Journal Club

Influenza vaccination reveals sex dimorphic imprints of prior mild COVID-19

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May 31, 2023

https://www.nature.com/articles/s41586-022-05670-5

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Position

He is currently Professor of Immunobiology and Biomedical Engineering at Yale University; he is also the founding Director of the Yale Center for Systems and Engineering Immunology (CSEI), which serves as a cross-departmental home, enabler, and center of collaborative research for systems, quantitative, and synthetic immunology at Yale.

Research Summary

The lab combines computational and experimental approaches, including multimodal immune profiling, data science, machine learning, quantitative dynamical modeling, and ex vivo experiments and animal models, to investigate the basis of human immune response variability.

Long-term immunological effects of viral infections

Examples:

1. After recovery from natural acute measles (麻疹) infection, there is marked reduction in humoral immunity and increased susceptibility to non-measles infections for months to years.

2. COVID-19 can result in persistent clinical sequelae (后遗症) for months after infection, both in hospitalized and mild cases.

Science

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RESEARCH ARTICLE

Measles virus infection diminishes preexisting antibodies that offer protection from other pathogens

MICHAEL J. MINA, TOMASZ KULA, YUMEI LENG, MAMIE LI, RORY D. DE VRIES, MIKAEL KNIP, HELI SILJANDER, MARIAN REWERS, DAVID F. CHOY, [...], AND STEPHEN J. ELLEDGE +5 authors Authors Info & Affiliations

Review Article | Published: 22 March 2021

Post-acute COVID-19 syndrome

Ani Nalbandian, Kartik Sehgal, Aakriti Gupta, Mahesh V. Madhavan, Claire McGroder, Jacob S. Stevens, Joshua R. Cook, Anna S. Nordvig, Daniel Shalev, Tejasav S. Sehrawat, Neha Ahluwalia, Behnood Bikdeli, Donald Dietz, Caroline Der-Nigoghossian, Nadia Liyanage-Don, Gregg F. Rosner, Elana J. Bernstein, Sumit Mohan, Akinpelumi A. Beckley, David S. Seres, Toni K. Choueiri, Nir Uriel, John C. Ausiello, Domenico Accili, ... Elaine Y. Wan + Show authors

Nature Medicine **27**, 601–615 (2021) | Cite this article

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Rationality of the research

1. Although post-acute COVID-19 syndromes are relatively widely reported, our understanding of the molecular and cellular immunological changes after recovery from SARS-CoV-2 infection is lacking.

2. A research on mild COVID-19 might have particularly important public health implications given that this population constitutes most COVID-19 recoverees.

3. It remains poorly understood whether baseline immune states may have been altered by viral infections, and whether any such alterations may affect responses to future virus challenges.

Overview of this study

Article | Published: 04 January 2023

Influenza vaccination reveals sex dimorphic imprints of prior mild COVID-19

Rachel Sparks, William W. Lau, Can Liu, Kyu Lee Han, Kiera L. Vrindten, Guangping Sun, Milann Cox, Sarah F. Andrews, Neha Bansal, Laura E. Failla, Jody Manischewitz, Gabrielle Grubbs, Lisa R. King, Galina Koroleva, Stephanie Leimenstoll, LaQuita Snow, OP11 Clinical Staff, Jinguo Chen, Juanjie Tang, Amrita Mukherjee, Brian A. Sellers, Richard Apps, Adrian B. McDermott, Andrew J. Martins, Evan M. Bloch, Hana Golding, Surender Khurana & John S. Tsang — Show fewer authors

Nature **614**, 752–761 (2023) | Cite this article

Received: 3 February 2022

Accepted: 19 December 2022

Published online: 4 January 2023

Samples

(1) Individuals recovered from non-hospitalized, mild cases of COVID-19 (mean, 151 days after diagnosis)
(2) Age- and sex-matched controls who never had COVID-19

Multi-omics profiling

whole-blood transcriptomics (WBT)
cellular indexing of transcriptomes and epitopes by sequencing (CITE-seq)
complete blood count (CBC)
serum protein profiling
antibody characterization
…

