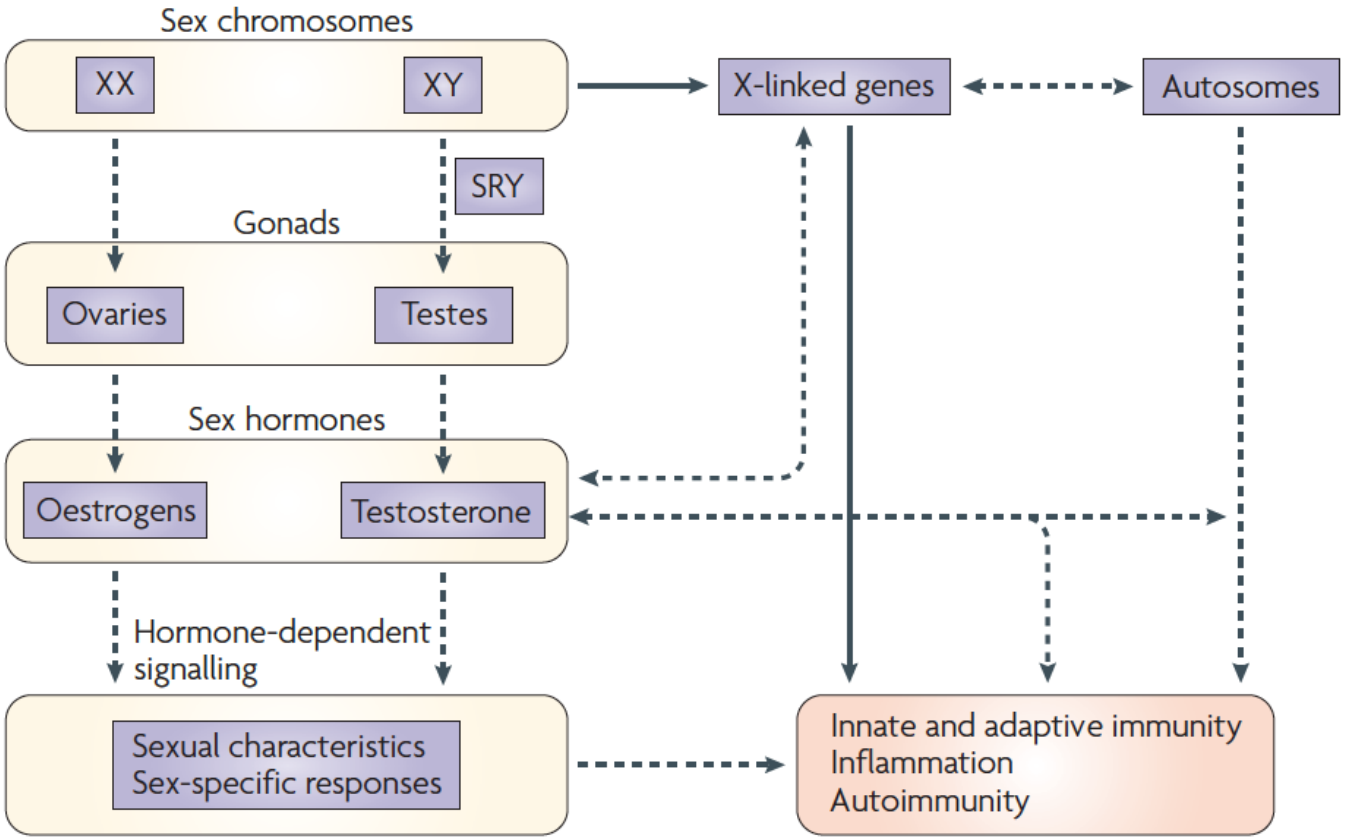
# Sex Differences in COVID-19 Immunity

Sabra L. Klein, Ph.D.
Professor
Molecular Microbiology and Immunology
Co-Director
Center for Women's Health, Sex, and Gender Research

JOHNS HOPKINS
BLOOMBERG SCHOOL
*of* PUBLIC HEALTH

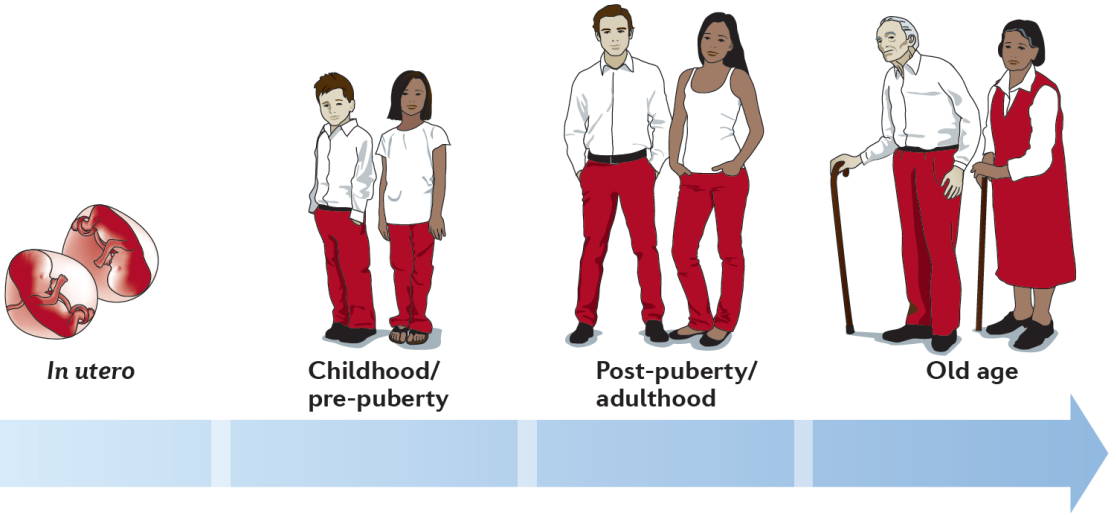
Specialized Center of Research Excellence
in Sex and Age Differences
in Immunity to Influenza

