

Implication of sex differences in myocarditis

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Disclosure

Teaching/Research Consultant

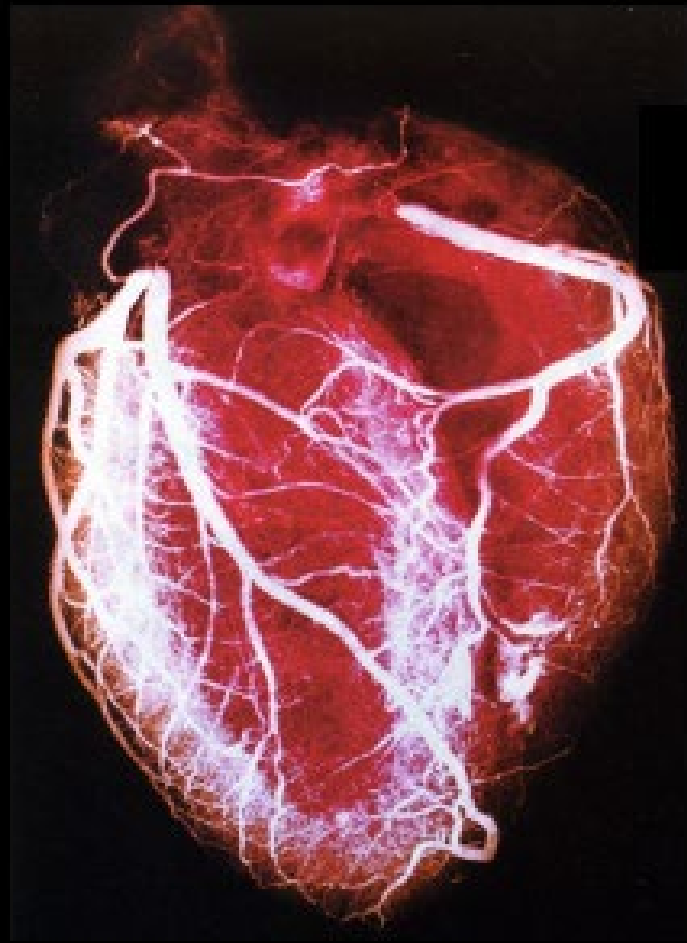
- University of North Florida
- Mayo Clinic Florida

Year	Country	n	Sex Ratio (F:M)	Main Findings	Ref
2013	Finland	3,198	1:3.3	<ul style="list-style-type: none"> *Myocarditis more common in men than women (p<0.0001) *Median age of patients 33 years *Males were significantly younger than females (p<0.0001) *Myocarditis most prevalent in men 16-20 years of age with a gradual decline with age thereafter *Women highest level after menopause *Hospital admissions inverse logarithmic association with age 	Kyto, 2013
2017	Israel	200	1:2.6	<ul style="list-style-type: none"> *More men had myocarditis than women (76% men) *Men had higher peak troponin levels (p<0.001) *Men were significantly younger than women (p<0.001) *More men were hospitalized (p=0.015) *Women had more chronic medical conditions 	Laufer-Per, 2017
2019	Many countries	303	1:3.5	<ul style="list-style-type: none"> *More men had myocarditis (78%) *sST2, a biomarker of heart failure, was increased in men with myocarditis <50 years of age *sST2 levels correlated with NYHA class heart failure in men but not in women 	Coronado, 2019
2019	Denmark	42	1:2.2	<ul style="list-style-type: none"> *More men were found to have myocarditis at autopsy for sudden cardiac death (SCD) (p=0.02) *SCD was higher in males for all ages from 16-45 *Highest SCD-myocarditis incidence from autopsy observed in those aged 36–45 years 	Lynge, 2019
2019	USA	27,129	1:2	<ul style="list-style-type: none"> *More men had myocarditis than women *More men were hospitalized for myocarditis *Hospitalized men were younger than women (p<0.001) *In hospital complications and death were higher in women (p<0.001) 	Shah, 2019
2020	Switzerland	51	1:4.1	<ul style="list-style-type: none"> *More men had myocarditis than women (82%) *Sex differences in symptoms: men chest pain, women dyspnea *Creatine kinase and myoglobin higher in men (p=0.04, p=0.004, respectively) 	Patriki, 2020
2020	New Zealand	178	1:2.5	<ul style="list-style-type: none"> *More men had myocarditis *Men were younger than women (36 vs. 53 years, p<0.001) *ST-elevation on electrocardiogram more often in men (p=0.01) 	Wong, 2020
2021	Poland	19,978	1:2.9	<ul style="list-style-type: none"> *More men were hospitalized with suspected myocarditis than women (74%) *Myocarditis occurred more often in patients 16-20 years of age *The proportion of males were higher in all age groups except patients >70 years of age *In the last 10 years, the incidence of myocarditis increased, especially in males 	Ozierański, 2021
2022	South Africa	82	1:1.9		Hassan, 2022
2022	Sweden	8,679	1:3	*Incidence rose from 6.3 to 8.6 per 100,000 from 2000-2014, mostly in men <50 years of age	Fu, 2022