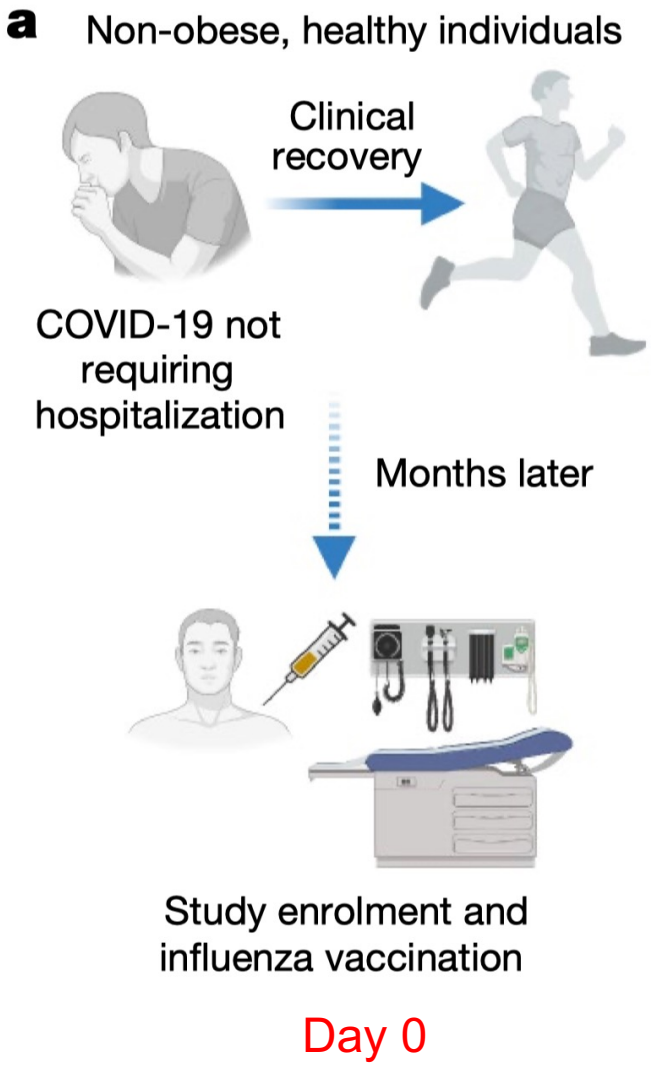
Main conclusions

(1) Revealing sex-dimorphic effects of previous mild COVID-19
(2) Suggesting that viral infections in humans can change immunological baseline that affects future immune responses

Results

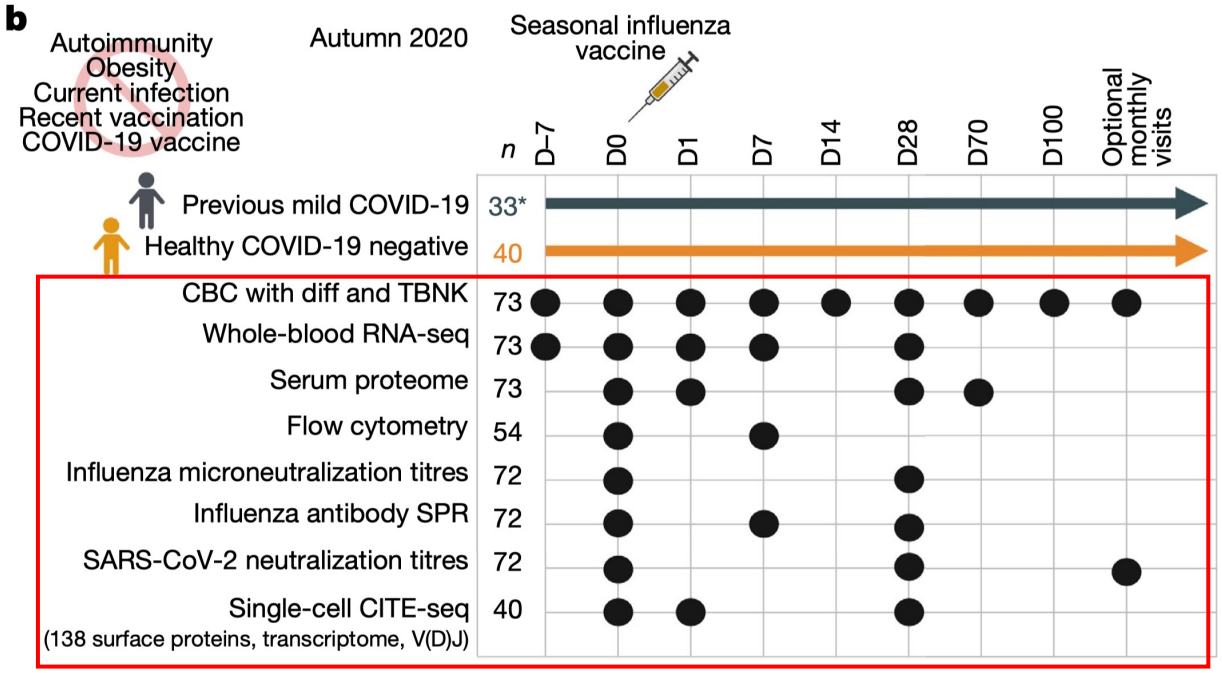
1. Baseline of mild COVID-19 recoverees
2. Contrasting influenza vaccination responses
3. Linking the baseline to innate response
4. Vaccination shifts monocyte imprints