# Sex is a biological variable that affects immune responses




Libert et al. 2010 *Nat Rev Immunol* 10:594

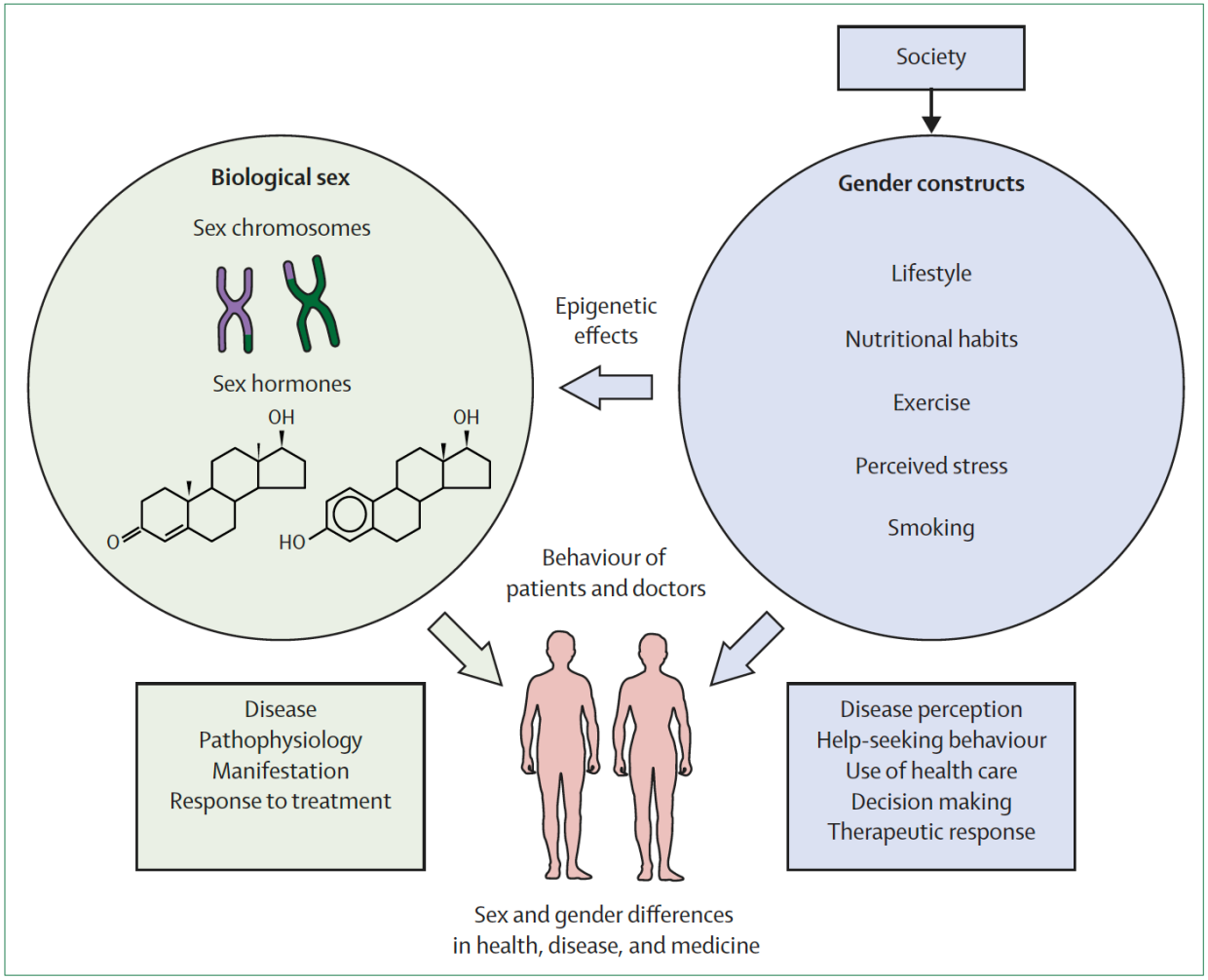
# Sex differences in immunity over the life course




