BIO-312 Genomic Solutions to Sustainable Development

For interactive questions

Web browser: **echo360poll.eu**

Session ID:

Sex differences in immunity

Sex Differences in Immunity

Sex-based Immune Differences

Explore the biological and physiological variations in immune function between males and females.

Genetic Factors

Examine the role of genetic factors in shaping sex-based differences in immunity.

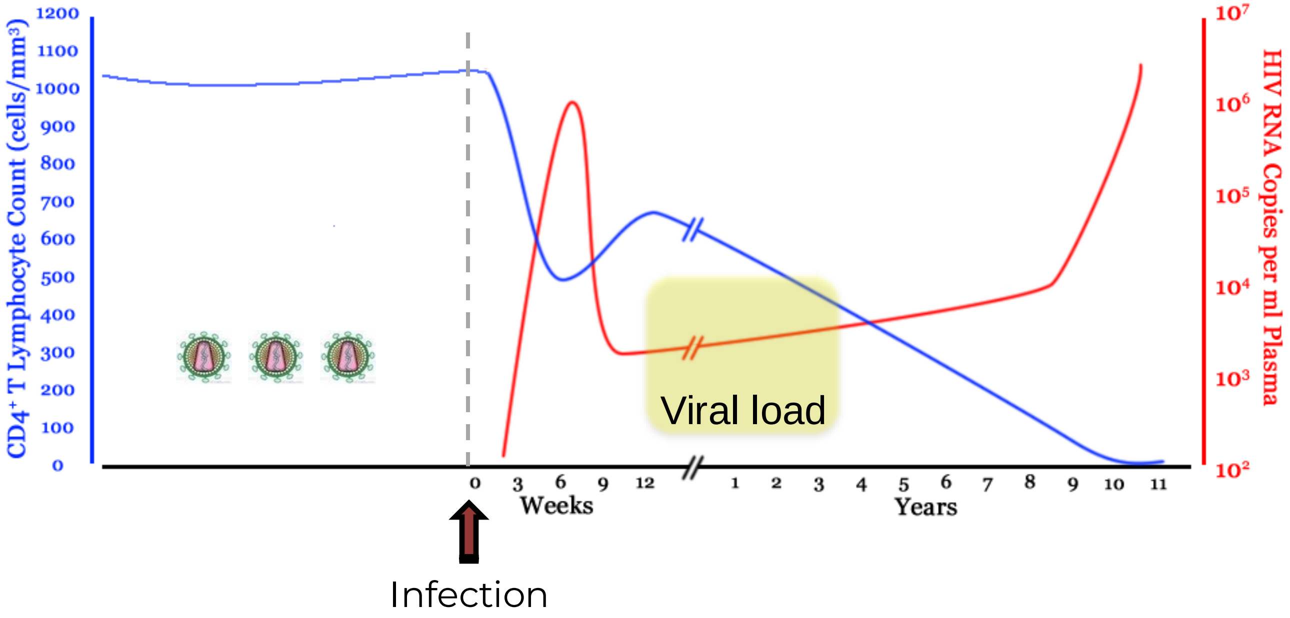
Hormonal Influences

Discuss how sex hormones, such as estrogen and testosterone, impact the immune system's response.

Implications for Health and Disease

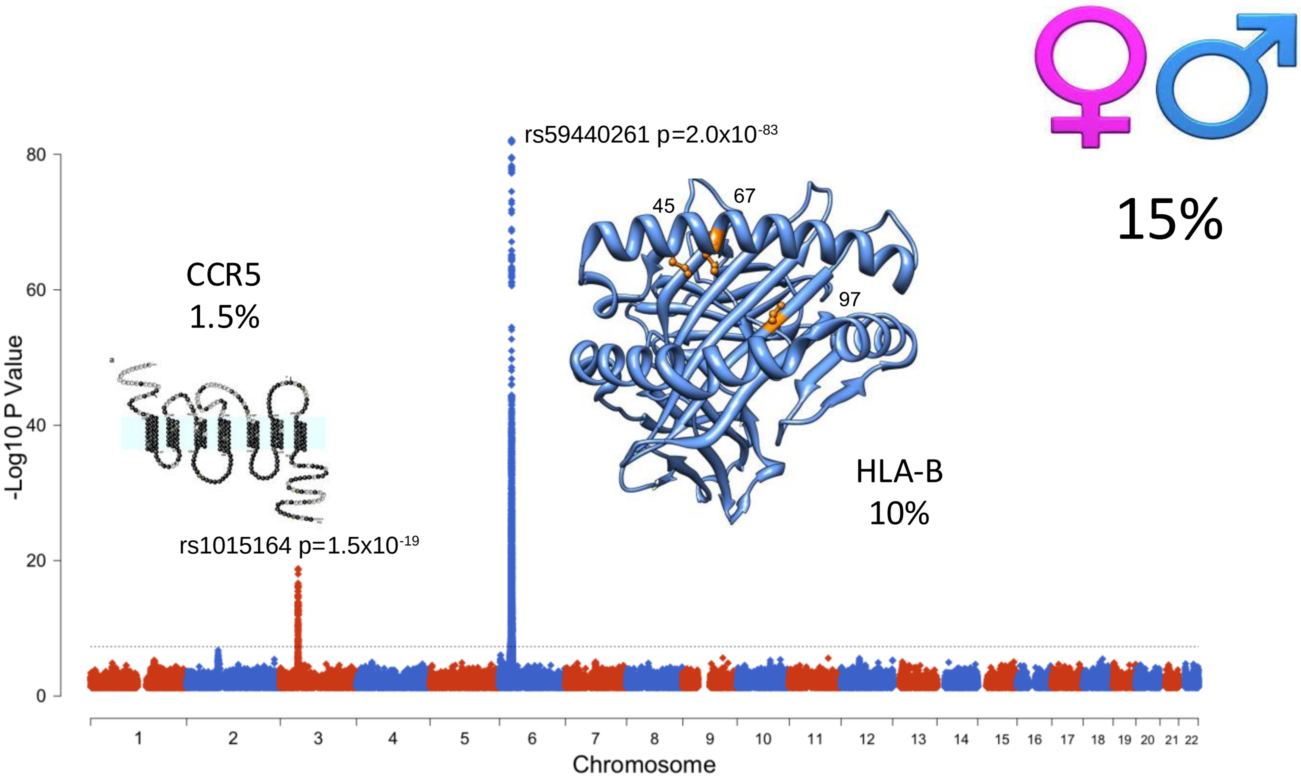
Explore how sex-based immune variations affect the prevalence, severity, and treatment of various health conditions.

