LUI &LEI:
la differenza di genere nella risposta immunitaria

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The female/male bias of immune-mediated diseases

Autoimmune diseases	Infectious diseases		Non-reproductive cancers
• Graves disease	• HIV	• Ebola	• Bladder
• Hashimoto thyroiditis	• Influenza	• MERS	• Bowel
• Multiple sclerosis	• Toxoplasmosis	• Hepatitis B	• Kidney
• Rheumatoid arthritis	• Legionella	• Tuberculosis	• Leukaemia
• Systemic lupus erythematosis	• Malaria	• Leptospirosis	• Liver
• Type 1 diabetes	• Zika	• Campylobacter	• Lung
		• Schistosomiasis	• Malignant melanoma
		• Amebiasis	• Oesophagus
		• Aspergillosis	• Stomach

The three items on the table

1. Sex and the immune system;
2. Sex differences in the response to infections and vaccines;
3. Sex and autoimmune diseases

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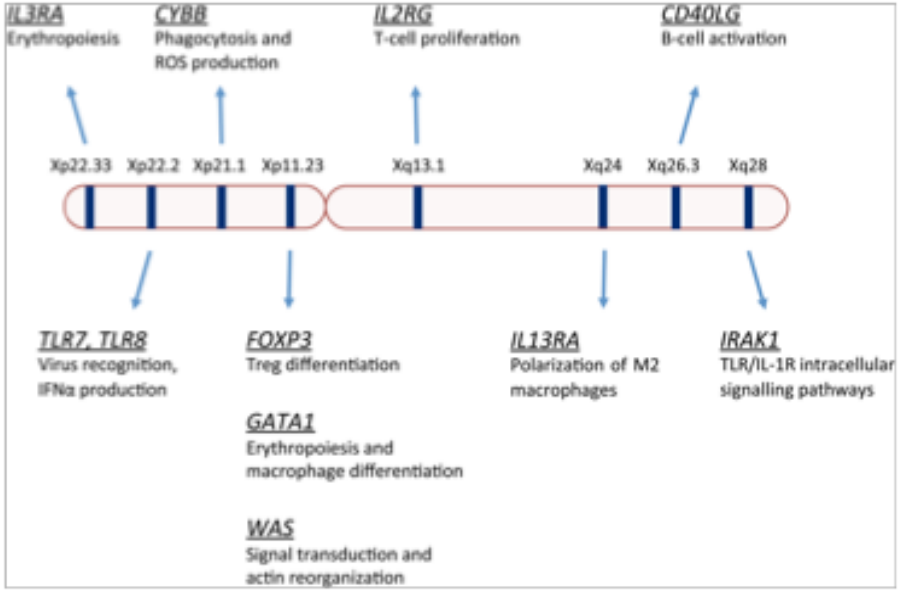
Sex modulates the *innate* immune response



Hormone	Role
Estrogen	• Dampens the expression of IL-6
	• Dampens the signaling of IL-1β in hepatocytes
	• Modulates the apoptosis of neutrophils
	• Modulates the chemotaxis and recruitment of neutrophils
	• Increases the expression of TLR4 and CD14 on macrophages
	• Increases the production of IFN-α by pDCs after stimulation with TLR7 ligands
	• Increases the differentiation of DCs from myeloid precursors
	• Increases the activation of DCs and their capability to activate CD4+ T cells
	• Beneficial effects on the immune system during hormone replacement therapy in women
Testosterone	• Immunosuppressive effects (dampens the production of cytokines and the proliferation of lymphocyte)
	• Increases neutrophil activation during non-infectious inflammatory states
	• Neutropenia is observed in mice lacking androgen receptor
	• Reduces the expression of TLR4 in macrophages

Jaillon S, CRAI. 2019

Sex modulates the *adaptive* immune response

Adaptive immunity functions	Males	Females
Thymus size	+++	
CD4 + T cell counts and CD4/CD8 T cell ratio		+++
CD8 + T cell counts	+++	
Active T cells		+++
T cell proliferation		+++
Increased cytotoxic T cells		+++
Th2 cell bias > Th1 cell bias		+++
Treg cells number	+++	
B cell number and antibody production		+++

Selmi C, Exp Rev Clin Immunol. 2019

Impact of sex hormones on immune homeostasis

Immune component	Effect of sex hormones*		
	Oestradiol	Progesterone	Androgens
TLRs	↑TLR4, TLR7 and TLR9	↓TLR3 and TLR7	↓TLR4
Macrophages	↑TLR4	↓iNOS and NO ↑FIZZ1 and YM1	↓iNOS/ NO ↓TNF
NF-κB	↓Activity	↓Activity	↓Activity
DCs	↑Activation ↑TLR7and TLR9 ↑CCL2 ↓CXCL10 ↓IFNα	↓CD40, CD80, CD86 and ↑CD11c ↑IL-18 and IL-10	ND
Neutrophils	↑Numbers ↑Degranulation ↑Elastase release	ND	↑Numbers ↓Kinases and leukotriene formation
NK cells	↑IFNγ ↑Granzyme B ↓FASL	↑Numbers ↑Apoptosis (caspase dependent)	ND
Eosinophils	↓Numbers ↓Mobilization	↑Numbers	ND