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


Klein and Flanagan 2016 *Nat Rev Immunol*, 16:626-38

# Sex and gender intersect to alter the outcome of infectious diseases

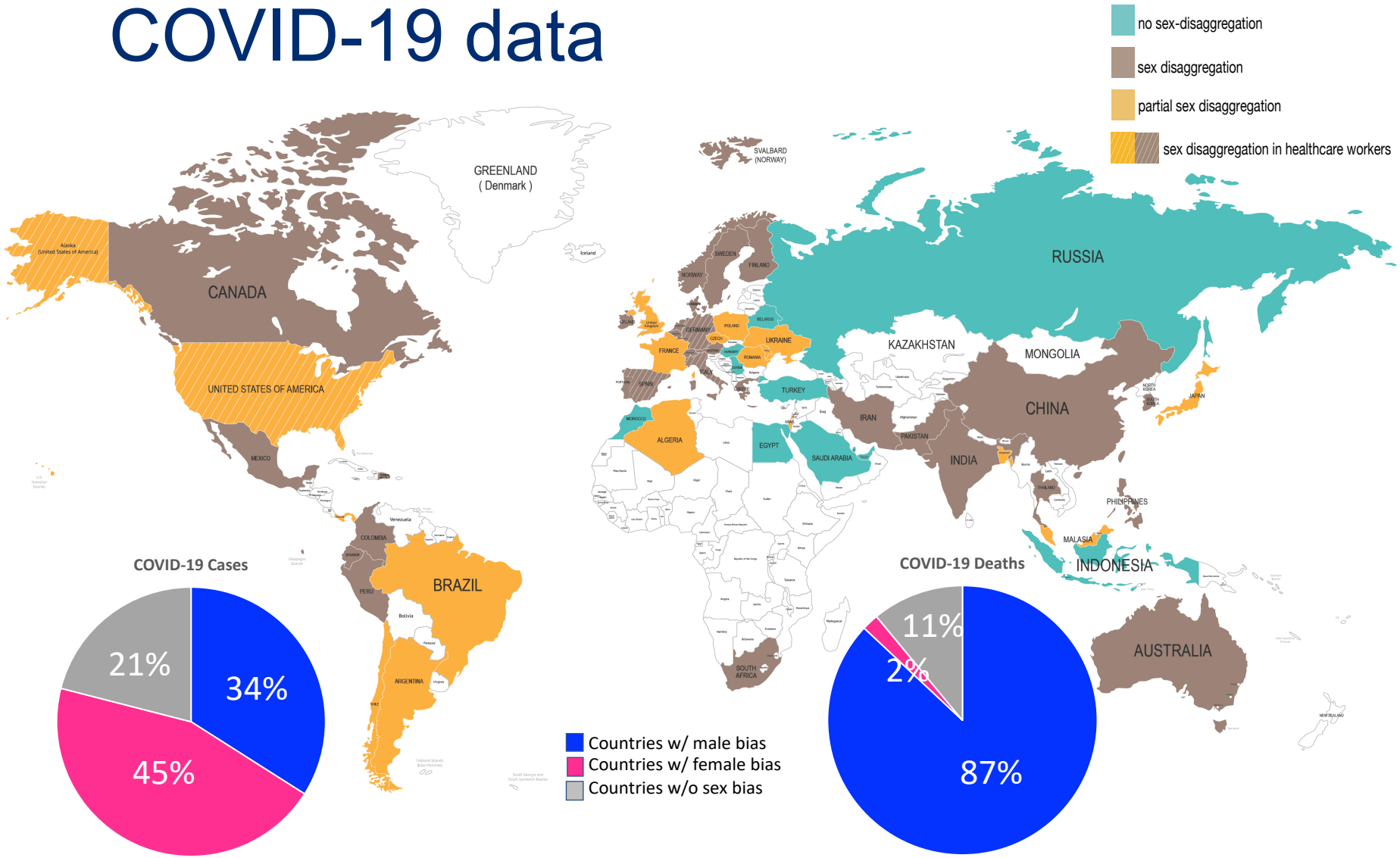



Mauvais-Jauvis et al. 2020 *Lancet 396:565*

# Females are more likely than males to survive SARS-CoV-2 infection

https://www.scientificamerican.com/article/why-some-people-get-terribly-sick-from-covid-19/?amp;text=Why

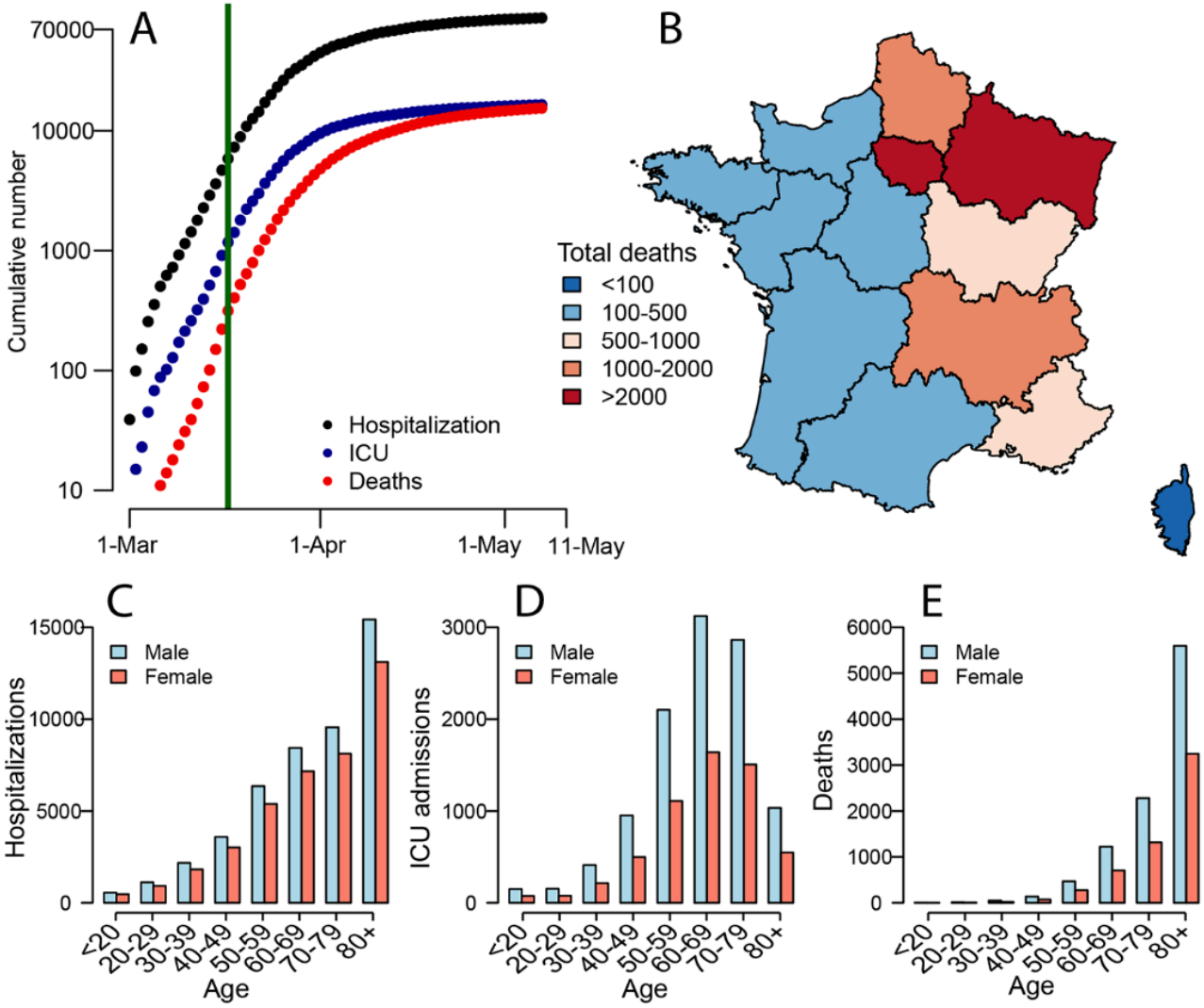
# Sex-disaggregated worldwide COVID-19 data