HIV control



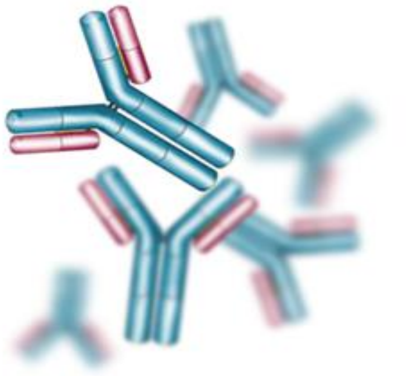
CD4+ T Lymphocyte Count (cells/mm3)
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
HIV RNA Copies per ml Plasma
107
106
105
104
103
102
0 3 6 9 12
Weeks
1 2 3 4 5 6 7 8 9 10 11
Years
Viral load
Infection

HIV control



McLaren et al., PNAS 2015 + JID 2017

IgG responses to common infections



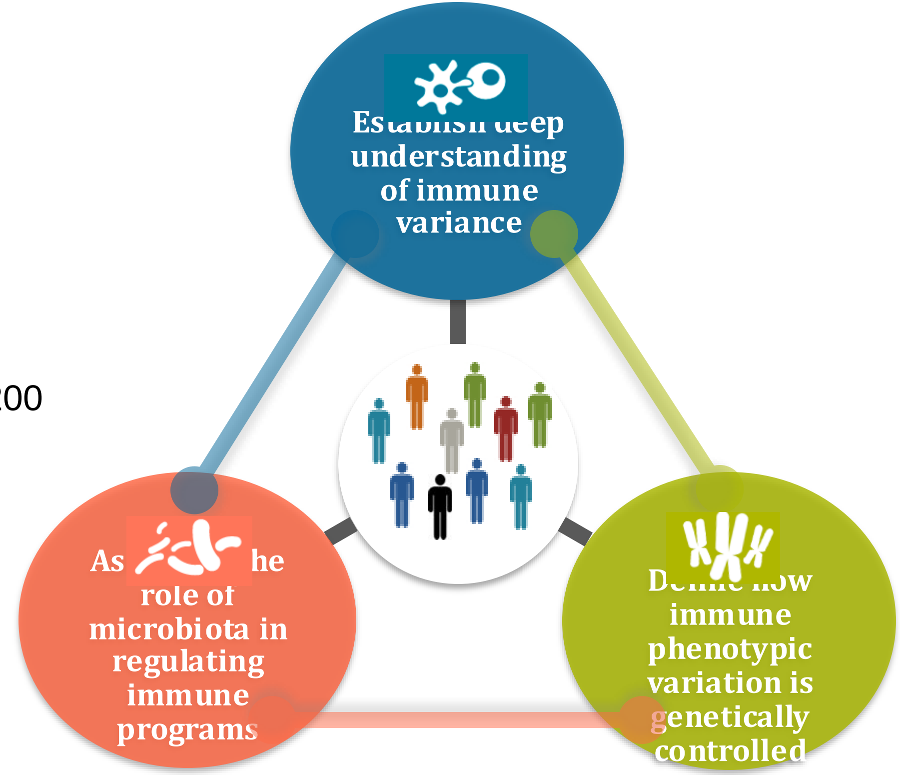
- Indicator of past infection or vaccination
- Correlate of protection (variable)
- Relevance for autoimmune disorders