Immune component	Effect of sex hormones*		
	Oestradiol	Progesterone	Androgens
Inflammatory cytokines	Low oestrogen: ↑IL-1β, IL-6, andTNF High oestrogen: ↓L-1β, IL-6 and TNF	↓TNF and IFNγ ↑IL-6	↑IL-1β and IL-2 ↓TNF
Suppressive cytokines	↑IL-4, IL-10 and TGFβ	↑IL-4, IL-5 and TGFβ	↑IL-10 and TGFβ
Chemokines	↓CCL2 ↑CXCL1	↓CXCL2	↓CCL3
T_H1 cells	Low oestradiol: ↑Activity	↓Activity	↓IFNγ
T_H2 cells	High oestradiol: ↑Activity	↑Activity	↓IL-4 and IL-5 ↓GATA3
T_H17 cells	↓Numbers ↓IL-17	↓Percentages	↑IL-17
T_{reg} cells	↑Numbers	↑Percentages	↑Numbers
$CD8^+$ T cells	↑Response	↓Response	↓Numbers ↓Activity
B cells	↑IgG and IgM	↓CD80 and CD86	ND
Antibody responses	↑Response	↑Total antibody ↓Autoantibodies	↓Response

Klein SR et al. Nat Rev Immunol 2016

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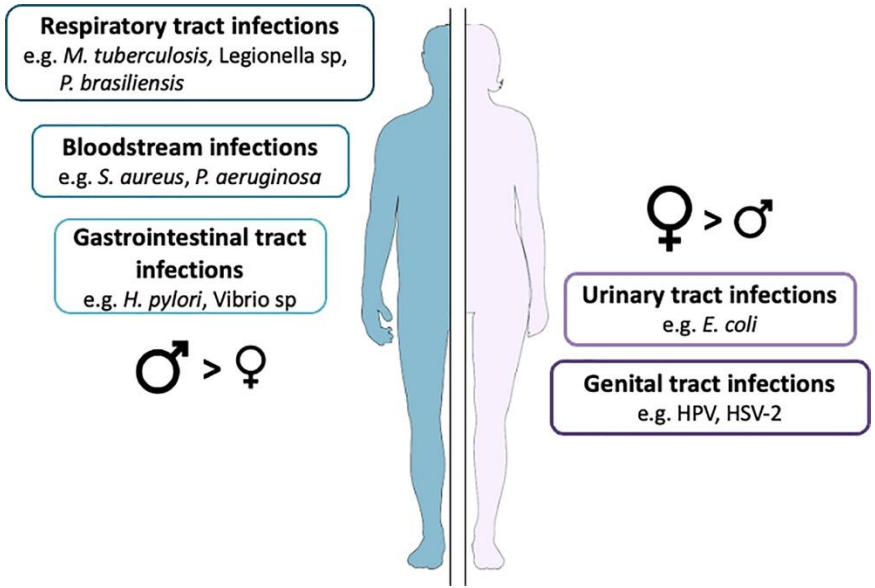
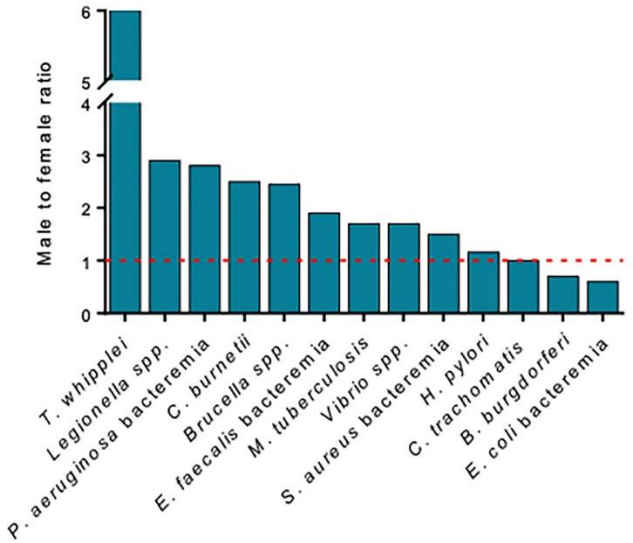
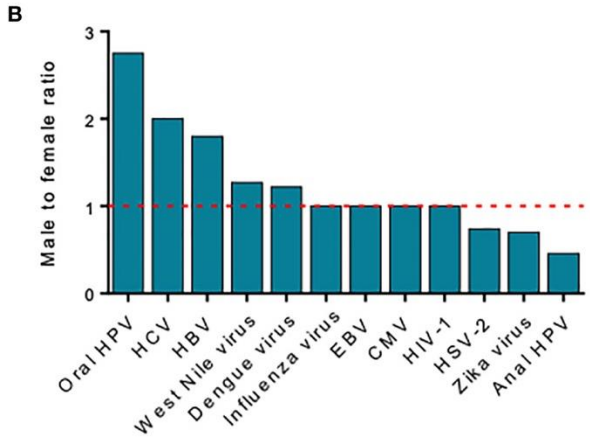
Sexual Dimorphism in the sites of infection and infectious agents