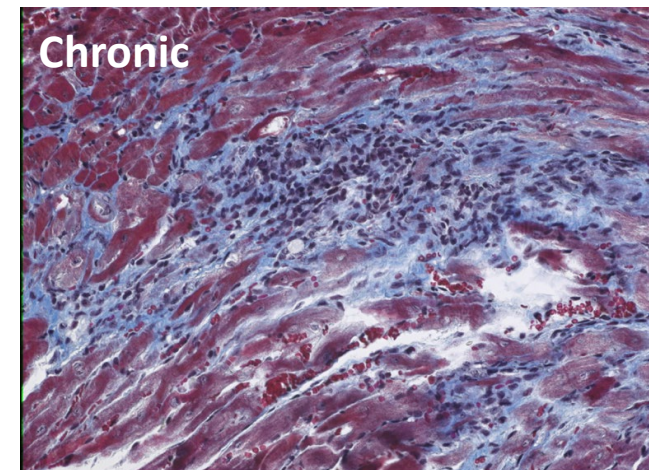
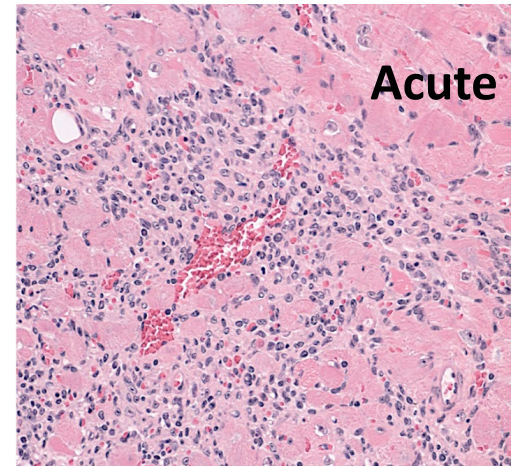
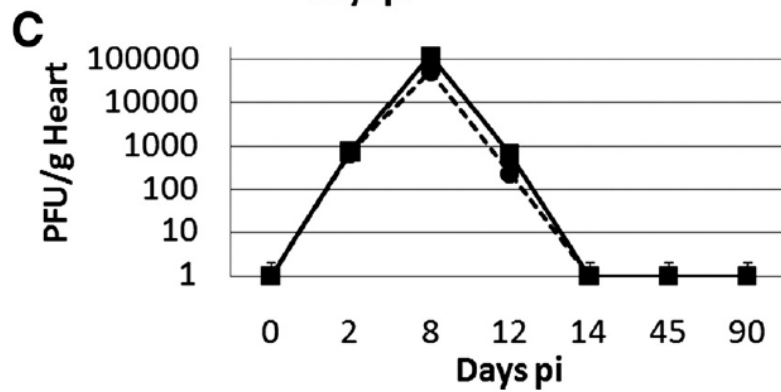
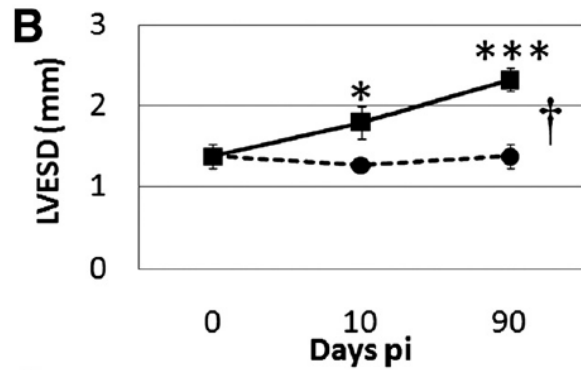
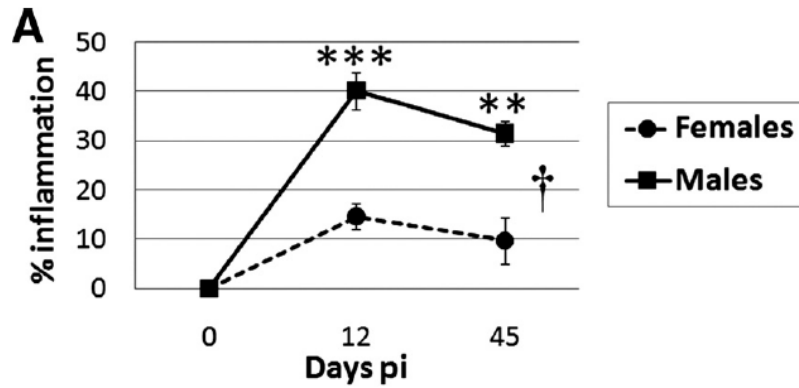
Epidemiology

- More men develop myocarditis (75-80% M)
- Sex ratio 1:2-4 F:M
- Myocarditis occurs before age 50 in M and after 50 in F
- Peak myocarditis 16-20yrs M, median 35; F 55
- Sudden cardiac death at autopsy M>F 16-45
- More men hospitalized, more complications and death in F
- Cardiac biomarkers Tpn, creatine kinase, myoglobin, sST2, IL-6, IL-17A higher in M
- In the last 10 years, the incidence of myocarditis increased, especially in males <50 years of age

Why is myocarditis more frequent in men?