Genomics of the healthy immune response

Milieu Intérieur
Vers une médecine personnalisée

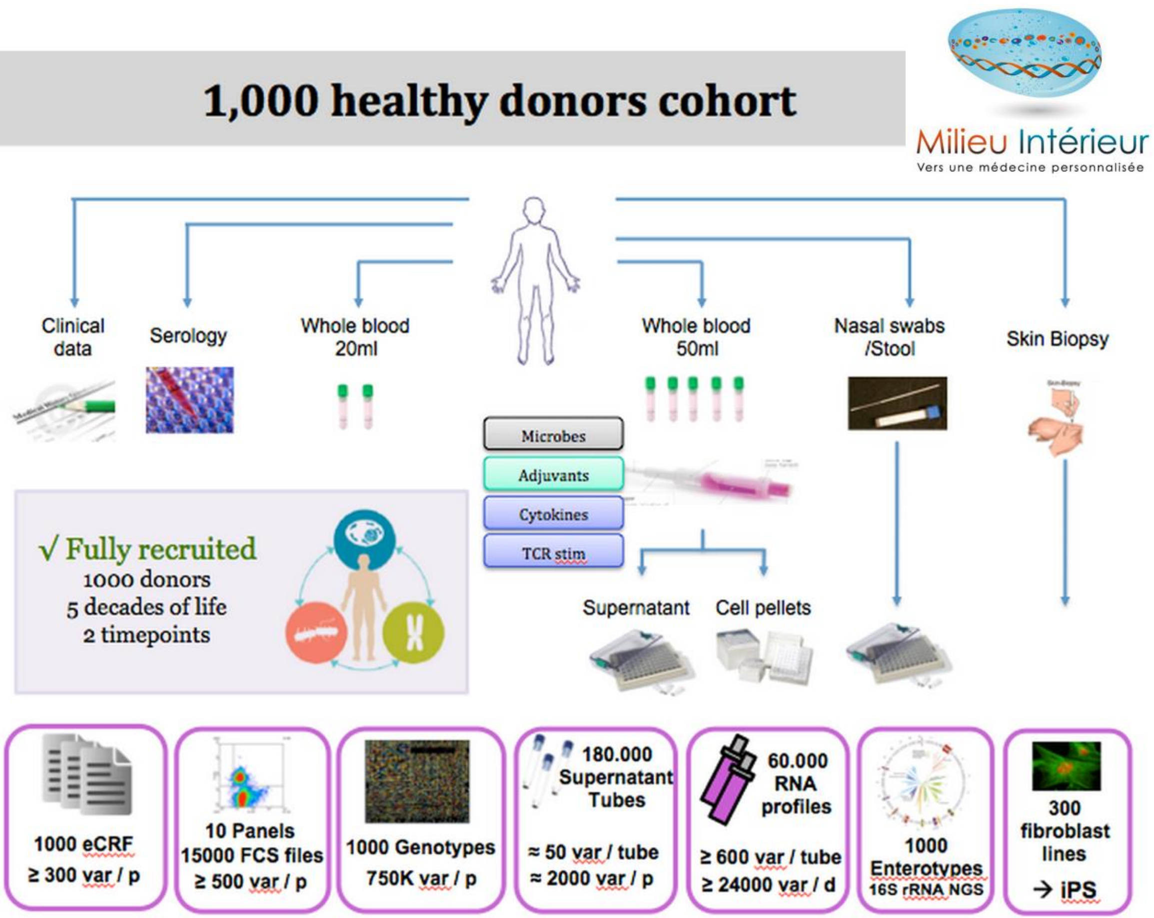
Healthy individuals, stratified by

- age (20 to 70, 200 per decade)
- **gender (1:1 ratio)**

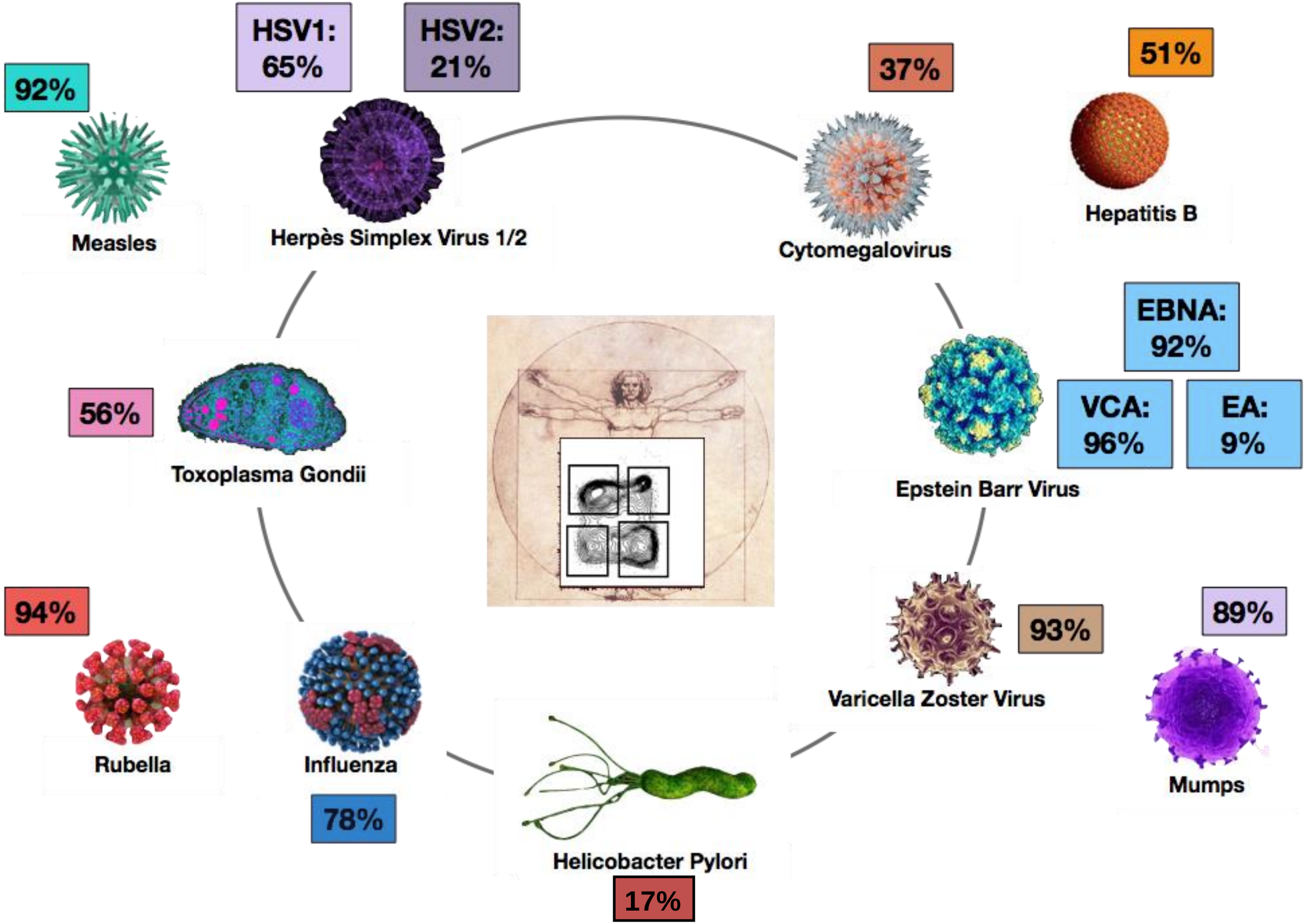


http://www.milieuinterieur.fr/

1,000 healthy donors cohort

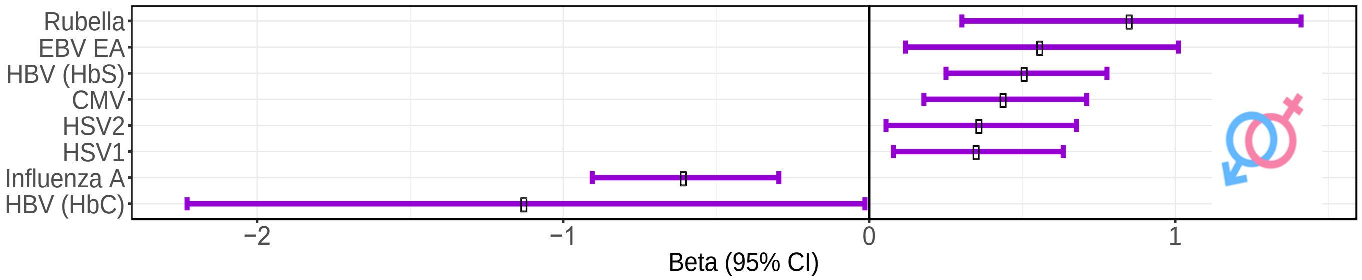


http://www.milieuinterieur.fr/



92%
Measles
HSV1: 65%
HSV2: 21%
Herpès Simplex Virus 1/2
37%
Cytomegalovirus
51%
Hepatitis B
56%
Toxoplasma Gondii
EBNA: 92%
VCA: 96%
EA: 9%
Epstein Barr Virus
94%
Rubella
Influenza
78%
93%
Varicella Zoster Virus
89%
Mumps
Helicobacter Pylori
17%

Impact of sex on IgG levels



Scepanovic et al. Genome Medicine 2018

Science

Why the coronavirus is killing more men than women

Men have weaker immune systems that, in some cases, may actually sabotage the body's response to an invader. But social and cultural factors may also play a role.

The Washington Post
Democracy Dies in Darkness

Why are women more prone to long Covid?