Schematic of the study concept and design



- Recoveree (COVR), recovered from non-hospitalized, mild cases of COVID-19
- Healthy control (HC), age- and sex-matched controls who never had COVID-19
- Male (M), Female (F)

Schematic of the study concept and design



multi-omics profiling

The impact of previous COVID-19 on

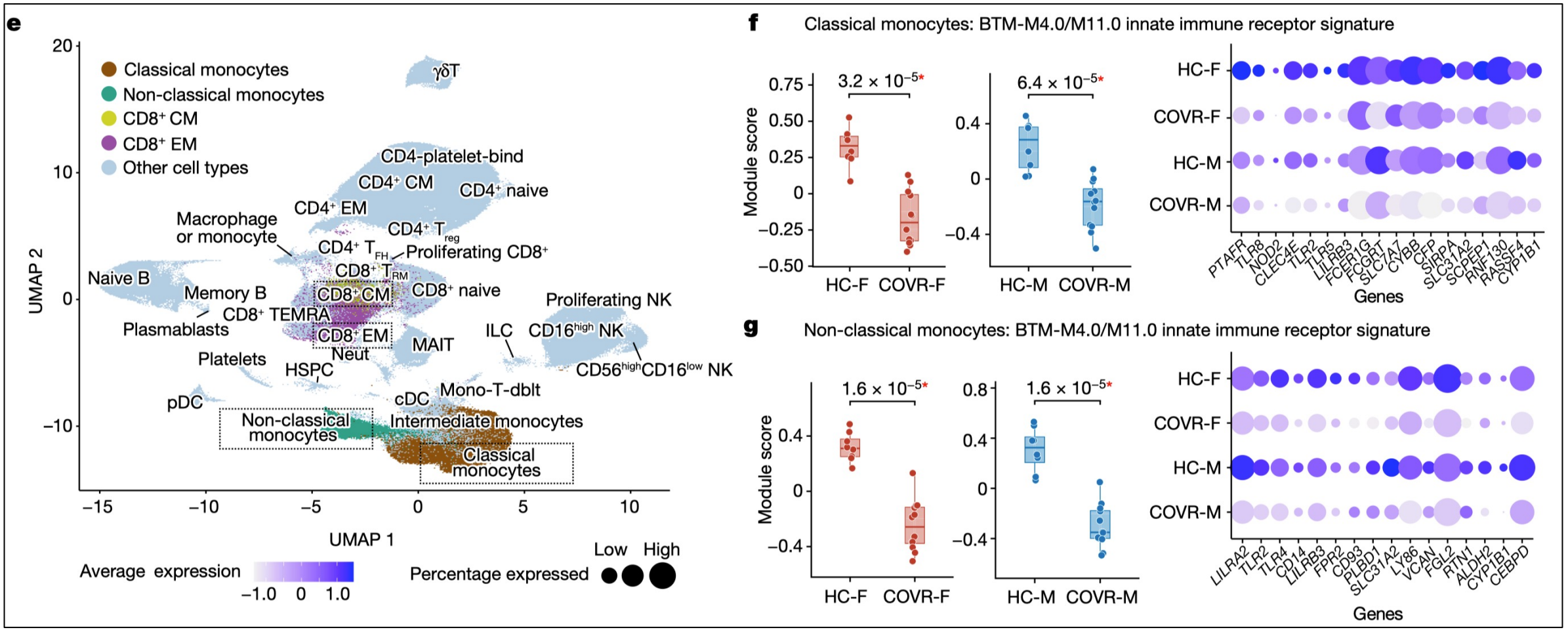
1. baseline immunological states: D0 data
2. future influenza vaccine-induced responses: D1-D0, D7-D0, D28-D0 data

COVR vs. HC

COVR-M vs. COVR-F

Recoverees had significantly lower expression of innate immune receptors in monocytes