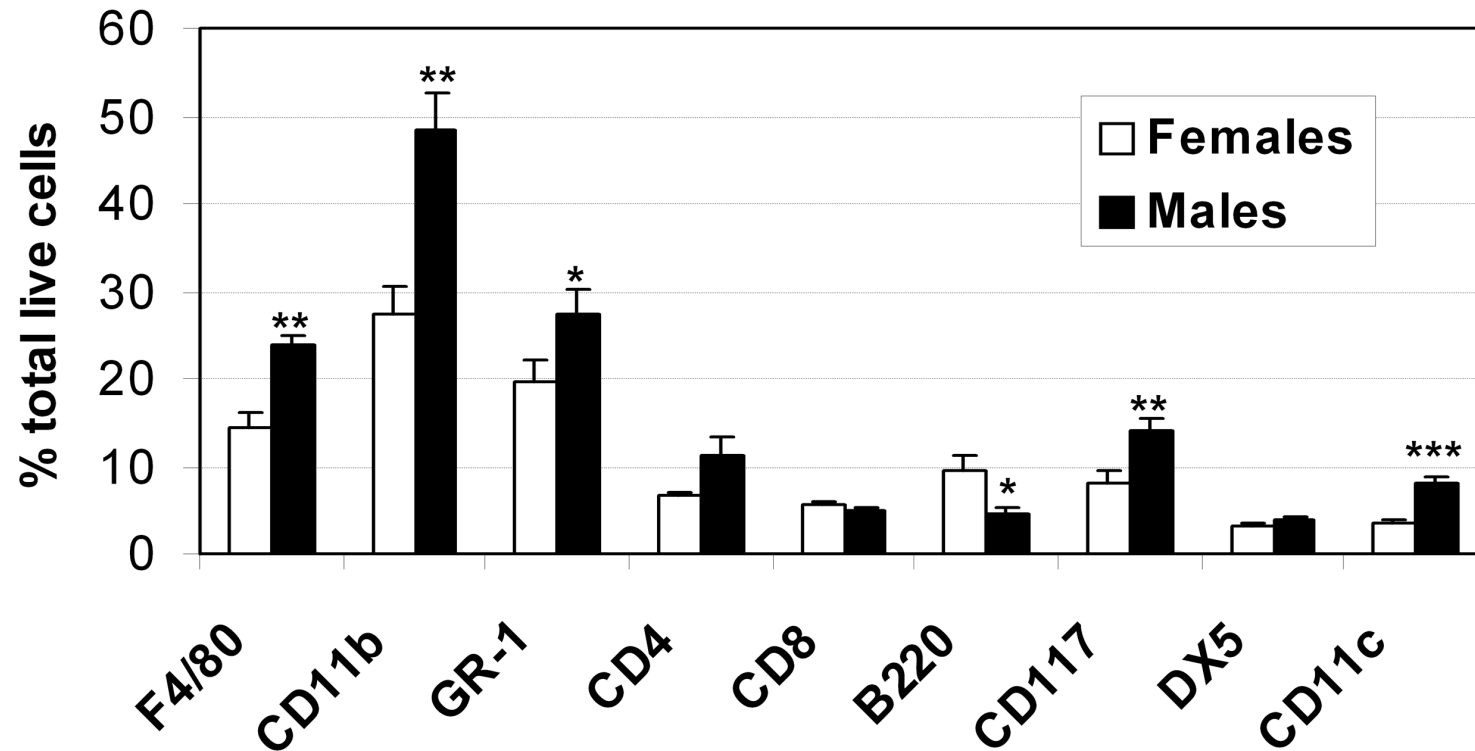
Greater inflammation & dilation in male mice



Myers JM, Fairweather D, Huber SA & Cunningham MW (2013) *Curr. Protoc. Immunol.* Ch15, Unit 15.14

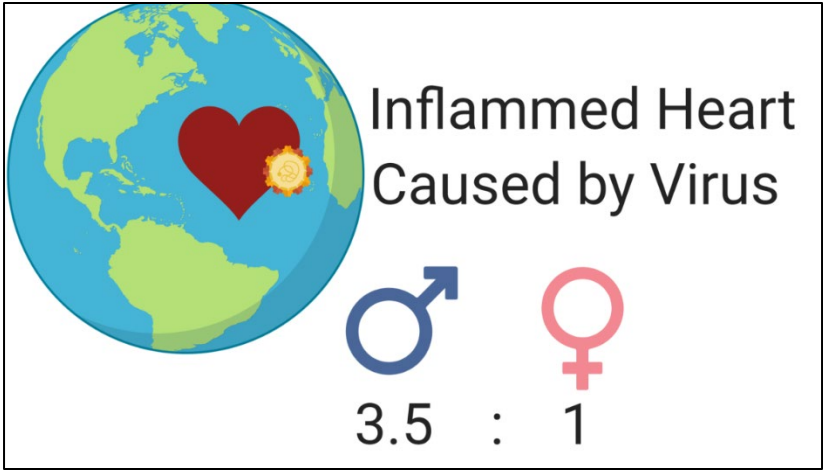
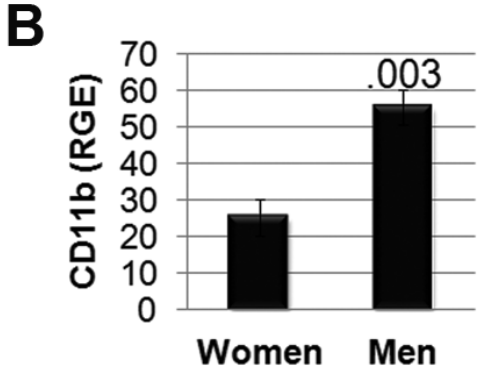
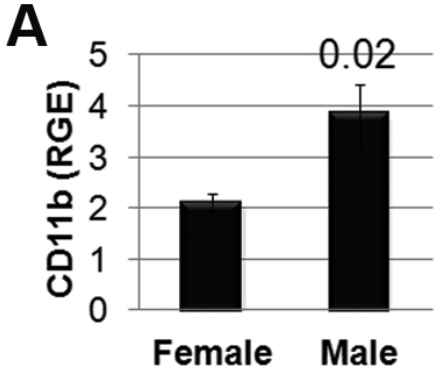
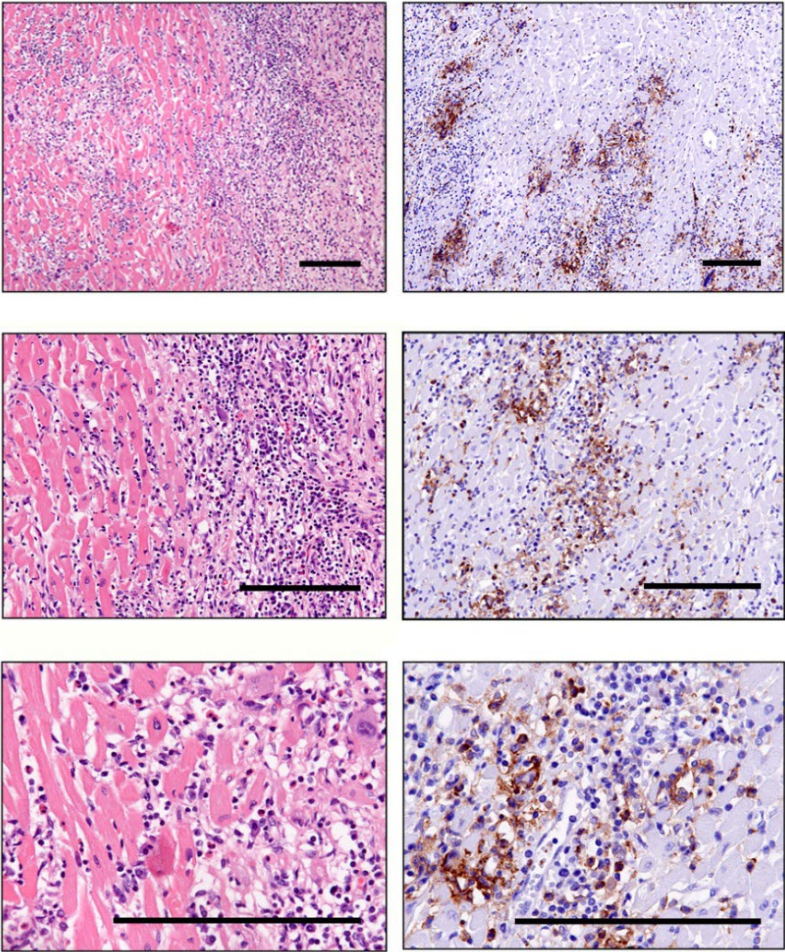
Am J Physiol Heart Circ Physiol 302: H1726–H1736, 2012.