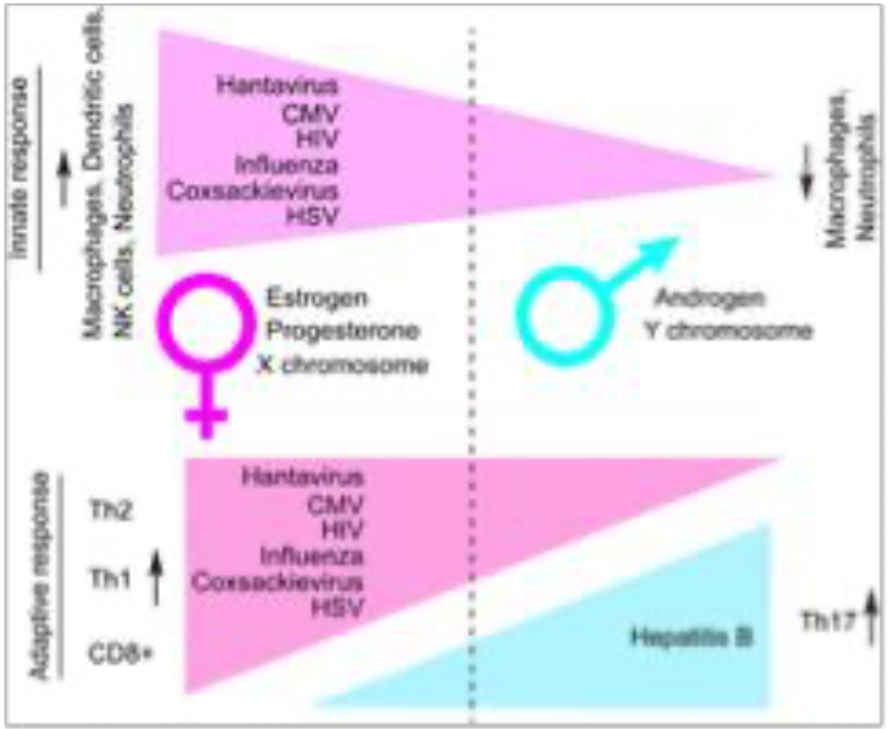






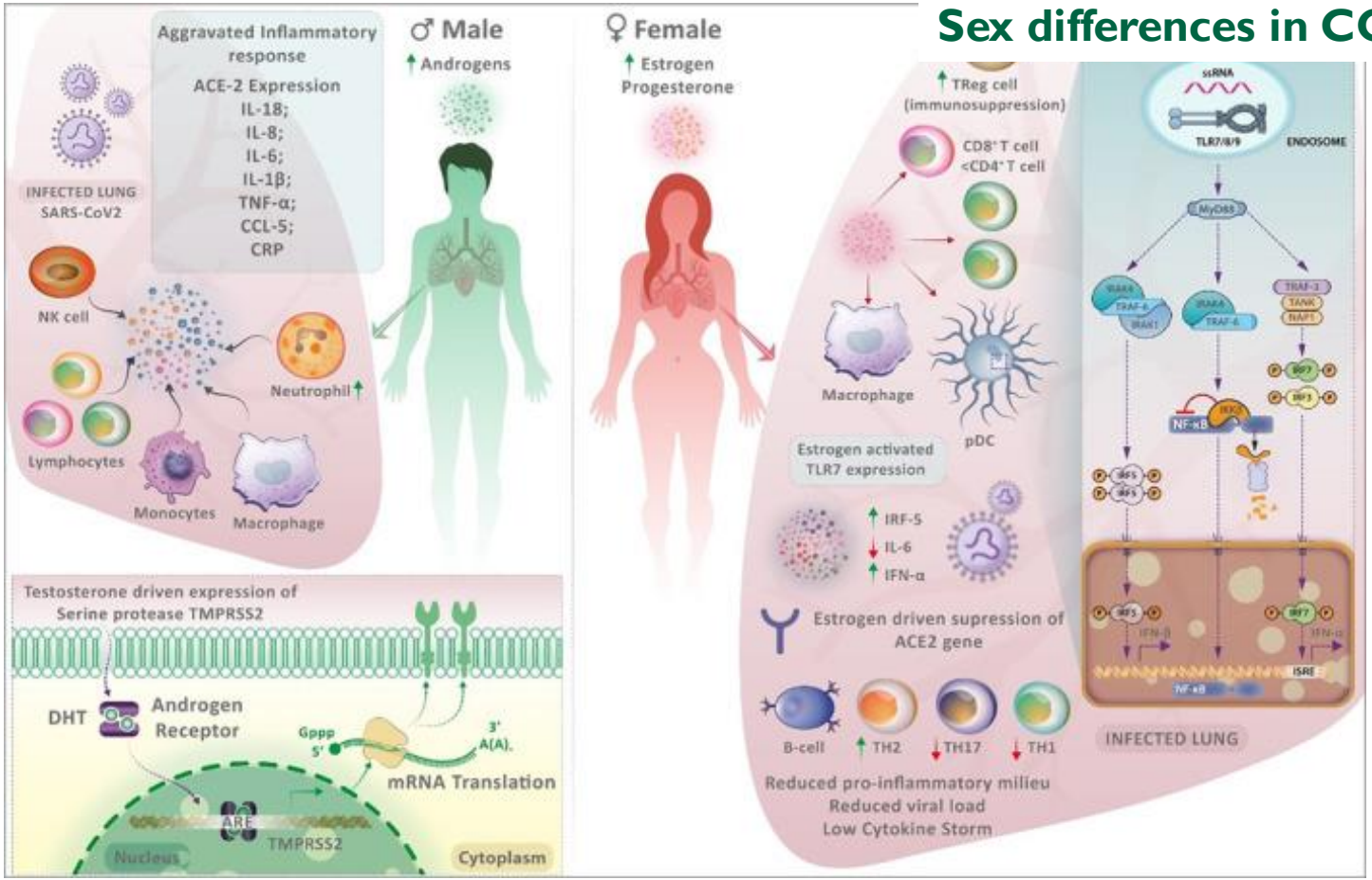
Gay L, Front Immunol. 2021; Plummer, Lancet Glob Health. 2016