Bischof, Wolfe, & Klein. 2020 *J Clin Invest* 10.1172/JCI13930610.1172/JCI139306; https://globalhealth5050.org/covid19/

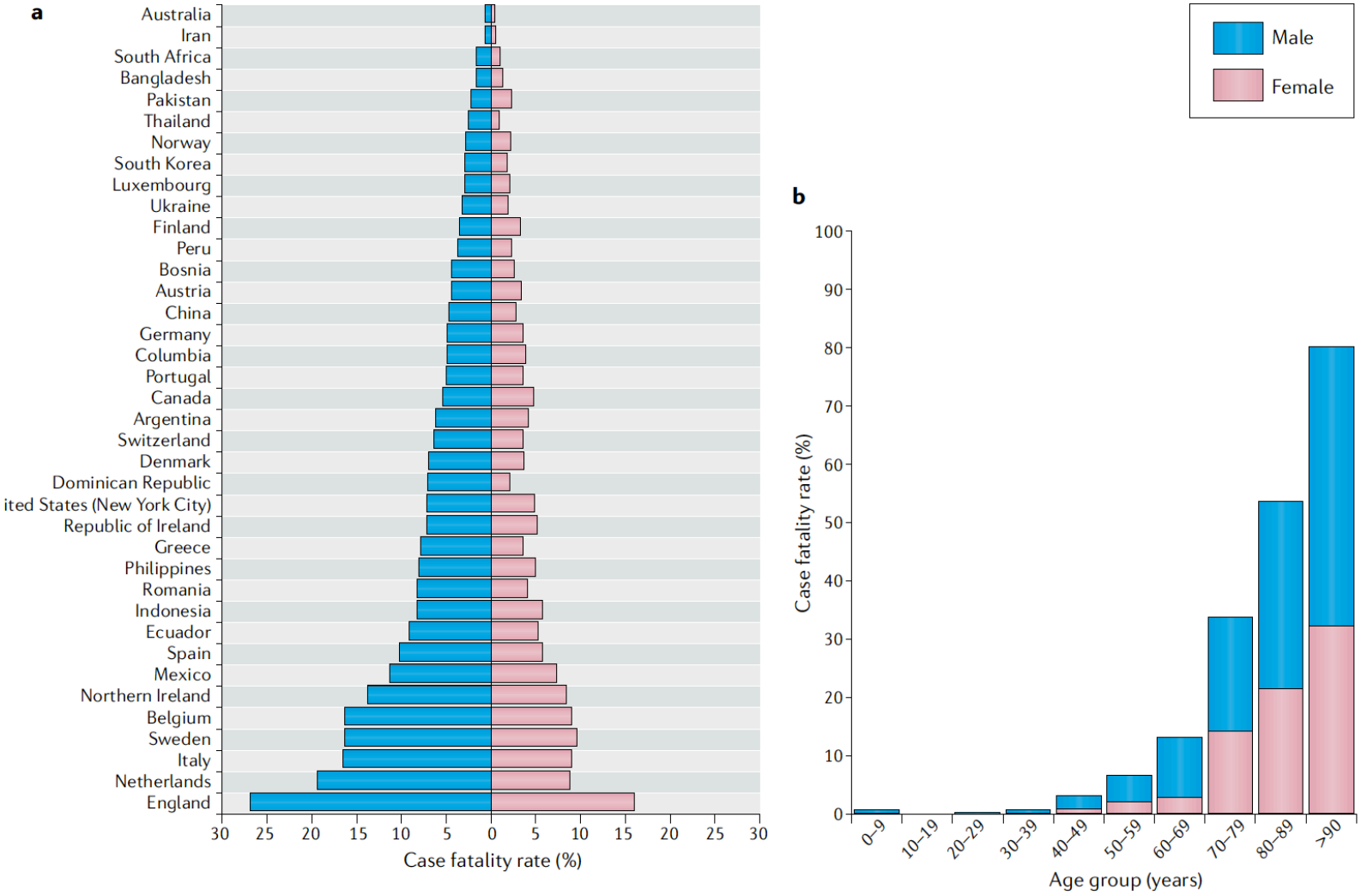
# The burden of SARS-CoV-2 is worse for men (data from France)