Myocardial infiltrate primarily CD11b+

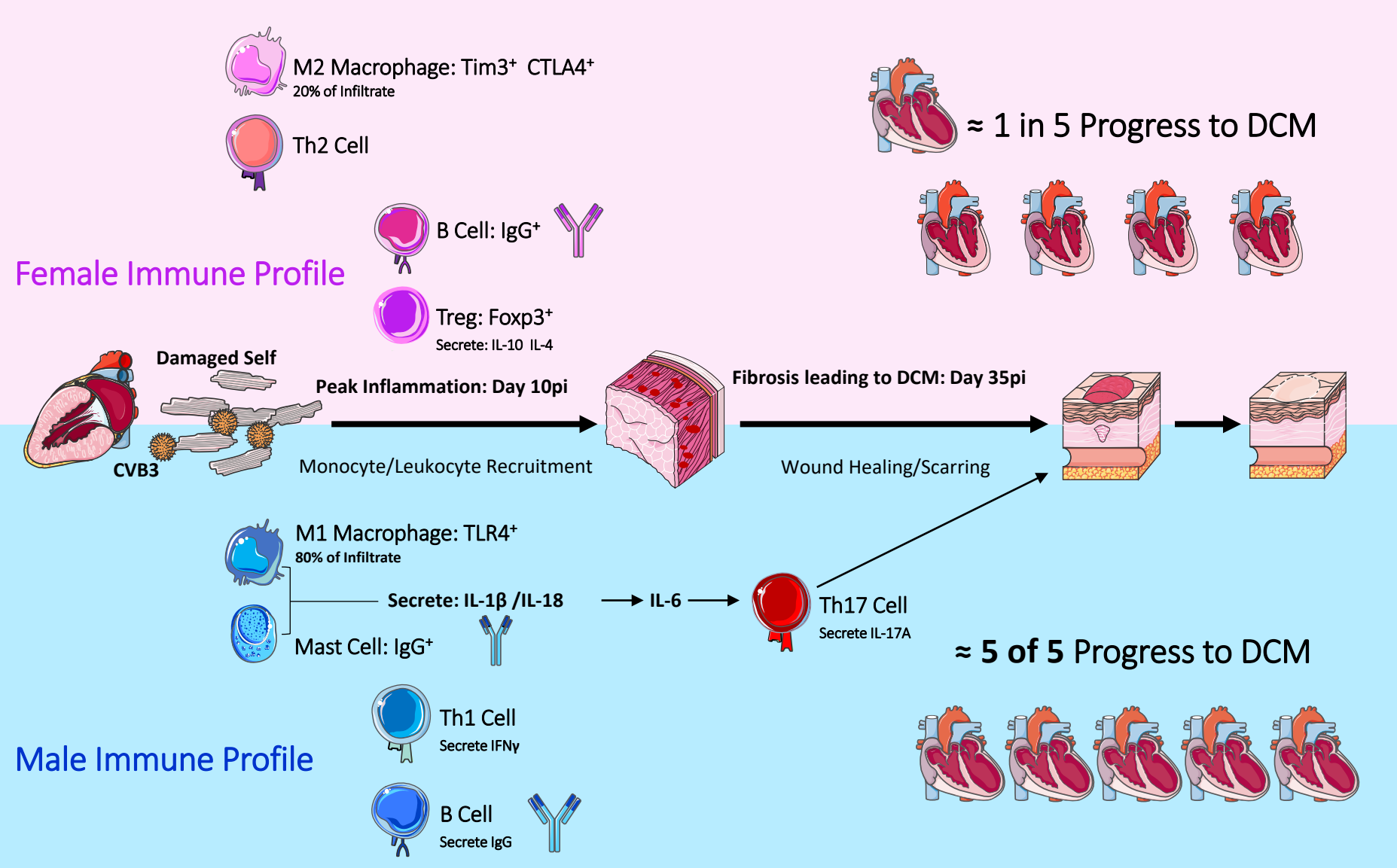


Frisancho-Kiss S, et al. (2007) *Cutting Edge J Immunol* 178: 6710-6714

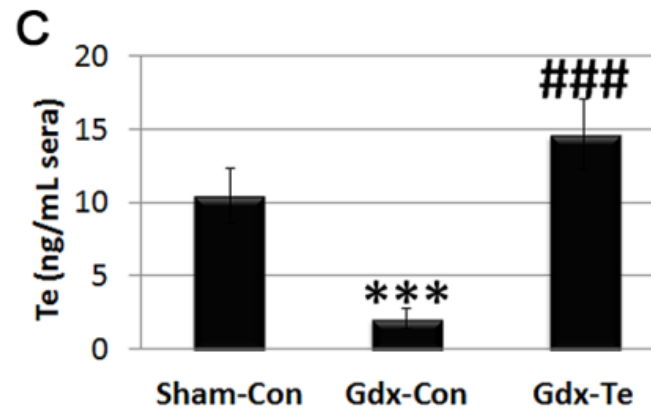
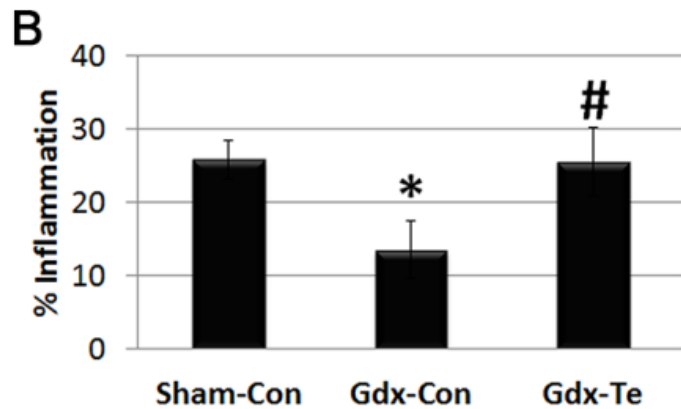
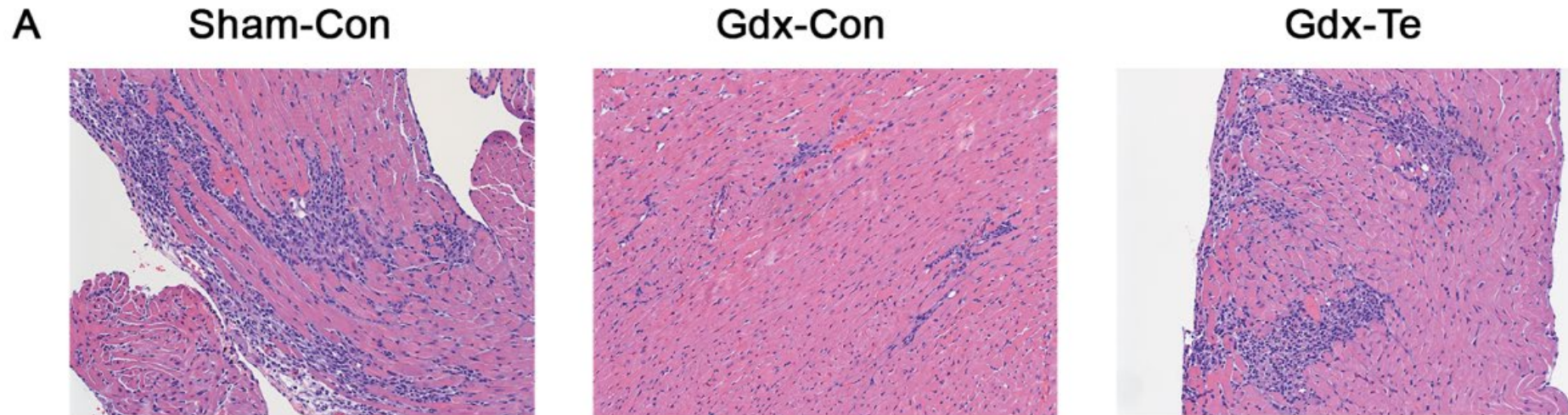
CD11b increased in male mice and men with myocarditis