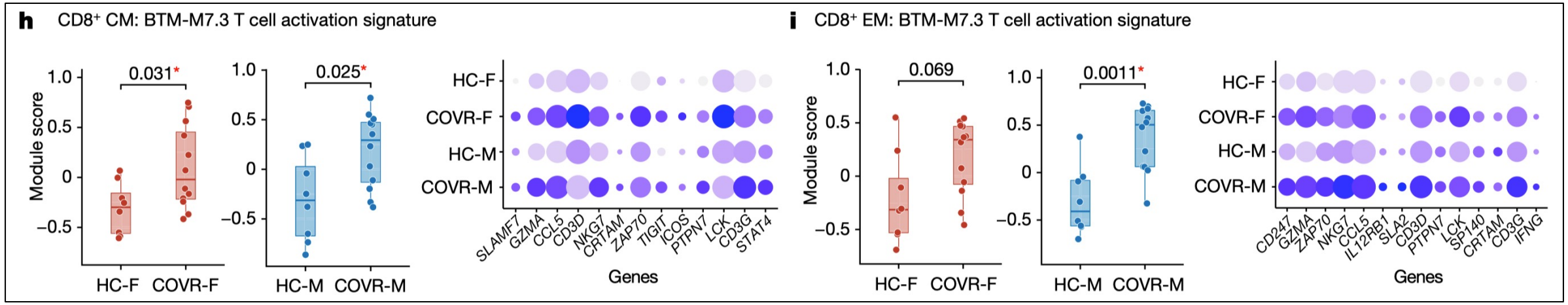
Single-cell CITE-Seq (simultaneously quantifying cell surface protein and transcriptome)



Recoveree (COVR)
Healthy control (HC)

Female (F)
Male (M)

Recoverees had higher transcriptional signatures of T cell activation



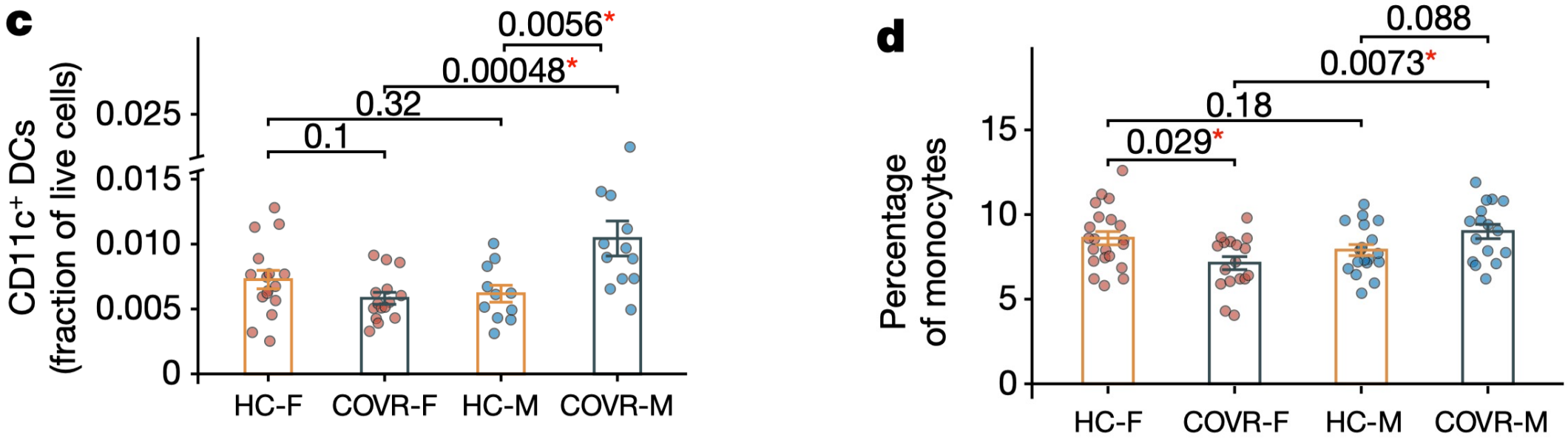
central memory (CM)
effector memory (EM)

Recoveree (COVR)
Healthy control (HC)

Female (F)
Male (M)

Male recoverees had higher myeloid-cell frequencies than female recoverees and healthy controls

The frequencies of myeloid cells such as conventional dendritic cells (cDCs) and monocytes tended to be higher in the COVR-M group compared with the HC and COVR-F groups.