Sex Drives Dimorphic Immune Responses to Viral Infections



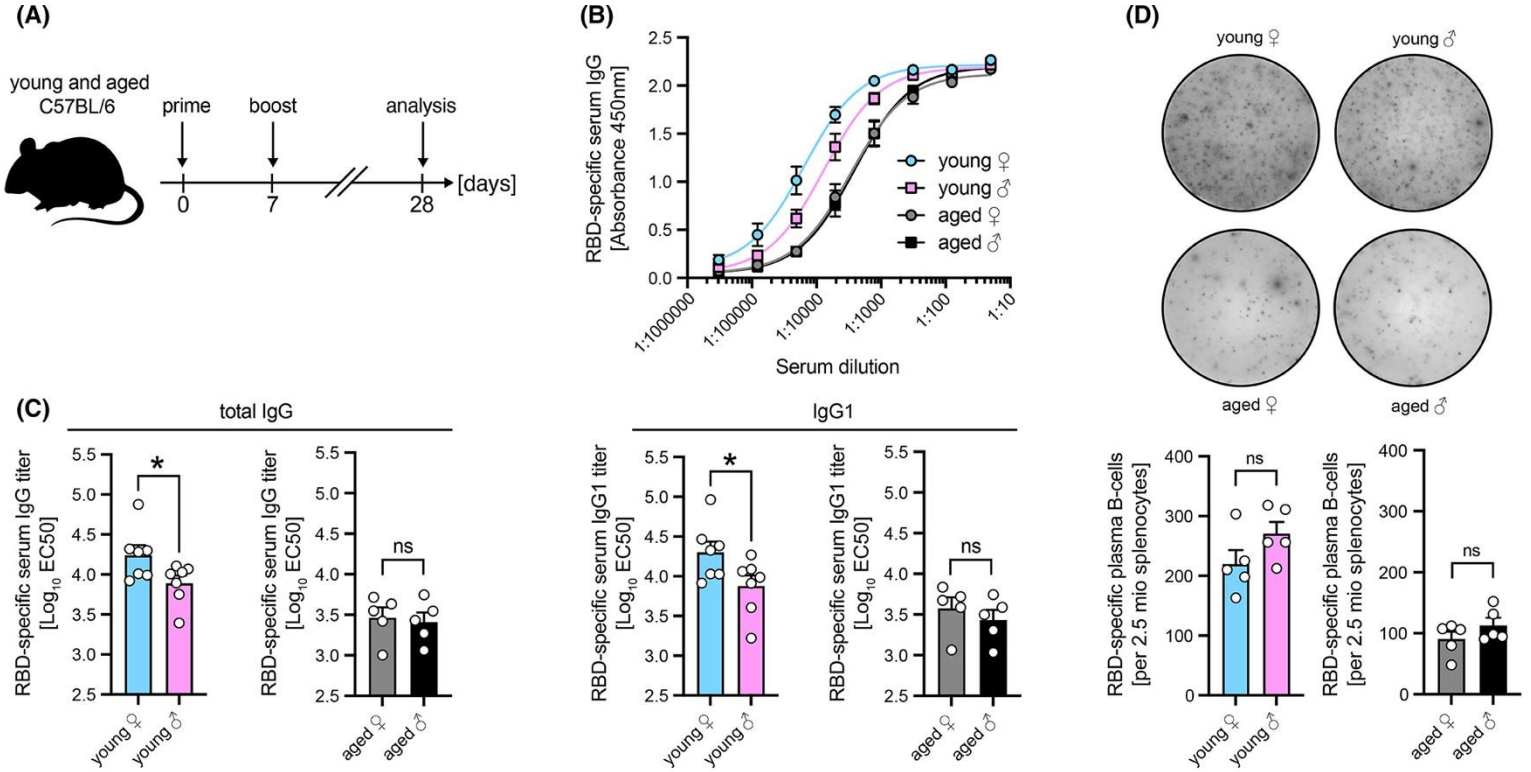
Ghosh, J Immunol. 2017

Sex differences in COVID-19



Ho, Immunology 2022

Sex-specific differences in immune response to SARS-CoV-2 vaccination



Brigger, Allergy 2023

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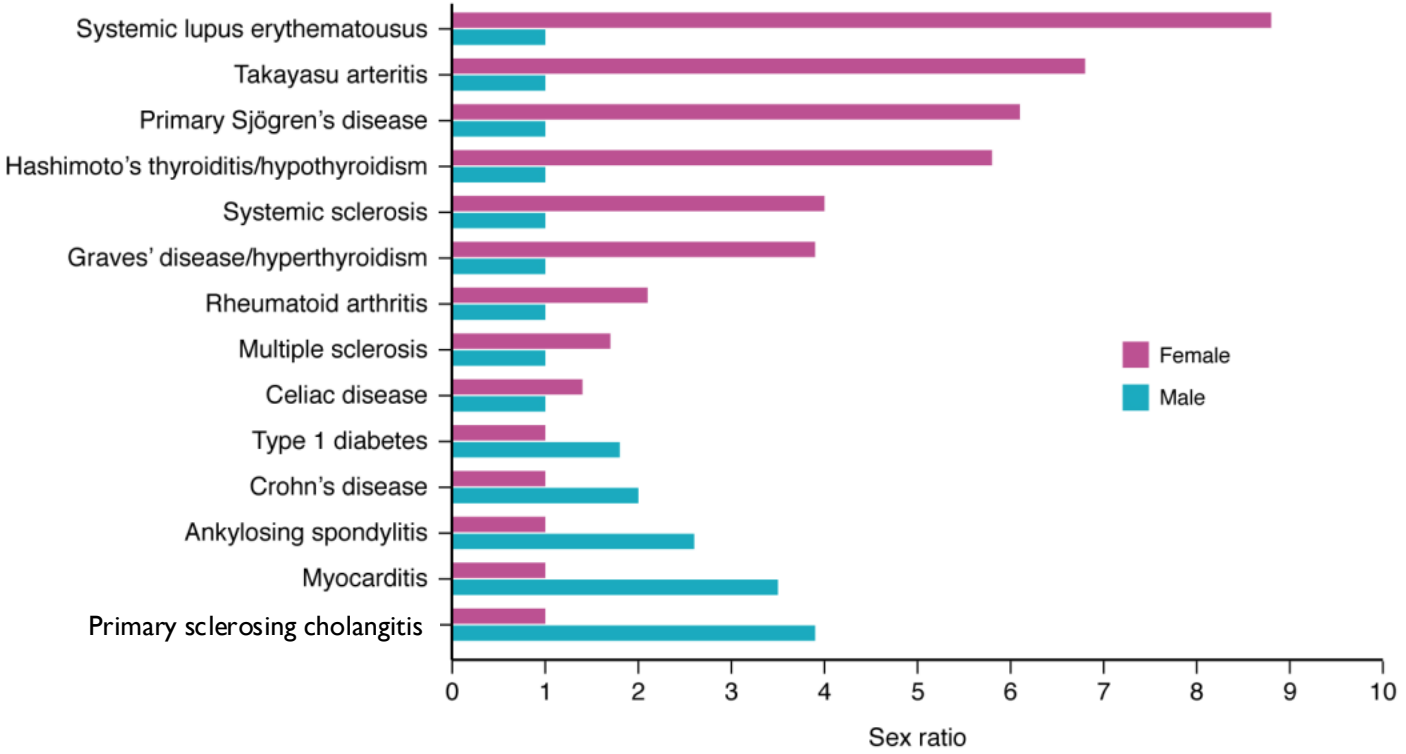
Sex ratio in autoimmune diseases



DeLisa Fairweather, et al. J Clin Invest 2024

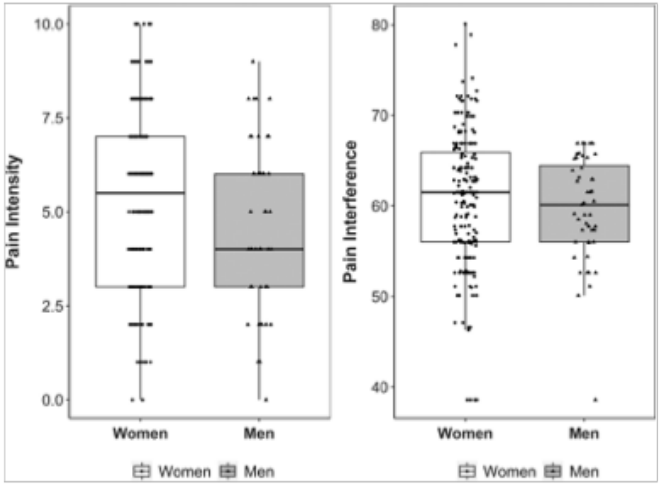
Sex differences in clinical features

J Rheumatol. 2025 Jun 1;52(6):553-562. doi: 10.3899/jrheum.2024-1258.

Sex Differences in Rheumatoid Arthritis: New Insights From Clinical and Patient-Reported Outcome Perspectives

Gonul Hazal Koc [1], Agnes E M Looijen [2], Irene E van der Horst-Bruinsma [3], Pascal H P de Jong [2]

- higher disease activity
- greater need for bDMARDs
- lower efficacy of bDMARDs
- more functional impairment



Sex Differences in Pain and Quantitative Sensory Testing in Patients With Rheumatoid Arthritis

Kelly Vogel,[1] Lutfiyya N. Muhammad,[1] Jing Song,[1] Tuhina Neogi,[2] Clifton O. Bingham,[3] Marcy B. Bolster,[4] Wendy Marder,[5] Alyssa Wohlfahrt,[6] Daniel J. Clauw,[5] Dorothy Dunlop,[1] and Yvonne C. Lee[1]