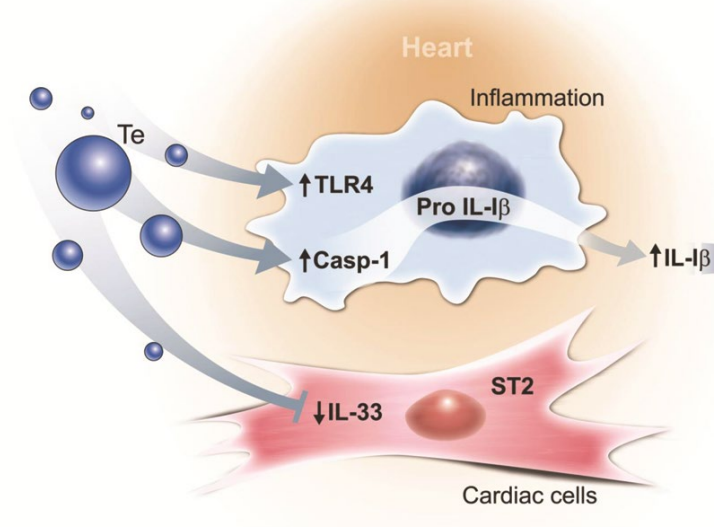
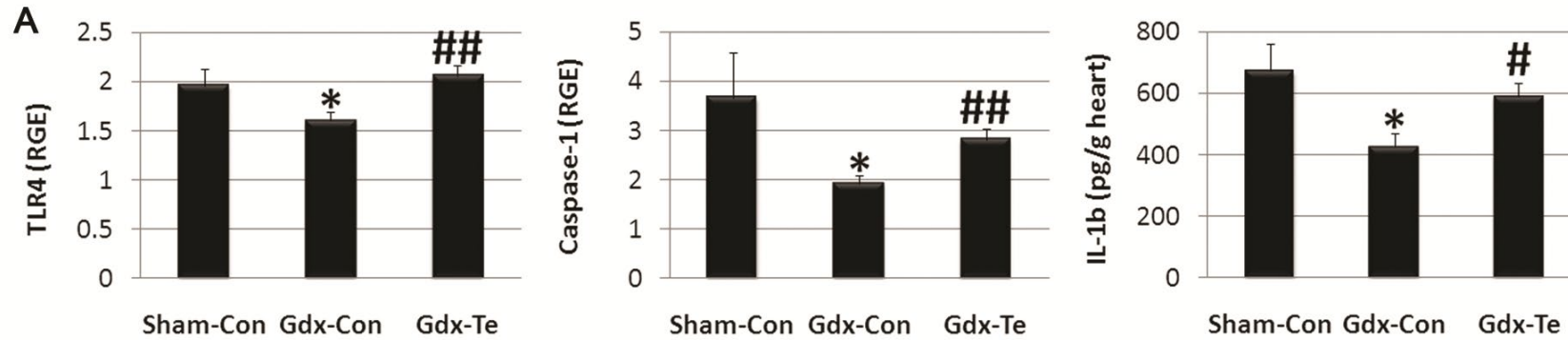
Sex Differences in the Immune Response in Myocarditis