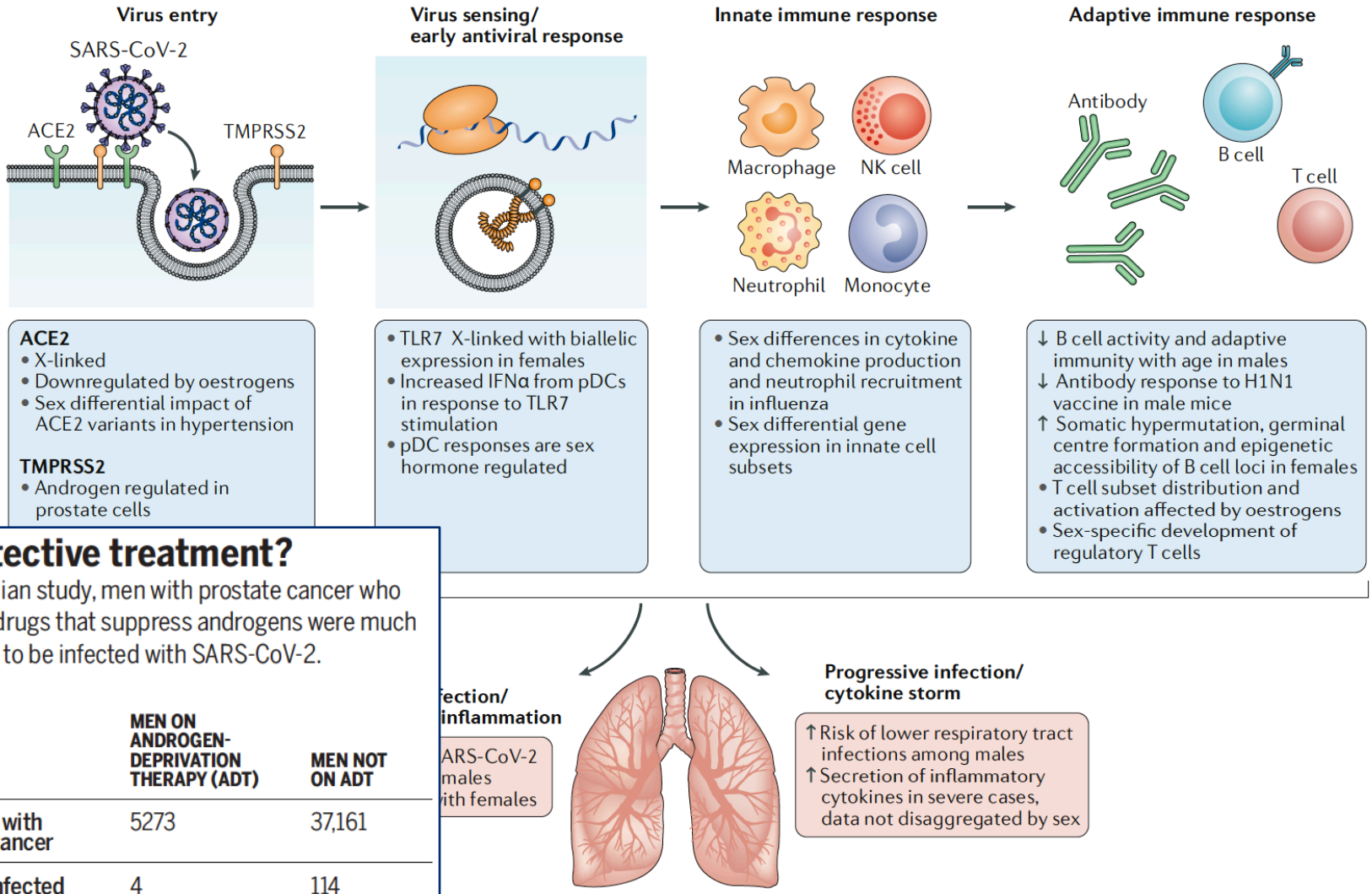

Salje et al. 2020 *Science* 10.1126/science.abc3517

# Male-biased fatality rates across countries and ages




Scully et al. 2020 *Nat Rev Immunol* 10.1038/s41577-020-0348-8

# How sex could impact COVID-19




## A protective treatment?

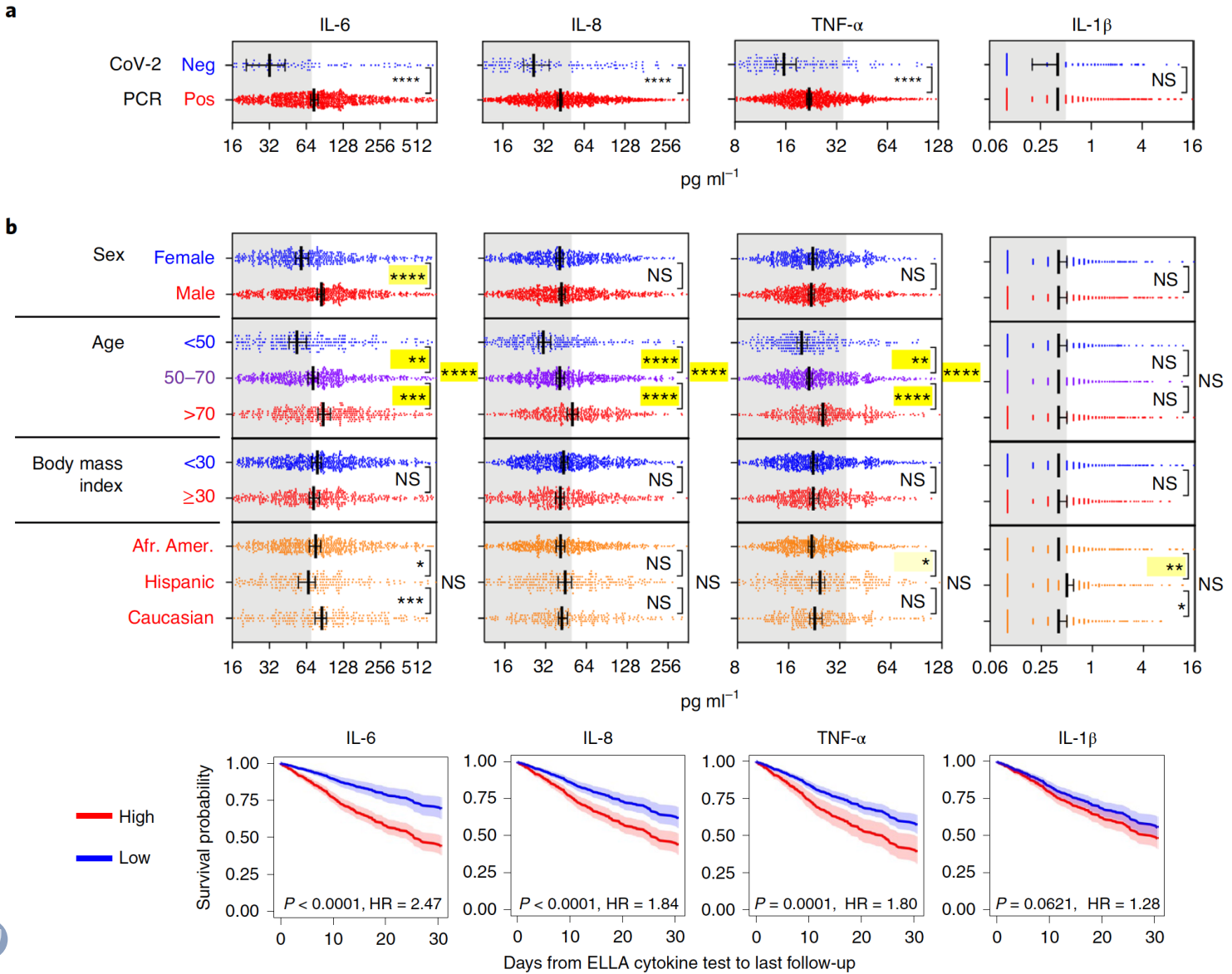
In one Italian study, men with prostate cancer who received drugs that suppress androgens were much less likely to be infected with SARS-CoV-2.