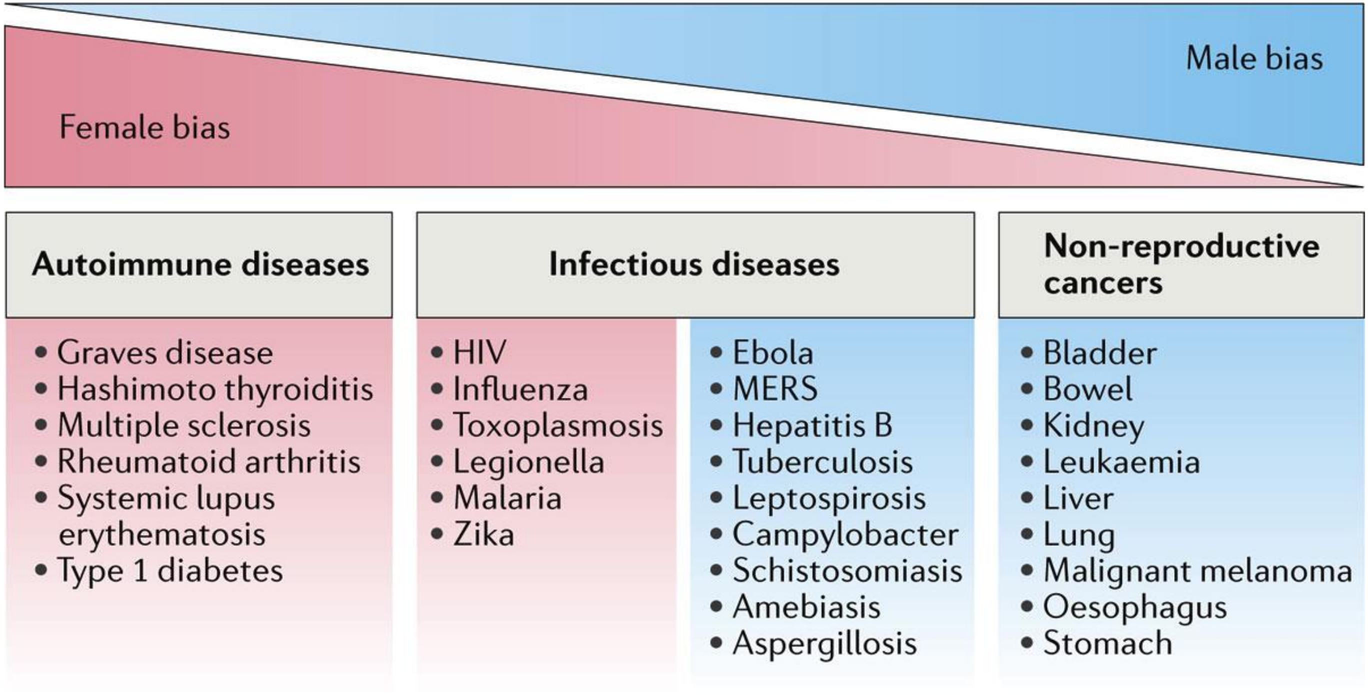
theguardian

Table 1 | **Sex differences in immune responses in different species**

Common name	Species	Immune component	Sex difference
Sea urchin	*Paracentrotus lividus*	Number of immunocytes, cytotoxic activity, phagocytosis and haemolysis	Greater in females than in males
Fruit fly	*Drosophila melanogaster*	Activation of Toll and immune deficiency signalling	Greater in females than in males
Scorpionfly	*Panorpa vulgaris*	Haemolysis and phagocytosis	Greater in females than in males
Wall lizard	*Podarcis muralis*	Macrophage phagocytosis	Greater in females than in males
Eurasian kestrels	*Falco tinnunculus*	Hypersensitivity responses	Greater in females than in males
Great tit	*Parus major*	Hypersensitivity responses	Greater in females than in males
House mouse	*Mus musculus*	Pro-inflammatory cytokine responses, T cell proliferation and antibody responses	Greater in females than in males
Rhesus macaque	*Macaca mulatta*	Pro-inflammatory cytokine responses and antibody responses	Greater in females than in males
Human	*Homo sapiens*	Type I interferon activity, T cell numbers and antibody responses	Greater in females than in males

Klein et al., Nature Reviews Immunology 2016

Clinical consequences of sexual dimorphism of immune responses



Klein et al., Nature Reviews Immunology 2016

Autoimmune Disorders and Sex Differences

Prevalence of Autoimmune Conditions in Females

Autoimmune disorders are more prevalent in females compared to males, often with a ratio of 3:1 or higher.

Potential Mechanisms

Hormonal differences, genetic factors, and immune system dynamics may contribute to the disproportionate prevalence of autoimmune conditions in females.

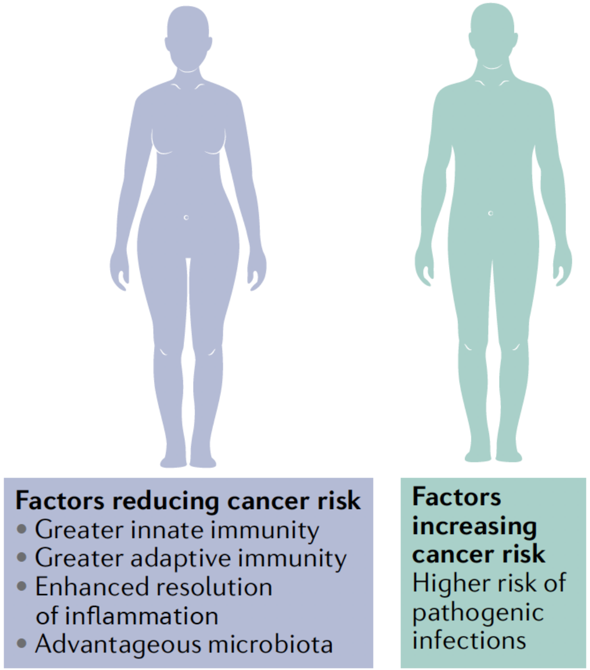
Diagnostic Challenges

The higher prevalence of autoimmune disorders in females can lead to diagnostic challenges, as symptoms may be more common or present differently in women compared to men. This can result in delayed diagnoses or misdiagnoses.