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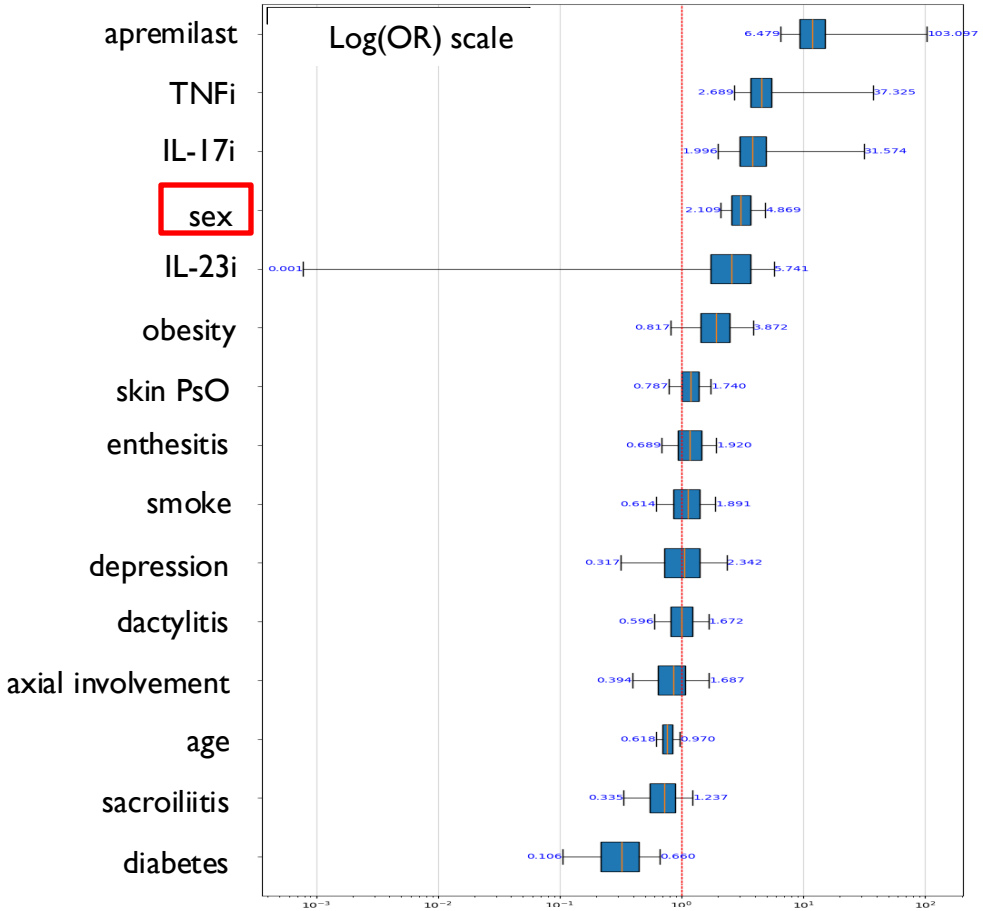

Predictors of b/tsDMARD discontinuation in psoriatic arthritis

Tonutti A et al (SIR 2025; *manuscript in preparation*)

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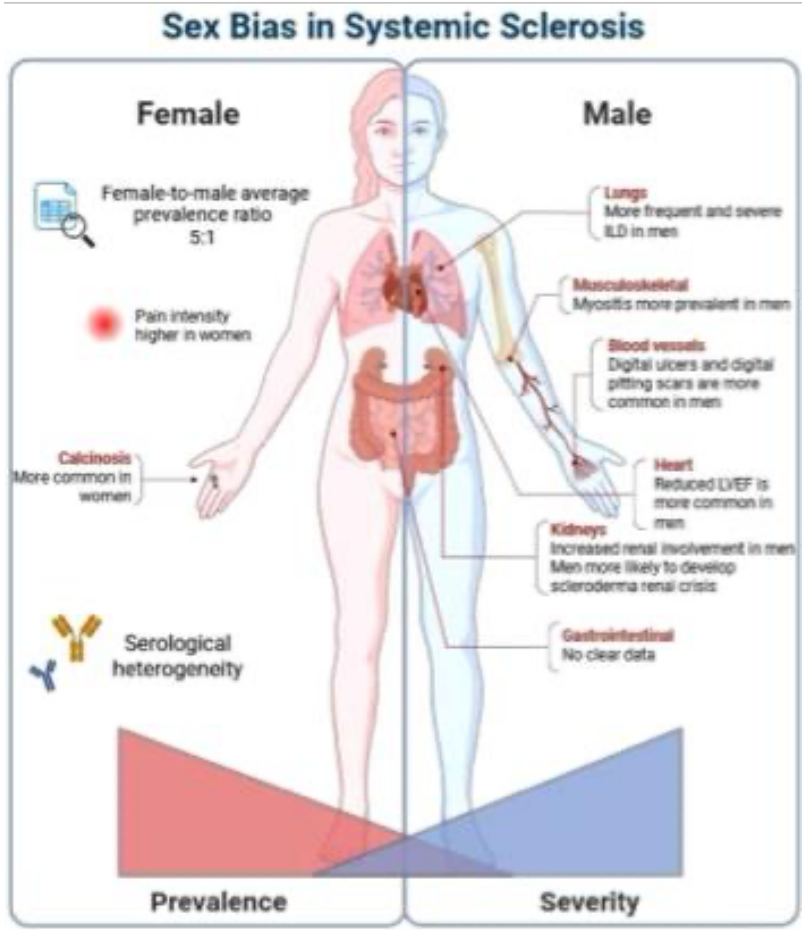
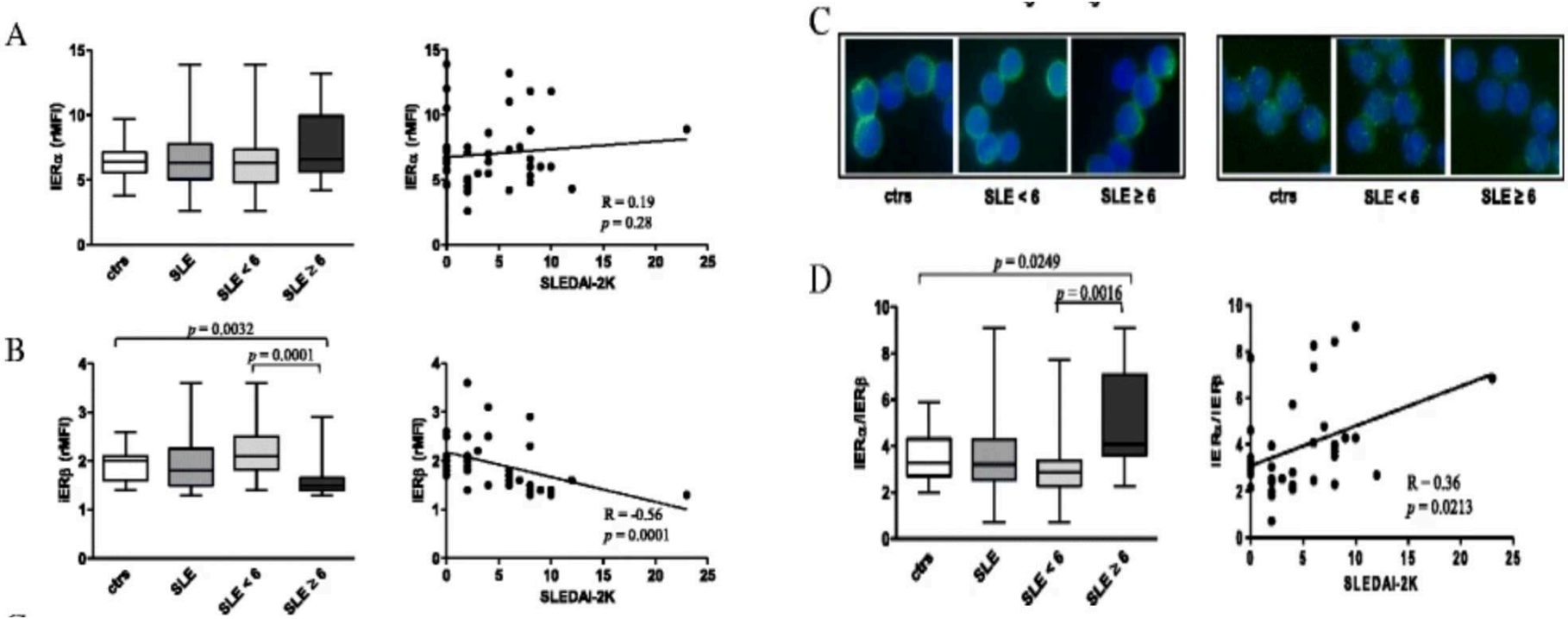