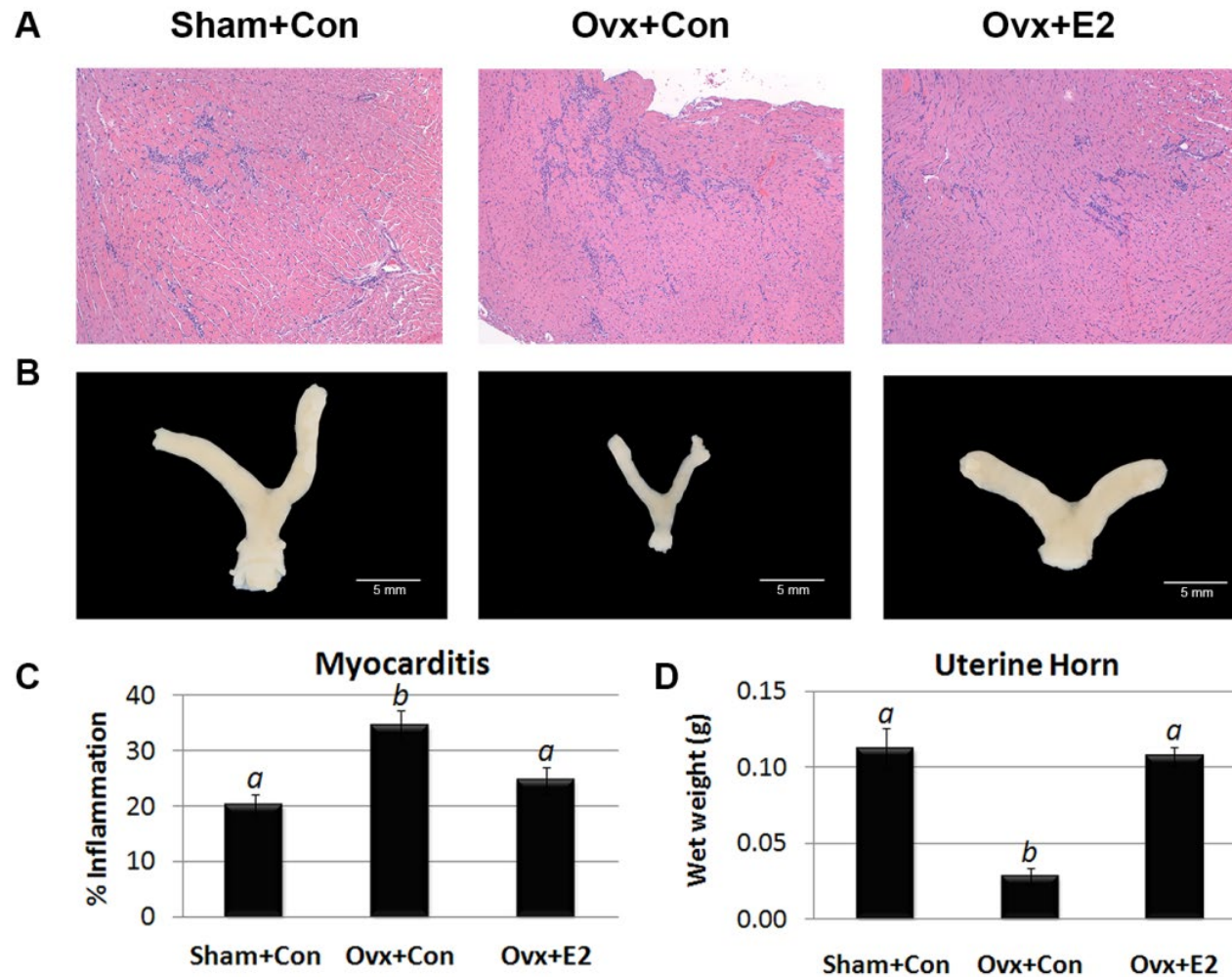
Testosterone increases myocarditis



Te increases TLR4/Casp1/IL-1 β and fibrosis

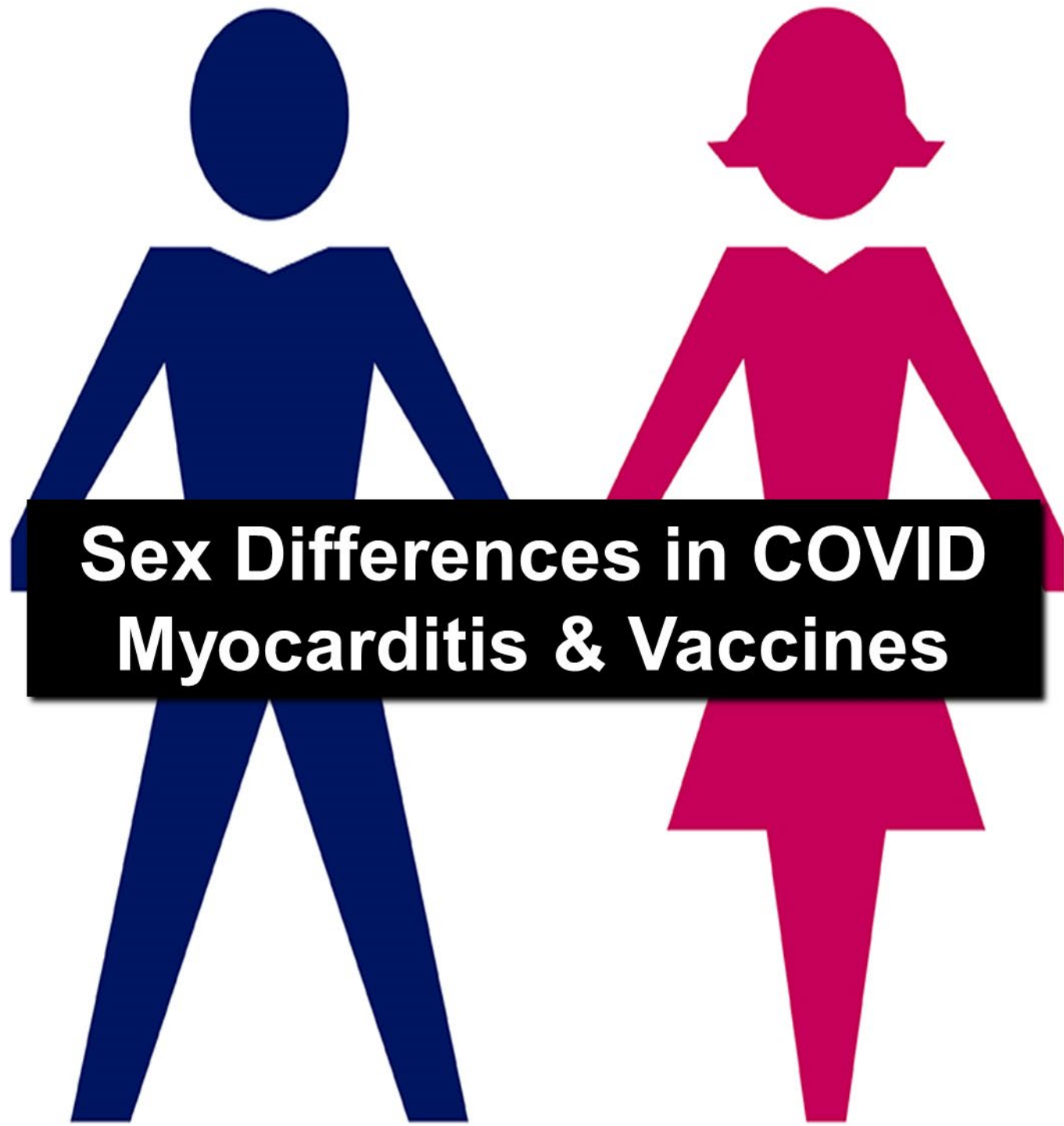


Estradiol reduces myocarditis



Summary Sex Differences Immune Response

- M increased TLR4, IL-1 β (proinflammatory & profibrotic), IL-18 (increases IFN γ /Th1), “Th1”
- M increased complement pathways: CD11b, C3, C4, C3aR, C5aR
- M increased Mast cells and Macrophages (M1 & M2b-TLR4)
- M increased IL-6, TGF β 1, IL-23, IL-17A, Th17 (profibrotic)