Treatment Considerations

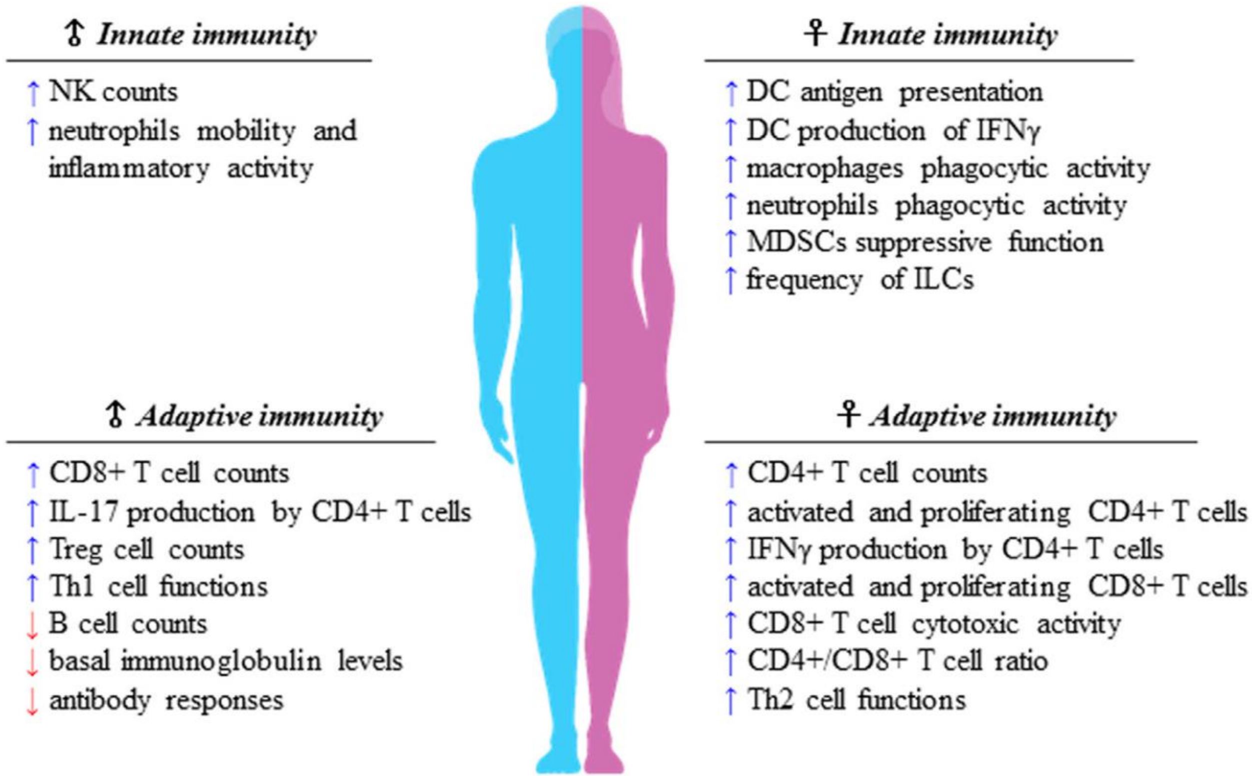
Addressing the sex-based differences in autoimmune disorders is crucial for improving treatment outcomes. Tailored therapies and dosing regimens may be necessary to account for the unique biological and hormonal profiles of females and males.

Sexual dimorphism and cancer risk



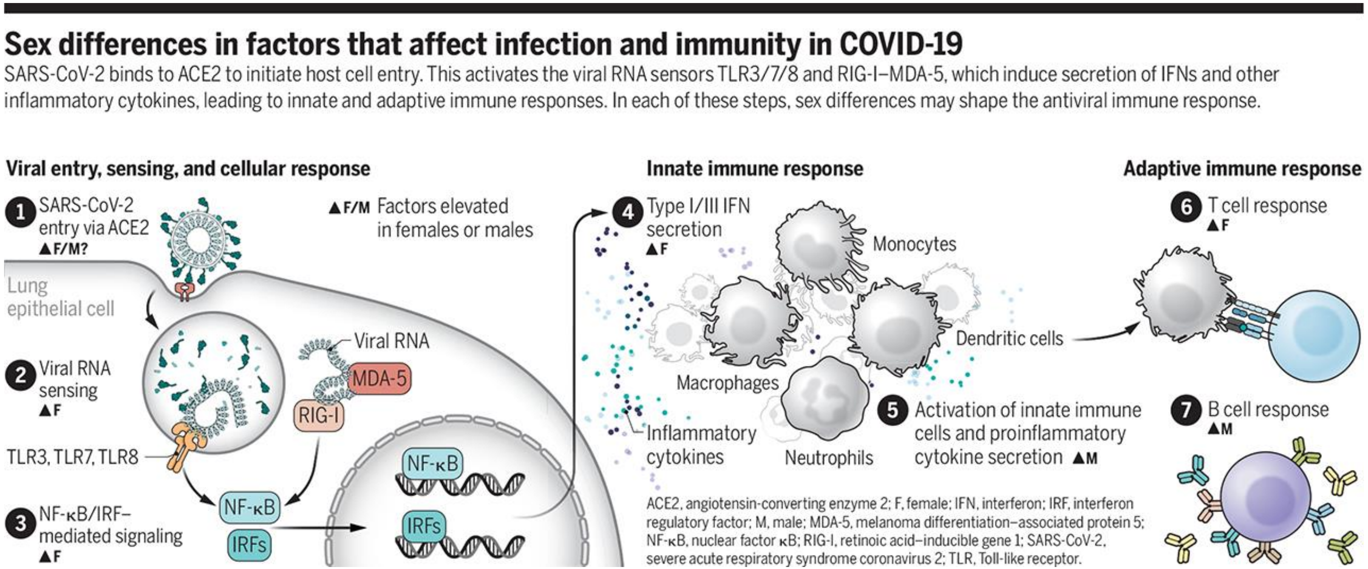
Haupt et al., Nature Reviews Cancer 2021

