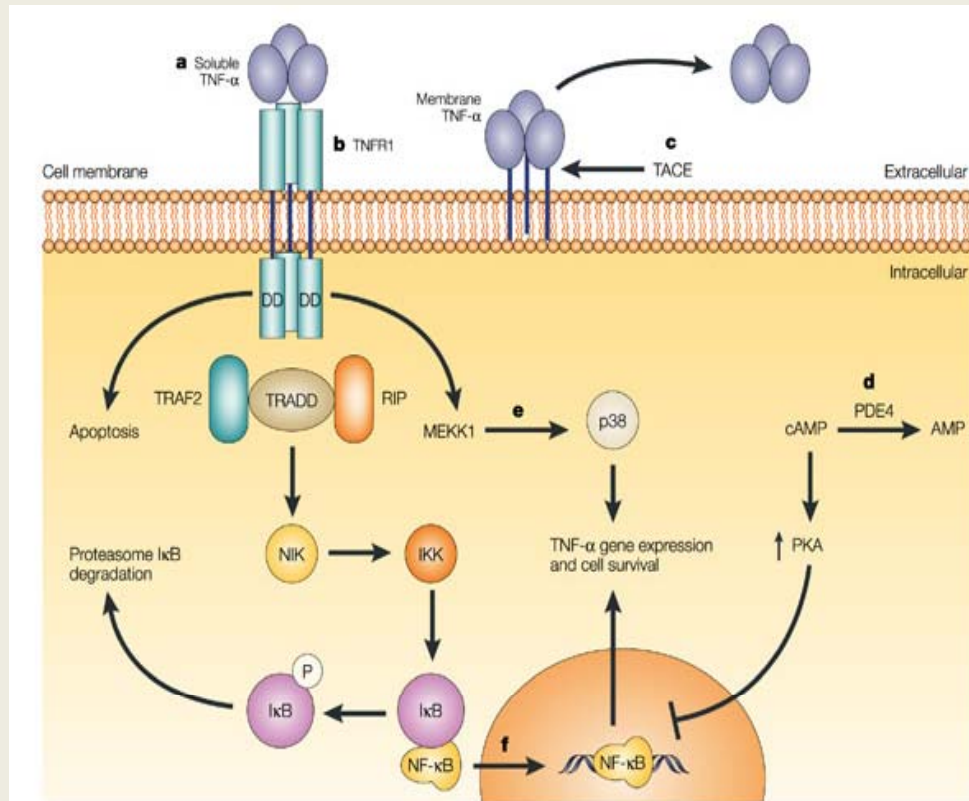
Microarray gene profiling revealed enrichment of NFκB and p38 pathways