| | MEN ON ANDROGEN-DEPRIVATION THERAPY (ADT) | MEN NOT ON ADT |
|---|---|---|
| Total men with prostate cancer | 5273 | 37,161 |
| Number infected with SARS-CoV-2 | 4 | 114 |
| Estimated cases per 10,000 | 8 | 31 |

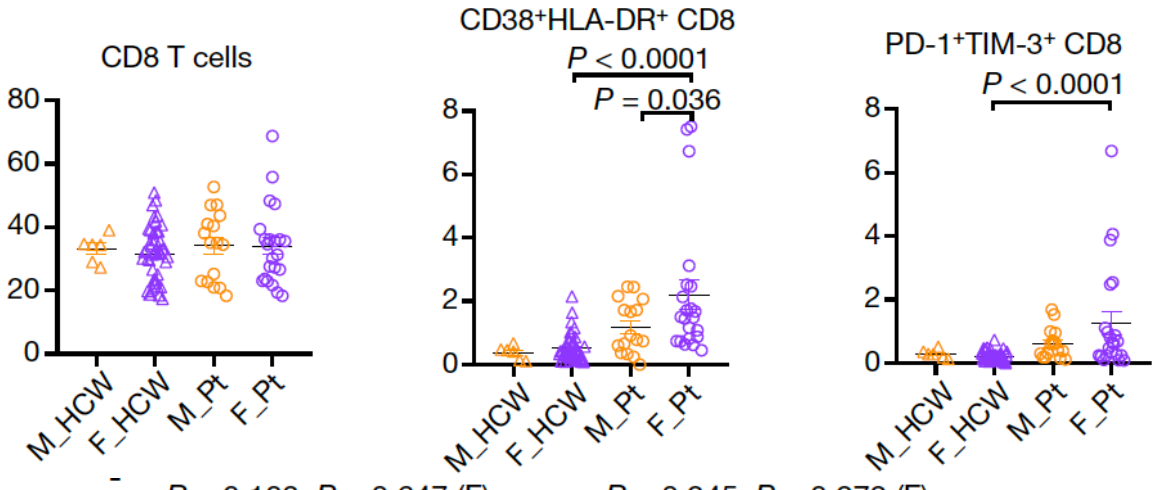
Scully et al. 2020 *Nat Rev Immunol* 10.1038/s41577-020-0348-8

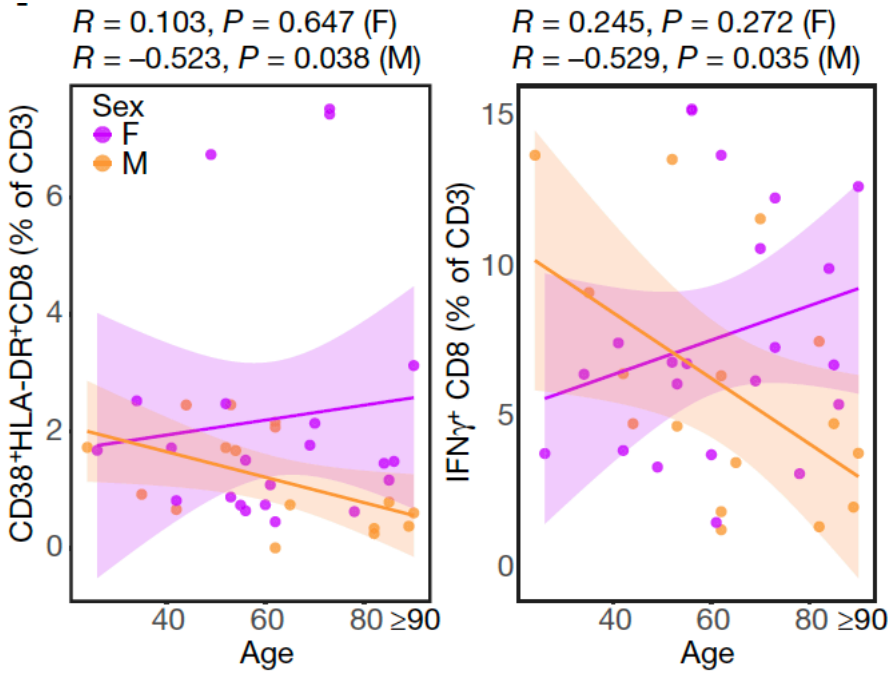
Del Valle et al. 2020 *Nat Med* doi.org/10.1038/s41591-020-1051-9