Sexual dimorphism of immune responses



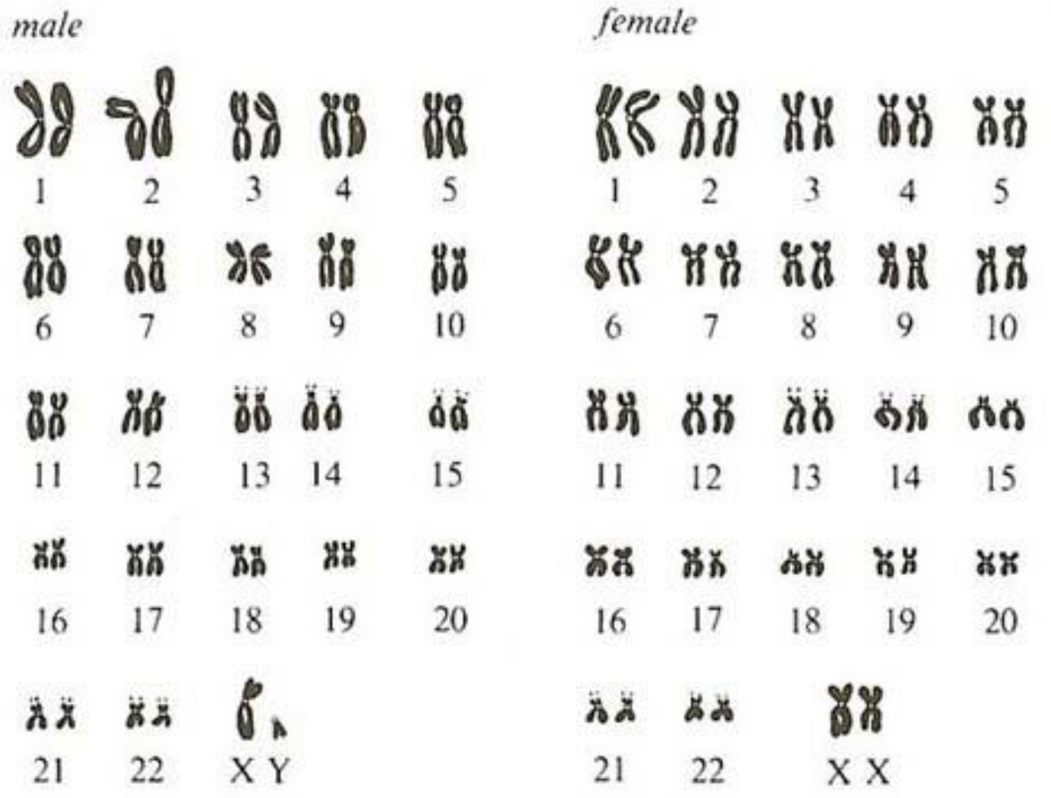
Capone et al., Front. Immunol. 2018

Sexual dimorphism in SARS-CoV-2 infection

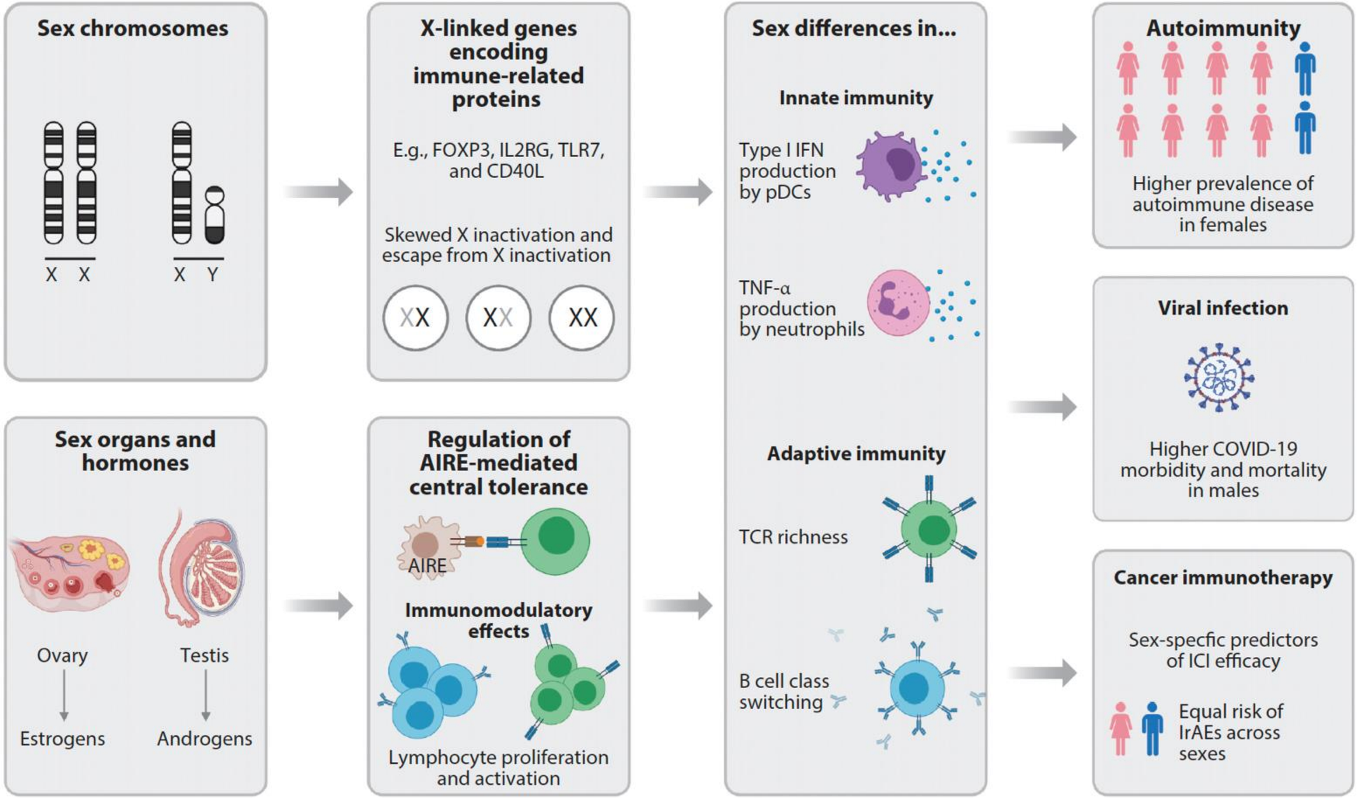


Takahashi & Iwasaki, Science 2021

Why?


male
1 2 3 4 5
6 7 8 9 10
11 12 13 14 15
16 17 18 19 20
21 22 X Y
female
1 2 3 4 5
6 7 8 9 10
11 12 13 14 15
16 17 18 19 20
21 22 X X

Why?



Wilkinson et al., Nature Reviews Immunology 2022

X chromosome

SCIENCE IMMUNOLOGY | RESEARCH ARTICLE

AUTOIMMUNE DISEASE

TLR7 escapes X chromosome inactivation in immune cells

Mélanie Souyris,[1] Claire Cenac,[1] Pascal Azar,[1] Danièle Daviaud,[1] Astrid Canivet,[1] Solange Grunenwald,[2] Catherine Pienkowski,[3] Julie Chaumeil,[4] José E. Mejía,[1] Jean-Charles Guéry[1]*

"… the TLR7 gene evades silencing by X chromosome inactivation in immune cells from women."

"… enhanced TLR7 expression owing to biallelism contributes to the higher risk of developing SLE and other autoimmune disorders in women."