Recoveree (COVR)
Healthy control (HC)

Female (F)
Male (M)

Brief summary

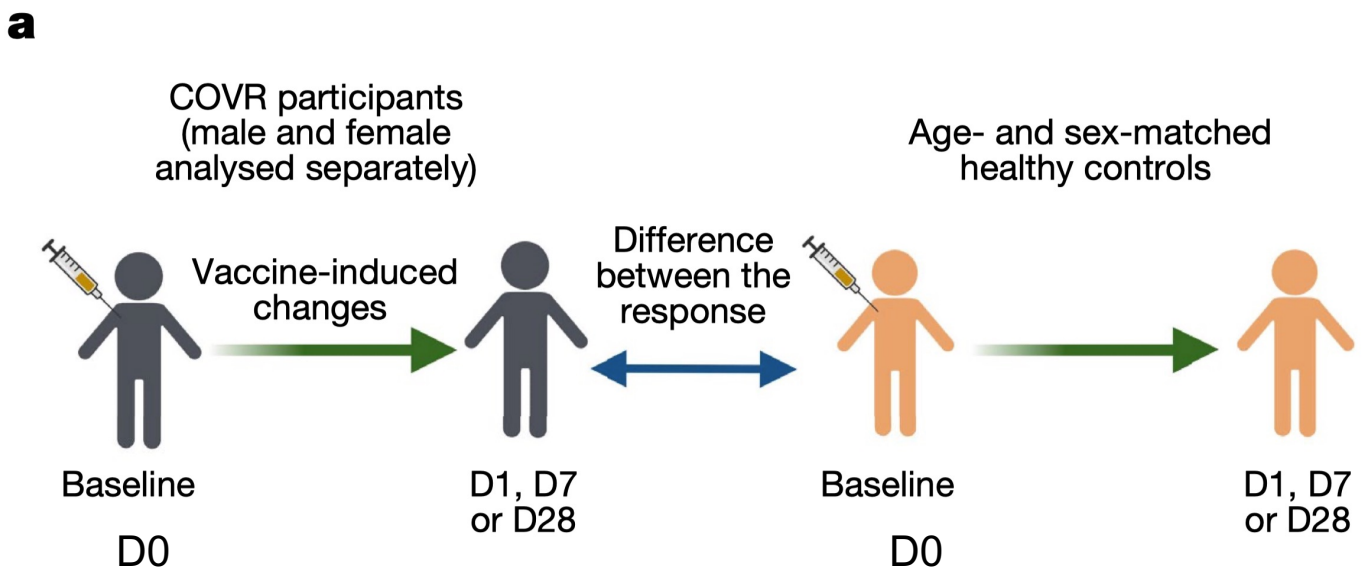
Even mild, non-hospitalized COVID-19 infections may establish new, sex-dependent immunological imprints detectable months after clinical recovery.

Results

1. Baseline of mild COVID-19 recoverees
2. Contrasting influenza vaccination responses
3. Linking the baseline to innate response
4. Vaccination shifts monocyte imprints

Can previous COVID-19 impact the recoverees' response to other viruses such as influenza virus?