- Th2 response (MCs, M2b, IL-4, IL-33) required for DCM
- Sex hormones (not chromosomes) drive effects
- F make the same response to virus as M, but they regulate it better
- F increased T, B, antibodies, CR1, Th2/M2a, Treg, IL-10, IC, TNF (anti-inflammatory and anti-fibrotic)



**Sex Differences in COVID
Myocarditis & Vaccines**

Risk of death from viral myocarditis, COVID-19 vs. COVID-19 vaccine

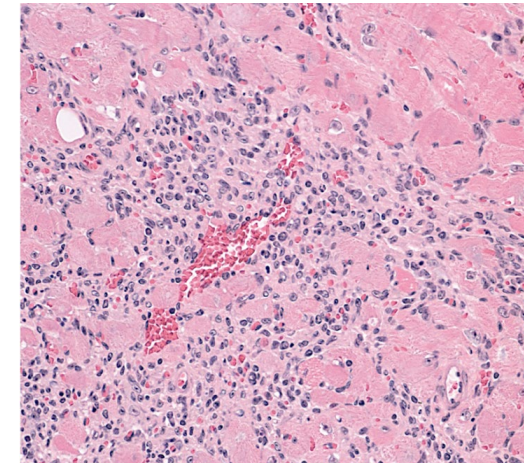
Table 1 | Characteristics of COVID-19-associated myocarditis and myocarditis after COVID-19 mRNA vaccination