TLR7 & Covid

eLife

SHORT REPORT

Association of Toll-like receptor 7 variants with life-threatening COVID-19 disease in males: findings from a nested case-control study

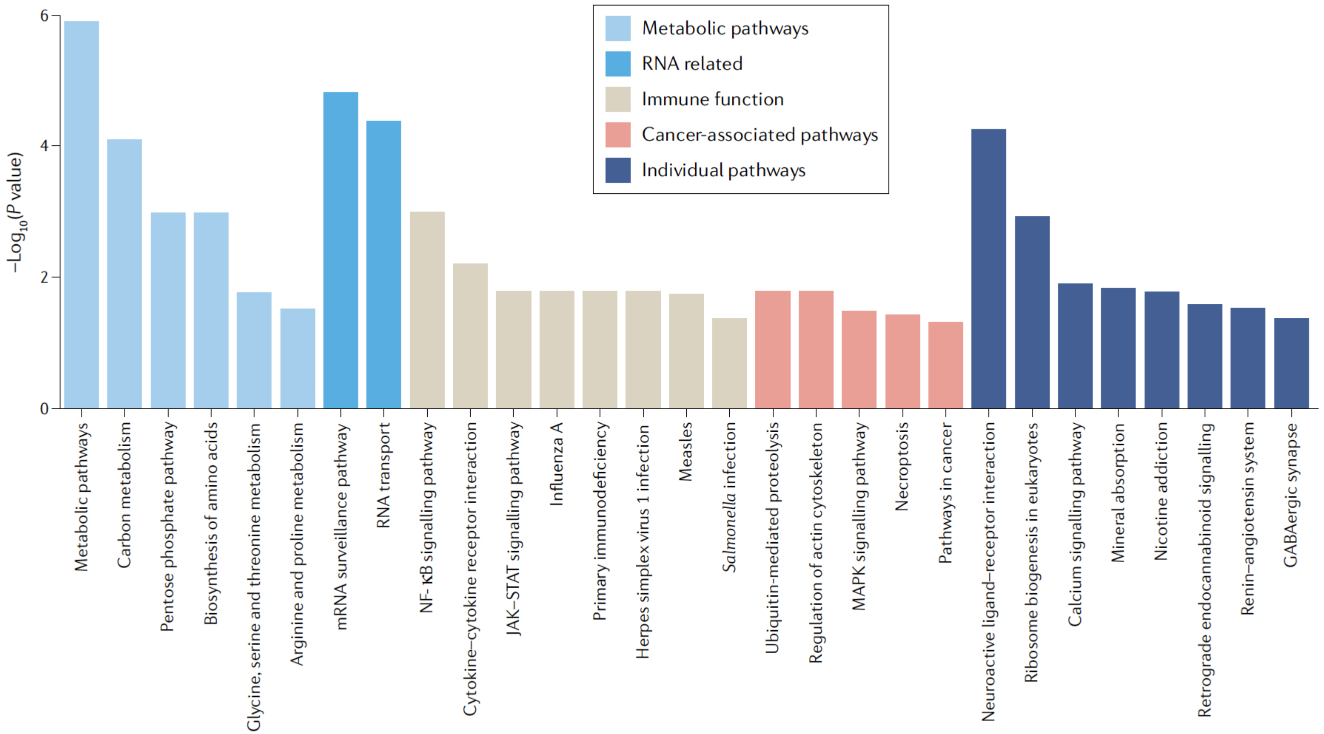
Chiara Fallerini[1,2†], Sergio Daga[1,2†], Stefania Mantovani[3†], Elisa Benetti[2], Nicola Picchiotti[4,5], Daniela Francisci[6,7], Francesco Paciosi[6,7], Elisabetta Schiaroli[6], Margherita Baldassarri[1,2], Francesca Fava[1,2,8], Maria Palmieri[1,2], Serena Ludovisi[3,9], Francesco Castelli[10], Eugenia Quiros-Roldan[10], Massimo Vaghi[11], Stefano Rusconi[12,13], Matteo Siano[12], Maria Bandini[14], Ottavia Spiga[5,15], Katia Capitani[1,16], Simone Furini[2], Francesca Mari[1,2,8], GEN-COVID Multicenter Study[1], Alessandra Renieri[1,2,8]*, Mario U Mondelli[3,9], Elisa Frullanti[1,2]

JAMA | Preliminary Communication

Presence of Genetic Variants Among Young Men With Severe COVID-19

Caspar I. van der Made, MD; Annet Simons, PhD; Janneke Schuurs-Hoeijmakers, MD, PhD; Guus van den Heuvel, MD; Tuomo Mantere, PhD; Simone Kersten, MSc; Rosanne C. van Deuren, MSc; Marloes Steehouwer, BSc; Simon V. van Reijmersdal, BSc; Martin Jaeger, PhD; Tom Hofste, BSc; Galuh Astuti, PhD; Jordi Corominas Galbany, PhD; Vyne van der Schoot, MD, PhD; Hans van der Hoeven, MD, PhD; Wanda Hagmolen of ten Have, MD, PhD; Eva Klijn, MD, PhD; Catrien van den Meer, MD; Jeroen Fiddelaers, MD; Quirijn de Mast, MD, PhD; Chantal P. Bleeker-Rovers, MD, PhD; Leo A. B. Joosten, PhD; Helger G. Yntema, PhD; Christian Gilissen, PhD; Marcel Nelen, PhD; Jos W. M. van der Meer, MD, PhD; Han G. Brunner, MD, PhD; Mihai G. Netea, MD, PhD; Frank L. van de Veerdonk, MD, PhD; Alexander Hoischen, PhD