Design of the influenza-vaccination-response experiment

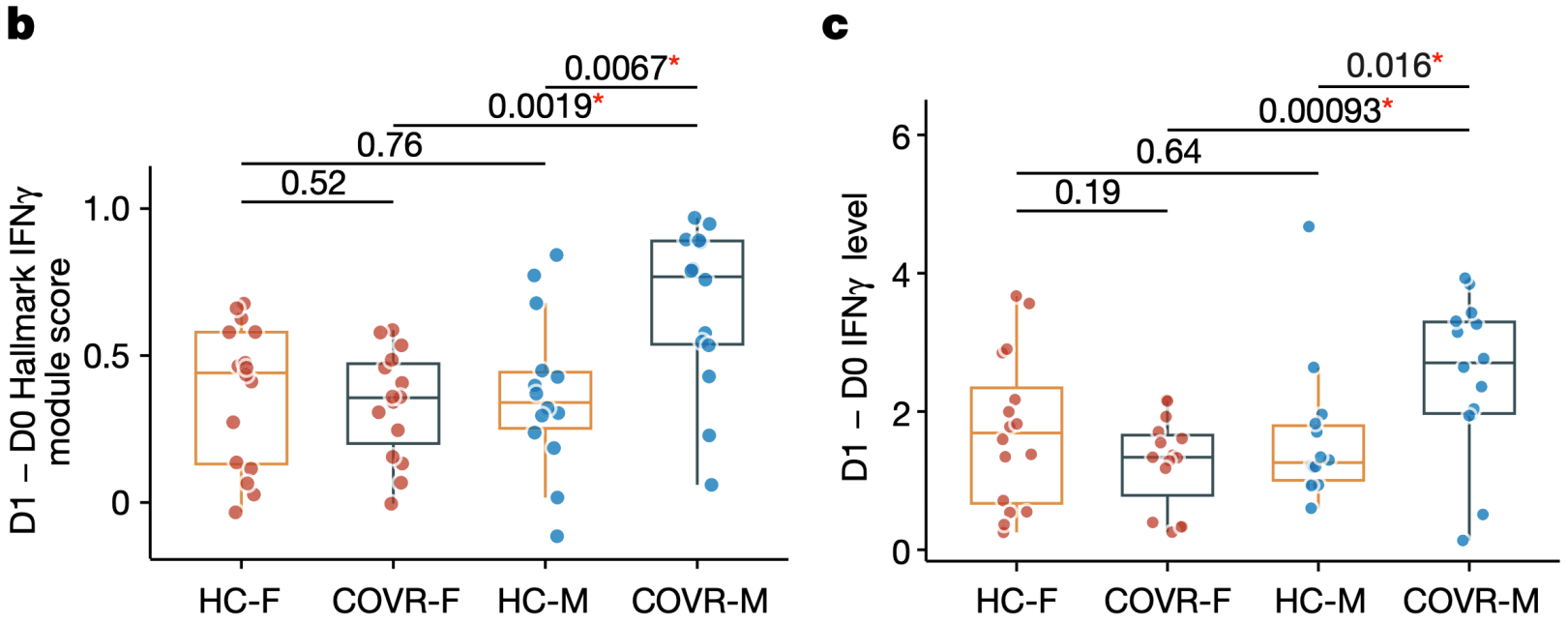


Contrasting the influenza vaccine-induced responses (D1-D0, D7-D0, D28-D0)

COVR vs. HC
COVR-M vs. COVR-F

Male recoverees have stronger inflammatory responses compared with the healthy control and female recoverees

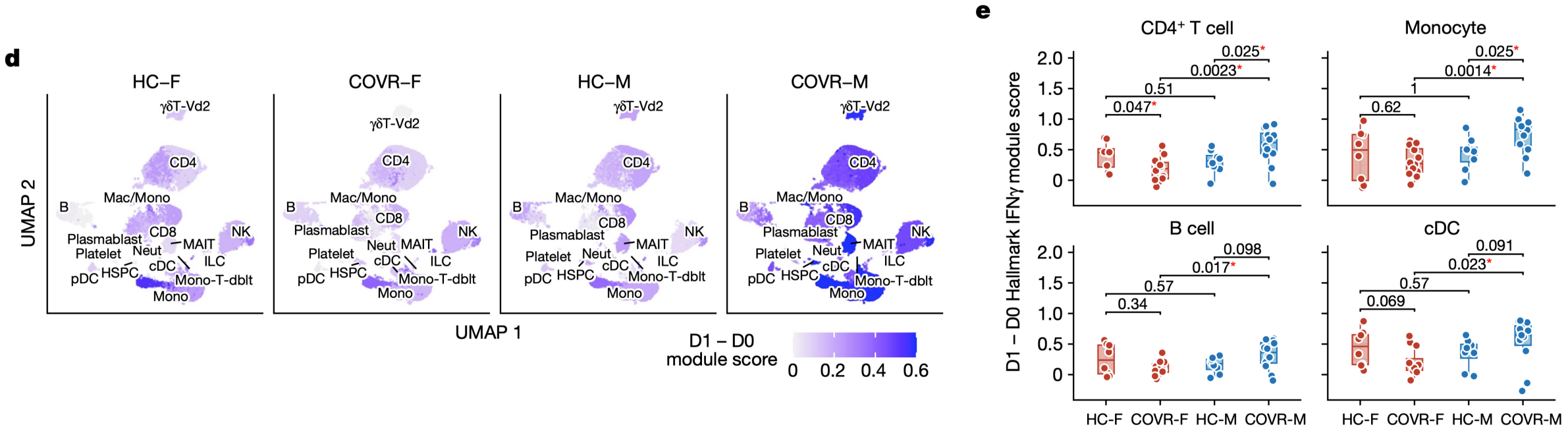
Stronger IFN-related transcriptional responses, with corresponding greater increases in circulating IFNγ protein levels in the serum by D1 in the COVR-M group.



IFN-γ is a cytokine that is critical for innate and adaptive immunity.