# Males, older adults, and patients with severe COVID-19 have greater cytokine



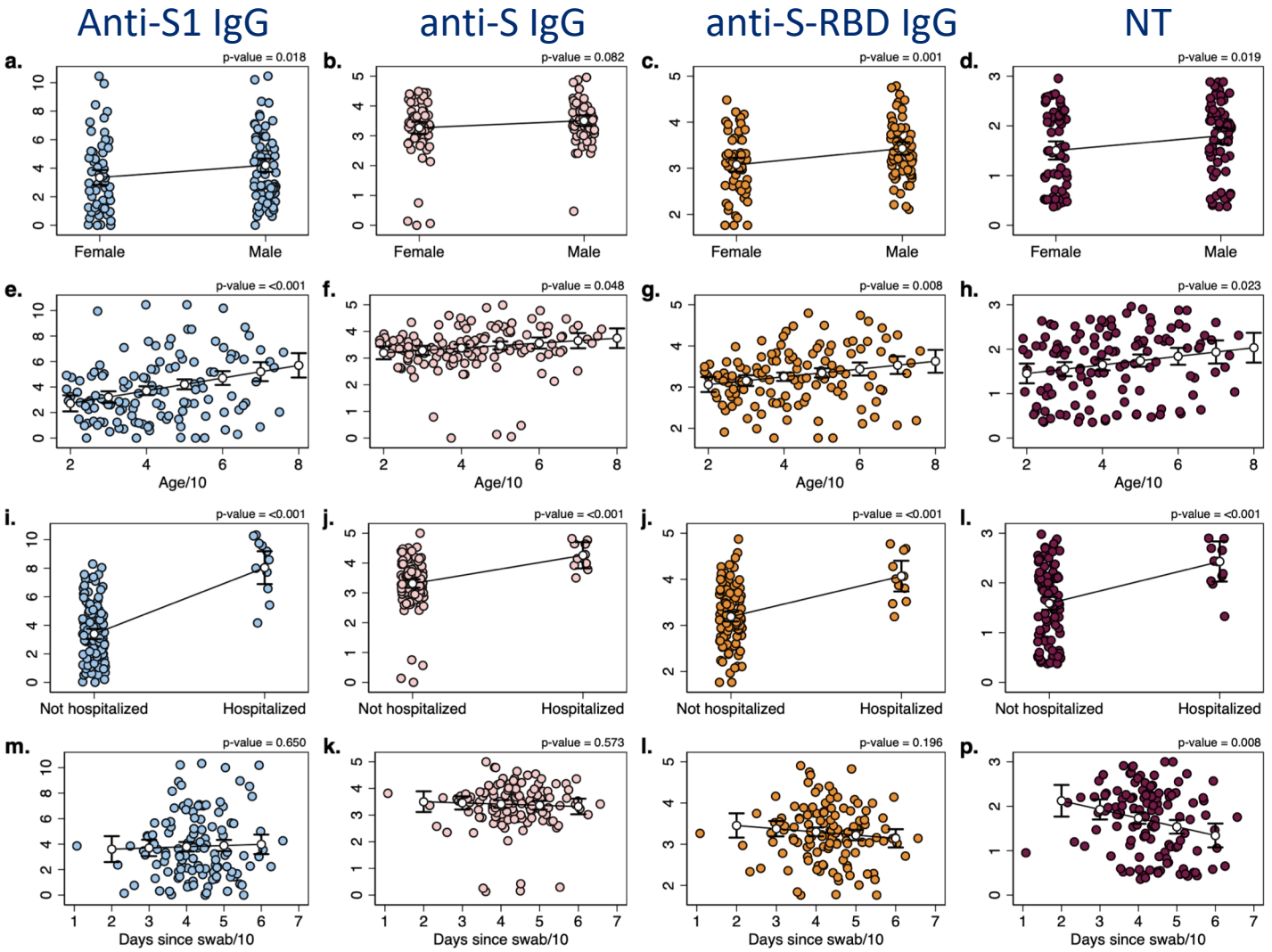
# Women have greater CD8+ T cell activity than men during COVID-19




Takahashi et al. 2020 *Nature*
doi.org/10.1038/s41586-020-2700-3

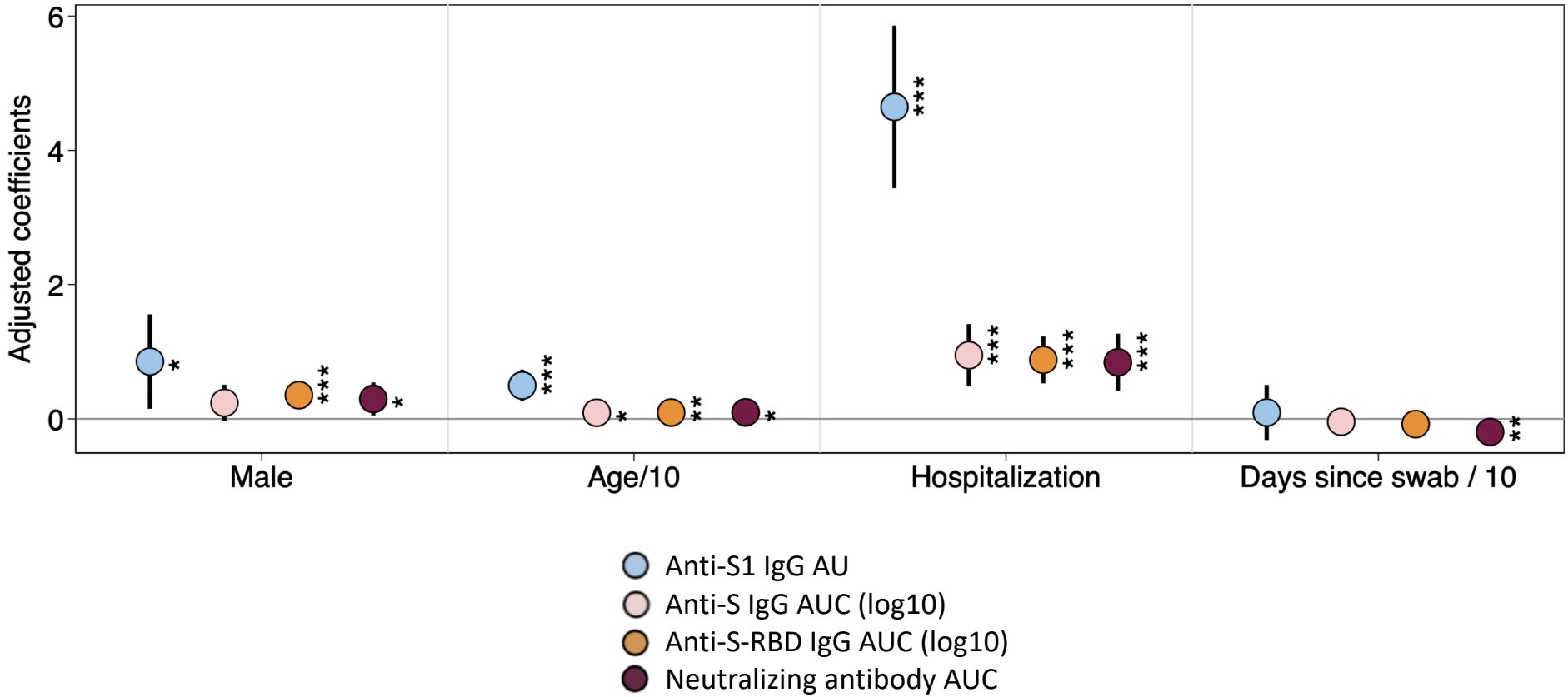
# Which factors contribute to greater antibody responses?