Myocarditis type	Incidence	Survival (%)	Potential mechanisms
'Common' viral myocarditis	1–10 per 100,000 people per year	>80	Myocardial injury Genetic (variants in genes encoding HLA, desmosomal, cytoskeletal or sarcomeric proteins) Immune crossreactivity Sex-related factors
COVID-19-associated myocarditis and cardiac injury	1,000–4,000 per 100,000 people with SARS-CoV-2 infection	30–80	Endothelial injury and microthrombosis Genetic (variants in genes encoding HLA, desmosomal, cytoskeletal or sarcomeric proteins) Sepsis and shock
Myocarditis after COVID-19 mRNA vaccination	0.3–5.0 per 100,000 vaccinated people	>99	Hypersensitivity reaction Genetic (variants in genes encoding HLA, desmosomal, cytoskeletal or sarcomeric proteins) Immune crossreactivity Sex-related factors

COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Myocarditis after Covid-19 Vaccination

- **COVID-19:** Risk ratio of myocarditis associated with COVID-19 estimated to be 18.28
- 2.5 million vaccinated from health care system in Israel
- **Vaccine:** Risk ratio from a large study from Israel was 3.24
 - Incidence of myocarditis **2.13/100,000** cases 42 days after the first dose of the Pfizer-BioNTech mRNA vaccine
 - 4.12/100,000 **males** all ages
 - 0.23/100,000 **females** all ages
 - **10.69/100,000 for males age 16-29**
- 70% developed myocarditis after 2nd vaccine
- 80-100% presented with chest pain and elevated troponin
- 76% mild, 22% intermediate, 1 readmitted to hospital, 1 died



Males w/ COVID same level of virus but increased inflammatory markers

Open Forum Infectious Diseases

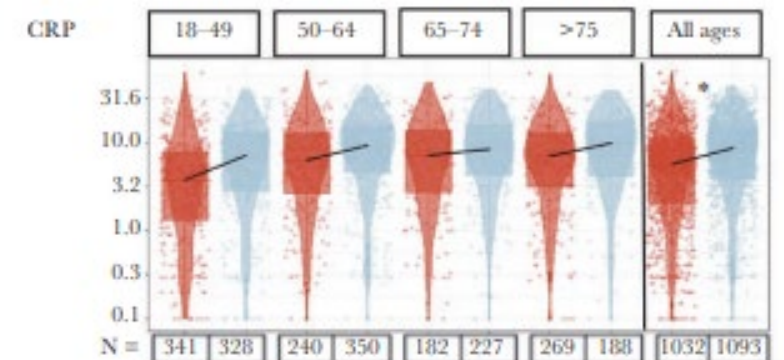
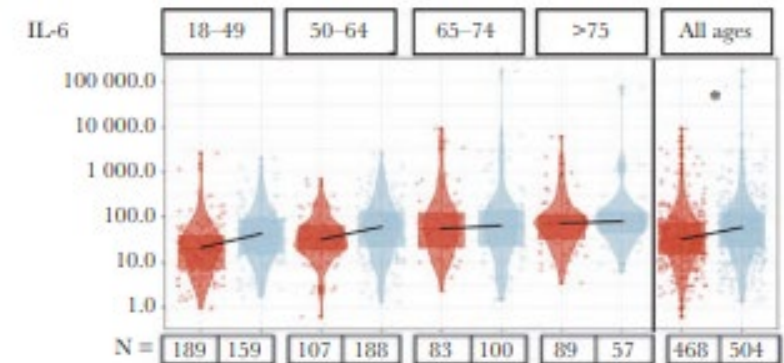
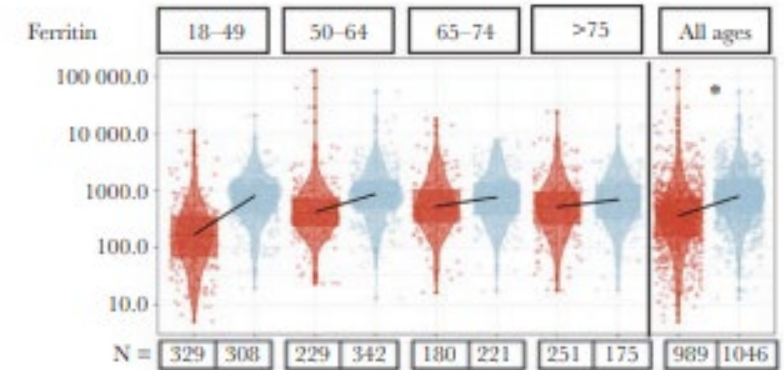
MAJOR ARTICLE



Sex and Gender Differences in Testing, Hospital Admission, Clinical Presentation, and Drivers of Severe Outcomes From COVID-19

Eileen P. Scully,^{1,4} Grant Schumock,² Martina Fu,² Guido Massaccesi,¹ John Muschelli,² Joshua Betz,² Eili Y. Klein,³ Natalie E. West,⁴ Matthew Robinson,¹ Brian T. Garibaldi,⁴ Karen Bandeen-Roche,² Scott Zeger,² Sabra L. Klein,^{5,6,4} and Amita Gupta^{1,7,4,8}, for the JH-CROWN registry team

Scully EP et al., Open Forum Infect Dis. 2021 Aug 31;8(9):ofab448.



COVID immune response 'same' as CVB3 myocarditis

- Elevated in COVID in males and during myocarditis in CVB3 animal model and myocarditis patients
 - Complement
 - CRP (not in mice)
 - TNF
 - IL-1 β (TLR4)
 - IL-18 (TLR4)
 - IL-6
 - IL-17/Th17

Males- monocytes/macrophages

Females- T cells

Thank You & Questions!!



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Bruno Lab Members:
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Leslie Cooper, MD
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