- Gene set enrichment analysis (GSEA)
- Gene ontology and Biocarta pathways

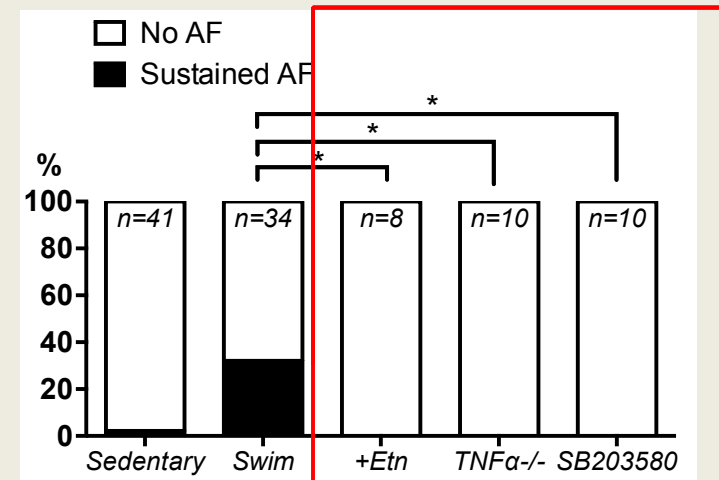
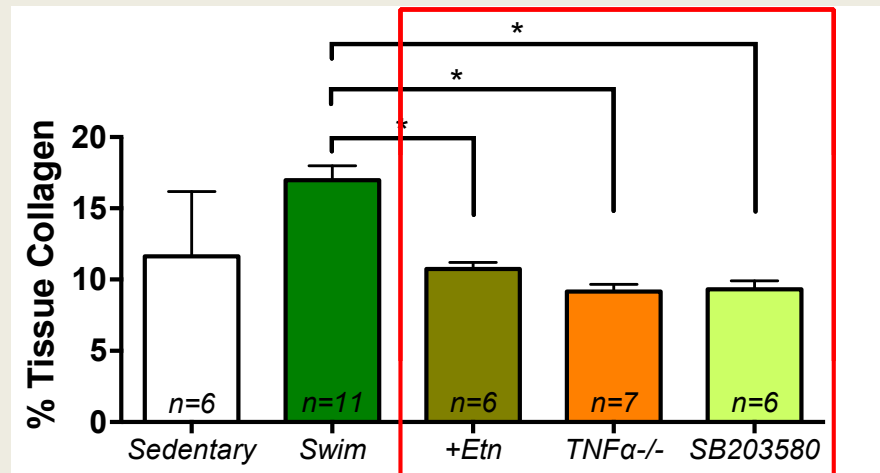
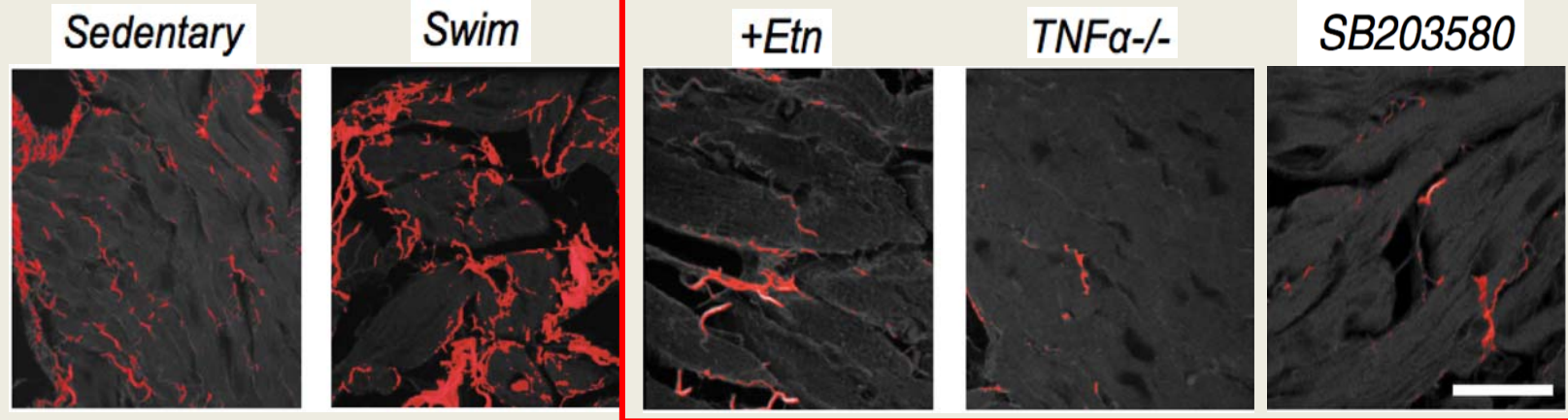


Hypothesis:

Changes in TNF α signaling are critical in atrial remodeling with exercise



TNF α Inhibition Rescues Pathological Atrial Remodeling



Bioinformatics Analysis of Data Generated Using Deep RNA Sequencing

(Swim-Sed)WT – (Swim-Sed)TNF α KO

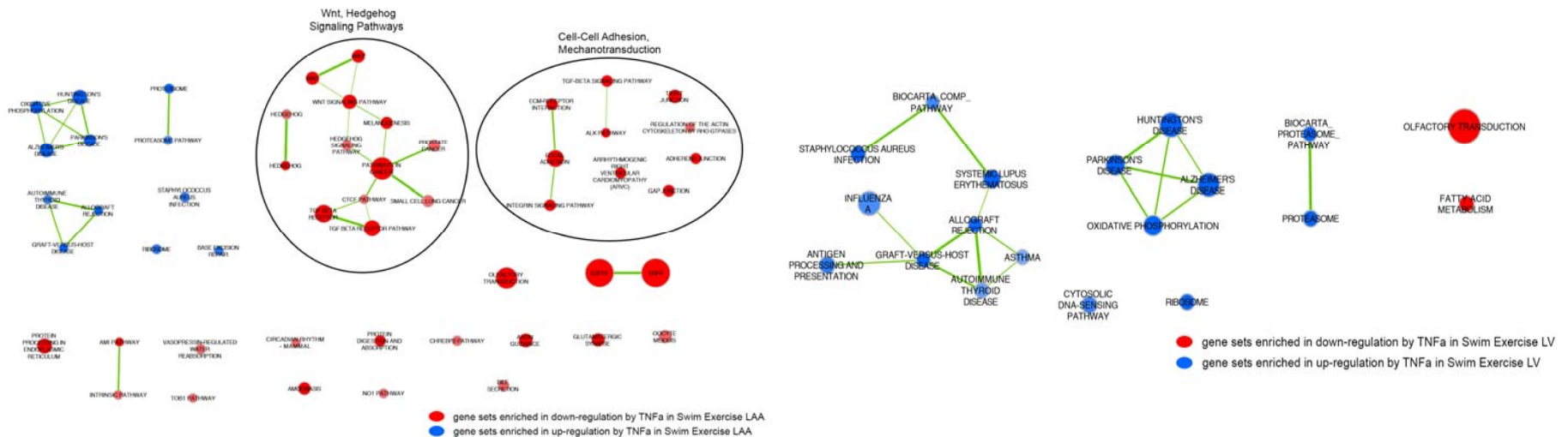
Effects of Swim on **WT**

Effects of Swim on **TNF α KO**

TNF α -mediated effects in **Swim** Exercise

Atria

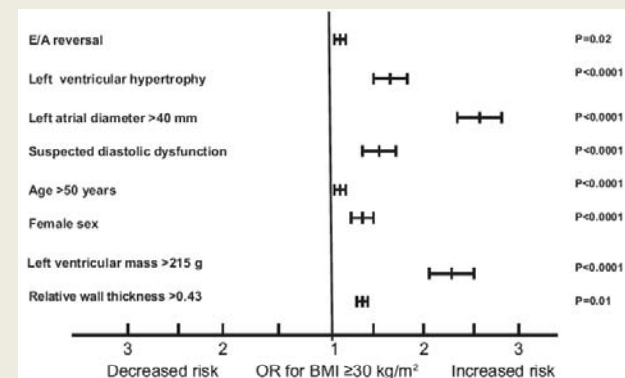
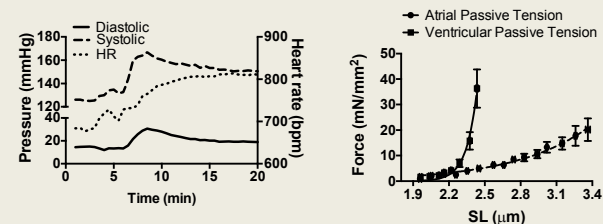
Ventricles



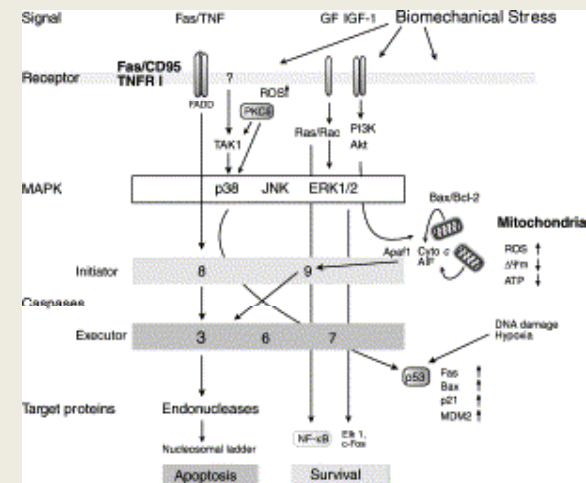
Far more gene sets/pathways are TNF α -sensitive in atria compared to ventricles
TNF α -sensitive gene changes in atria involve primarily mechanotransduction pathways

Conclusions

- AF has been shown to be an inflammatory condition
- Obesity/Metabolic Syndrome (lack of exercise) is tightly associated with AF and linked to inflammation in humans
- Intense endurance sport/exercise also linked to both AF and inflammation in humans
- Intense exercise in mice also leads to AF in association with inflammation/fibrosis
- Adverse effects of exercise in mice in atrial-specific and $\text{TNF}\alpha$ -mediated
- $\text{TNF}\alpha$ has been shown to be a mechanosensor in several cell types and we find the effects of exercise are linked to mechanotransduction pathways
- This suggests that exercise-induced AF might serve a similar mechanism to AF associated with risk factors the AF



Movahed et al, Exp Clin Cardiol 2008;13(2):89-91



Acknowledgments

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