Klein et al. 2020 *JCI* doi: 10.1172/JCI142004

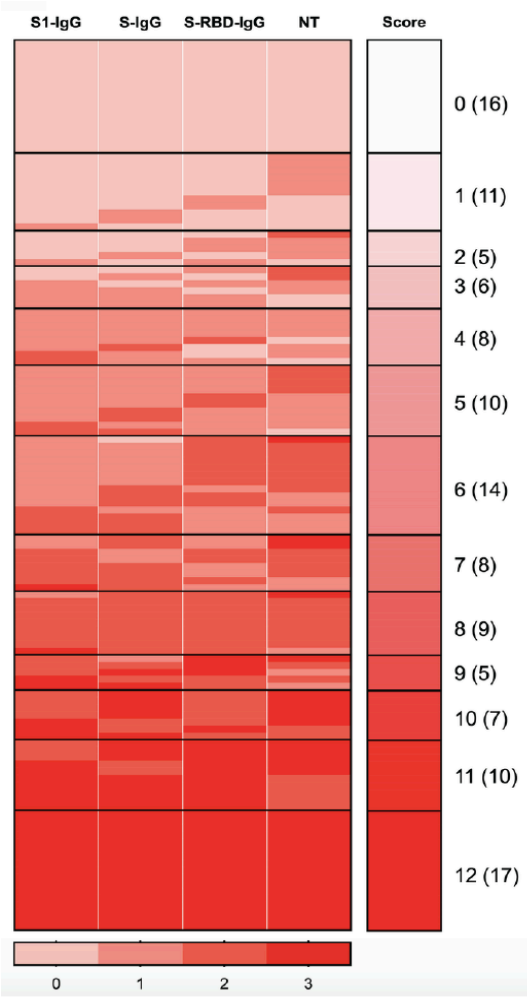
# Males, older adults, and hospitalized patients have greater antibody responses






Klein et al. 2020 *JCI* doi: 10.1172/JCI142004

# Being male and hospitalized are predictors of greater antibody responses







Klein et al. 2020 *JCI* doi: 10.1172/JCI142004

# Males shed more virus and for a longer duration of time than females

Clinical Infectious Diseases® 2020;71(15):799–806

## Factors Associated With Prolonged Viral RNA Shedding in Patients with Coronavirus Disease 2019 (COVID-19)

Kaijin Xu,[1,a] Yanfei Chen,[1,a] Jing Yuan,[2,a] Ping Yi,[1,a] Cheng Ding,[1,a] Wenrui Wu,[1,a] Yongtao Li,[1] Qin Ni,[1] Rongrong Zou,[2] Xiaohe Li,[2] Min Xu,[1] Ying Zhang,[1] Hong Zhao,[1] Xuan Zhang,[1] Liang Yu,[1] Junwei Su,[1] Guanjing Lang,[1] Jun Liu,[1] Xiaoxin Wu,[1] Yongzheng Guo,[1] Jingjing Tao,[1] Ding Shi,[1] Ling Yu,[1] Qing Cao,[1] Bing Ruan,[1] Lei Liu,[2] Zhaoqin Wang,[2] Yan Xu,[1] Yingxia Liu,[2] Jifang Sheng,[1] and Lanjuan Li[1]

[1]State Key Laboratory for Diagnosis and Treatment of Infectious Diseases, National Clinical Research Center for Infectious Diseases, Collaborative Innovation Center for Diagnosis and Treatment of Infectious Diseases, Department of Infectious Diseases, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou City, China, and [2]Diagnosis and Treatment of Infectious Diseases Research Laboratory, Shenzhen Third People's Hospital, Shenzhen, China

the bmj | *BMJ* 2020;369:m1443 | doi: 10.1136/bmj.m1443

## Viral load dynamics and disease severity in patients infected with SARS-CoV-2 in Zhejiang province, China, January-March 2020: retrospective cohort study

Shufa Zheng,[1,2,3,4] Jian Fan,[2,3,4] Fei Yu,[2,3,4] Baihuan Feng,[2,3,4] Bin Lou,[2,3,4] Qianda Zou,[2,3,4] Guoliang Xie,[2,3,4] Sha Lin,[2,3] Ruonan Wang,[2,3] Xianzhi Yang,[2,3] Weizhen Chen,[2,3,4] Qi Wang,[2,3,4] Dan Zhang,[2,3,4] Yanchao Liu,[2,3] Renjie Gong,[2,3] Zhaohui Ma,[2,3] Siming Lu,[2,3] Yanyan Xiao,[2,3] Yaxi Gu,[2,3] Jinming Zhang,[2,3] Hangping Yao,[1] Kaijin Xu,[1] Xiaoyang Lu,[5] Guoqing Wei,[6] Jianying Zhou,[7] Qiang Fang,[8] Hongliu Cai,[8] Yunqing Qiu,[1] Jifang Sheng,[1] Yu Chen,[1,2,3,4] Tingbo Liang[9,10,11]

# Acknowledgements


**Financial support provided by:**

NIH/NIA SCORE U54 AG062333
NIH/NCI SERONET U54 CA260492
NIH/NIAID HHS N272201400007C
NIH/NICHD R01HD097608
DoD W911QY-20-9-0012

- Sabra Klein, PhD and lab
  - Santosh Dhakal, PhD
  - Morgan Sherer, PhD
  - Patrick Creisher, PharmD
  - Abhinaya Ganesan
  - Harish Narasimhan, MHS
  - Han-Sol Park, PhD
  - Janna Shapiro, MS
  - Rebecca Ursin, MS
  - Yishak Woldetsadik
  - Aihui Wang
- Andy Pekosz, PhD and lab
- Sean Leng, MD
- Eileen Scully, MD
- David Sullivan, MD
- Aaron Tobian, MD
- Arturo Casadevall, MD, PhD
- Kim Davis, PhD and lab
- Anne Jedlicka, MS
- Amanda Dziedzic, MS
- Michael Betenbaugh, PhD
- The Gender and COVID-19 Working Group, including Rosemary Morgan, Eveylyn Bischof and Jeannette Wolfe