Toitou, TADM 2025; Tarannum, NRR 2022

Table 1 | **Sex and gender differences in development and symptoms of psoriatic arthritis (PsA)**

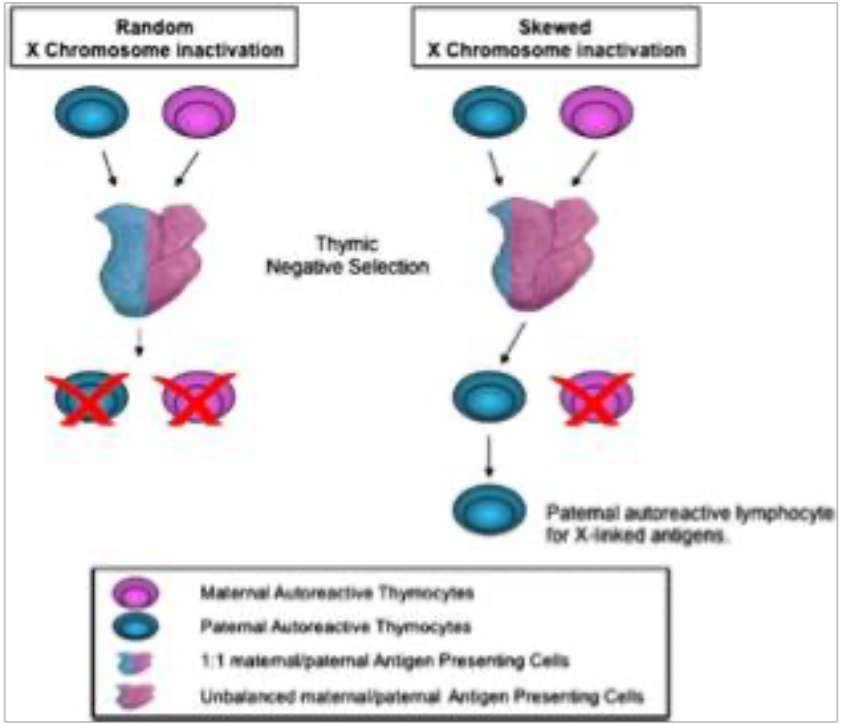
Factors related to PsA development	Sex and/or gender related	Evidence in the literature
Risk factors		
Genetic susceptibility	Sex related	Parent-of-origin effect (genomic imprinting); probands are more likely to have an affected father than mother[164,165].
Environmental	Sex and gender related	No sex difference in known risk factors, such as physical trauma, obesity, uveitis, severe psoriasis, flexural and scalp psoriasis and psoriatic nail lesions[167].
Sex hormones		
Testosterone	Sex related	Inversely correlated with disease activity in male patients with PsA[174].
		Low levels associated with chronic pain[180].
Oestrogen	Sex related	Not associated with disease activity in PsA[174].
		Inhibits development of arthritis in animal models[178].
		Has both pro-nociceptive and anti-nociceptive properties[181].
		Periods of fluctuation of female sex hormones in a woman's life, such as postpartum, breastfeeding and post-menopause, are not associated with PsA development[73,165].
		Sex hormone-containing medications, such as oral contraceptives, hormone replacement therapy and fertility treatments are not associated with PsA development[73,168].
Progesterone	Sex related	Has both pro-nociceptive and anti-nociceptive properties[181].
Prolactin	Sex related	Possible mediator of arthritis pain[180].
Selective oestrogen receptor modulator	Sex related	Inhibits joint inflammation in animal models[179].
Pain		
Pain processing	Sex related	Higher pain stress response in ovulating female mice[180].
		Spinal microglial cells mediate persistent pain hypersensitivity in male mice only[180].
		Significant upregulation of μ-opioid receptor in male mice only[168].
		Anti-depressant (fluoxetine) exerts analgesic effect in chronic pain in female mice only[168].
Pain perception	Gender related	Women experience pain in more sites, with greater severity, higher frequency and longer duration than men[160].
Pain reporting	Gender related	Women have less tolerance of pain and report pain more often than men[161].
		Men tend to ignore, suppress, or withstand pain.
		Pain sensitivity is influenced by childhood sexual abuse and family history of pain only in women[351].