Enrichment of gene pathways on the X chromosome



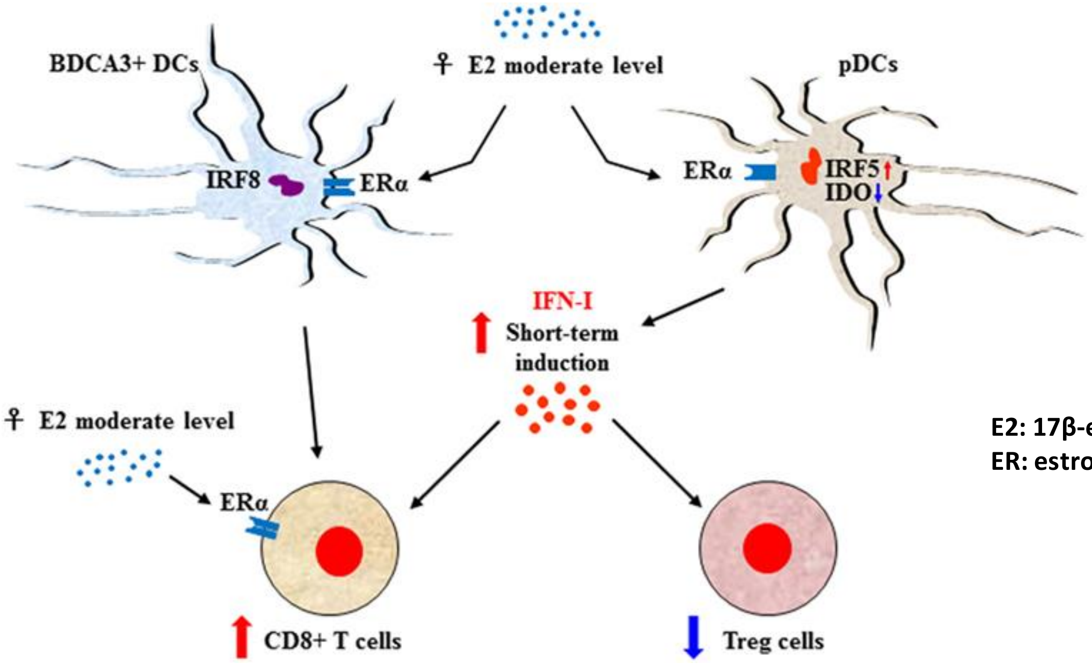
Haupt et al., Nature Reviews Cancer 2021

	Turner Syndrome	Klinefelter Syndrome
Chromosomal Abnormality	Missing one X chromosome (45,X)	Extra X chromosome (47,XXY)
Sex Hormone Levels	Low estrogen (ovarian insufficiency)	Low testosterone levels
Autoimmune Disease Risk	High risk	Moderately high risk
Autoimmune Diseases	Hashimoto's thyroiditis, Type 1 diabetes, Celiac disease, Rheumatoid arthritis	Lupus, Rheumatoid arthritis, Multiple sclerosis, Type 1 diabetes
Immune Cell Composition	↓ Naive T cells, ↓ Regulatory T cells (Tregs), ↑ B cells (autoantibody production)	↑ CD4+ T cells, ↓ CD8+ T cells, ↑ B cell
Infection Susceptibility	Higher risk of bacterial and viral infections	Higher risk of viral infections
Vaccination Response	Effective but may require booster doses due to weaker immune memory	Stronger vaccine responses due to higher B cell activity
Potential Interventions	Estrogen replacement therapy may improve immune function	Testosterone therapy may help regulate immune responses

Hormones

- Progesterone: has broad anti-inflammatory effects
- Estrogens: enhance cell-mediated and humoral immune responses
- Androgens: decrease immune cell reactivity

Hormones



E2: 17β-estradiol
ER: estrogen receptor α

Capone et al., Front. Immunol. 2018

Other influences: microbiome

Sex Differences in the Gut Microbiome Drive Hormone-Dependent Regulation of Autoimmunity

Janet G. M. Markle,[1,2] Daniel N. Frank,[3] Steven Mortin-Toth,[1] Charles E. Robertson,[4] Leah M. Feazel,[3] Ulrike Rolle-Kampczyk,[5] Martin von Bergen,[5,6,7] Kathy D. McCoy,[8] Andrew J. Macpherson,[8] Jayne S. Danska[1,2,9]*

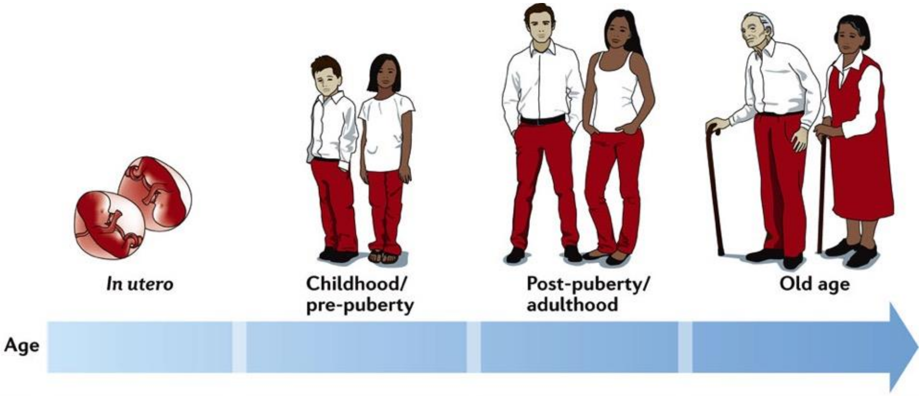
1 MARCH 2013 VOL 339 SCIENCE www.sciencemag.org

In the nonobese diabetic (NOD) mouse model of type 1 diabetes:

"… Transfer of gut microbiota from adult male [mice] to immature females altered the recipent's microbiota, resulting in elevated testosterone and metabolomic changes, reduced inflammation (…) and robust T1D protection."

"… the microbiota may be able to regulate sex hormones and influence an individual's susceptibility to autoimmunity."

Other influences: age - life course



	In utero	Childhood/ pre-puberty	Post-puberty/ adulthood	Old age
Innate immunity	• Increased inflammatory responses in males	↑ Inflammation in males ↑ NK cells in males	↑ Inflammation in females ↑ NK cells in males	↑ Inflammation in males ↑ IL-10 in females ↑ NK cells in females
Adaptive immunity	• Increased IgE levels in males	• CD4/CD8 ratios and $CD4^+$ T cell numbers equal • $CD8^+$ T cell numbers equal • IgA levels in males ≥ females • IgM levels in males ≥ females • IgG and IgM levels equal • B cell numbers equal • T_{reg} cell numbers in males ≥ females	• CD4/CD8 ratios and $CD4^+$ T cells ↑ in females • $CD8^+$ T cells ↑ in males • T cell activation/ proliferation ↑ in females • T_{reg} cells ↑ in males • B cells ↑ in females • Immunoglobulins ↑ in females	• CD4/CD8 ratios and $CD4^+$ T cells ↑ in females • $CD8^+$ T cells ↑ in males • T cell activation/ proliferation ↑ in females • T_{reg} cells ↑ in males • B cells ↑ in females • Immunoglobulins ↑ in females

Klein et al., Nature Reviews Immunology 2016

Conclusions

- Sex differences in immune responses are important
- In general, males have weaker immune responses and are at higher risk of infections and cancer
- In general, females have more robust immune responses leading to increased risk for autoimmunity
- Sex differences in immune responses reflect complex interactions between hormones, genes and environment
- Most studies of immune function did not include both sexes… and that's bad!