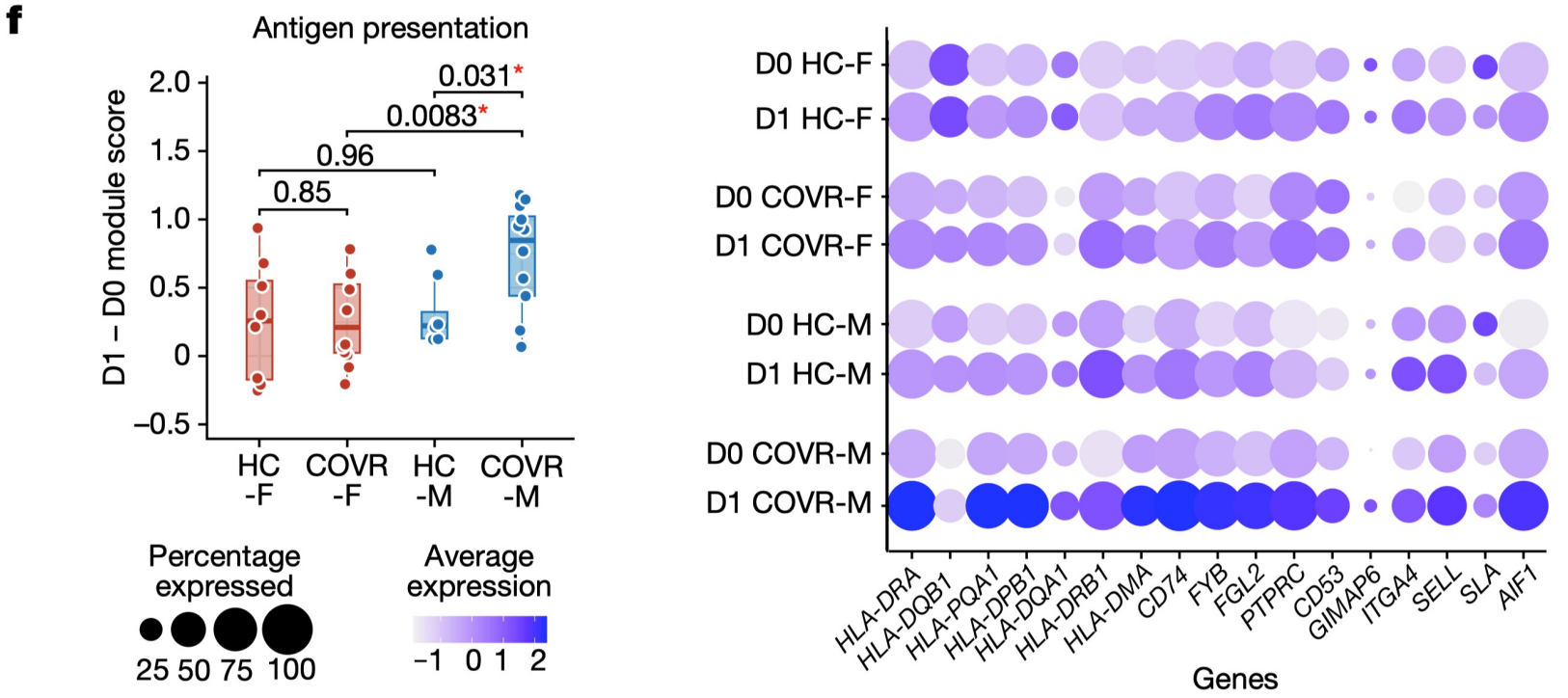
Male recoverees have stronger inflammatory responses compared with the healthy control and female recoverees

This systemic increase in IFNγ affects expression of IFNγ-induced genes in diverse cell types in male recoverees.



Male recoverees have stronger inflammatory responses compared with the healthy control and female recoverees