Estrogens and lymphocytes in SLE



Masellia A., et al. Biology of sex difference 2016

Defining the X in autoimmunity



Selmi C, Autoimmun Rev 2012; Dou D, Cell 2024

Ageing and sex-related differences in autoimmune diseases

Age attenuates sexual dimorphisms in SLE

	Early-onset SLE (age <50 y)	Late-onset SLE (age ≥50 y)
Epidemiology		
Frequency (compared to all SLE cases)	82–97%	3–18%
F/M sex ratio	Higher F/M sex ratio (from 9 to 14.4)	Lower F/M sex ratio (from 2.5 to 9)

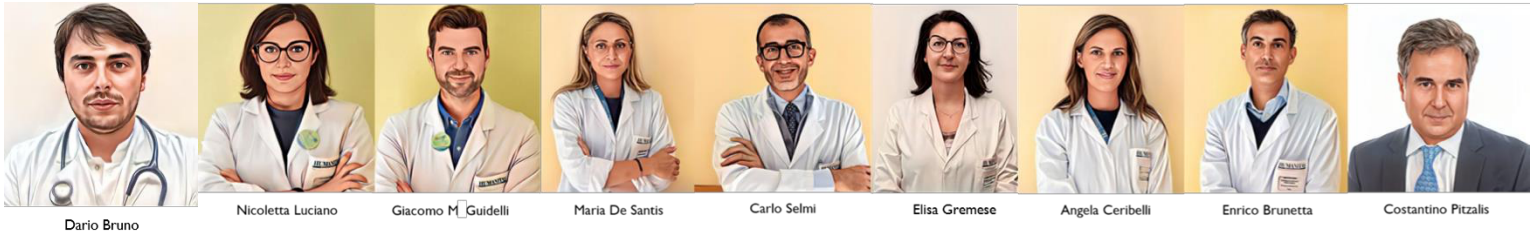
But has limited influence in SSc

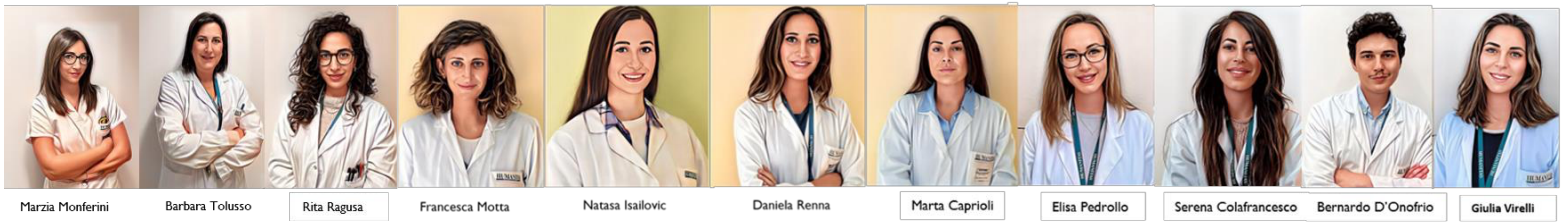
	Whole cohort (N = 1893)	SSc onset ≥70 (N = 160)	SSc onset <70 (N = 1733)	Adj. p (a)
Demographic features				
Female sex	1677/1889 (89)	149/160 (93)	1528/1729 (88)	0.149
Disease duration, yrs	8 (4–15) [1891]	4 (1–7) [160]	9 (4–15) [1731]	0.001*
Age at RP onset, yrs	45 (34–56) [1885]	72 (69–75) [158]	44 (33–54) [1727]	0.007*
Age at SSc onset, yrs	50 (39–60)	74 (72–76) [160]	48 (38–57) [1733]	0.012*

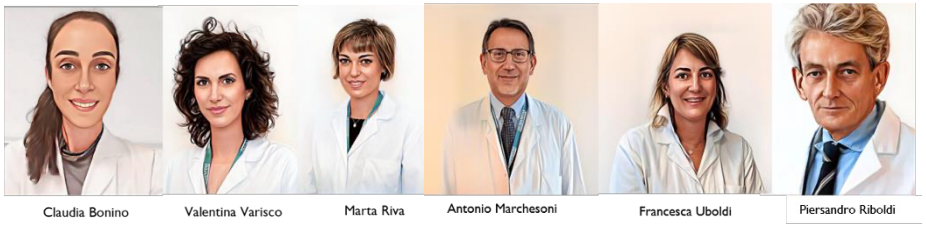
Arnaud L, Drugs and Ageing 2012; Tonutti A, J Autoimmun. 2025

Take-home messages

- Sex hormones regulate the innate and acquired immune response and decline differences in homeostasis between sexes;
- Different susceptibility and immune responses characterize sexes to infectious agents and vaccines;
- Impaired sex ratios for incidence and prevalence of autoimmunity;
- Sex differences in autoimmune diseases are not fully explained by mechanistic differences in the immune response (comorbidities and pain perception contribute to treatment response)







Thanks for your attention

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