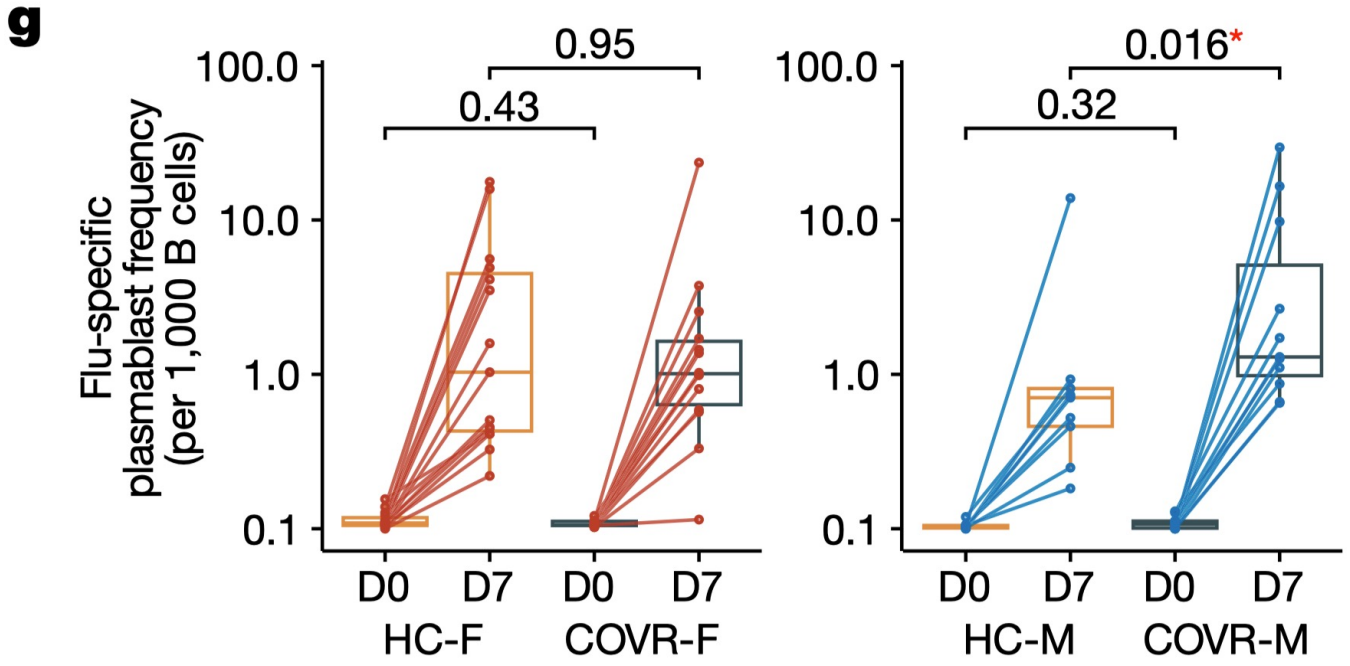
A more robust response was observed for antigen-presentation genes.



Antigen presentation is a vital immune process that is essential for T cell immune response triggering.

Male recoverees have stronger inflammatory responses compared with the healthy control and female recoverees

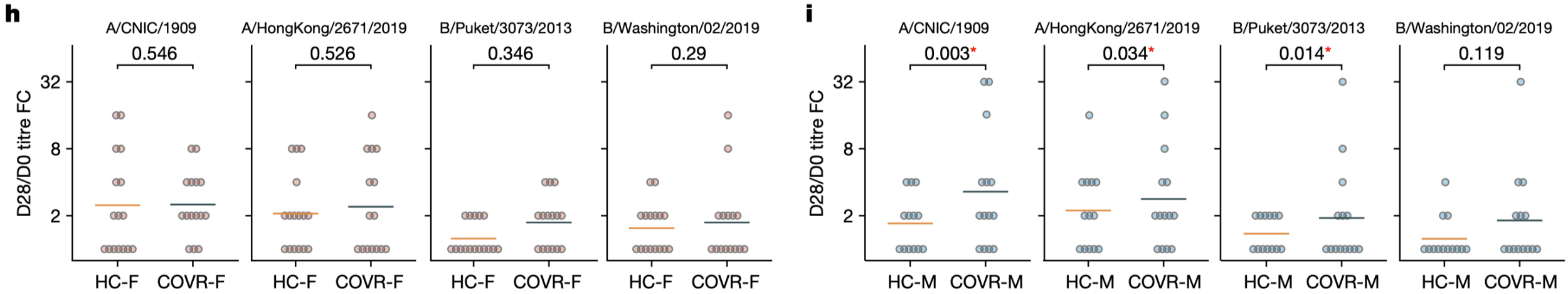
The COVR-M had a greater increase in influenza-specific plasmablasts compared with the HC-M at D7



Plasmablasts are immature plasma cells.
Plasma cells produce antibody.

Male recoverees have stronger inflammatory responses compared with the healthy control and female recoverees

The COVR-M group also had higher influenza-specific antibody responses at D28.



The influenza vaccine in this study is quadrivalent.

Results

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Linking the baseline before vaccination to male recoveree-specific responses after vaccination

Previous mild COVID-19 is associated with new baseline immune states before influenza vaccination (Fig. 1).

?

1. Identify and characterize cells related to elevated D1 IFN response .
2. Identify cell surface markers and transcriptional phenotypes marking these cells.

Previous mild COVID-19 is associated with COVR-M-group-specific responses after vaccination (Fig. 2).

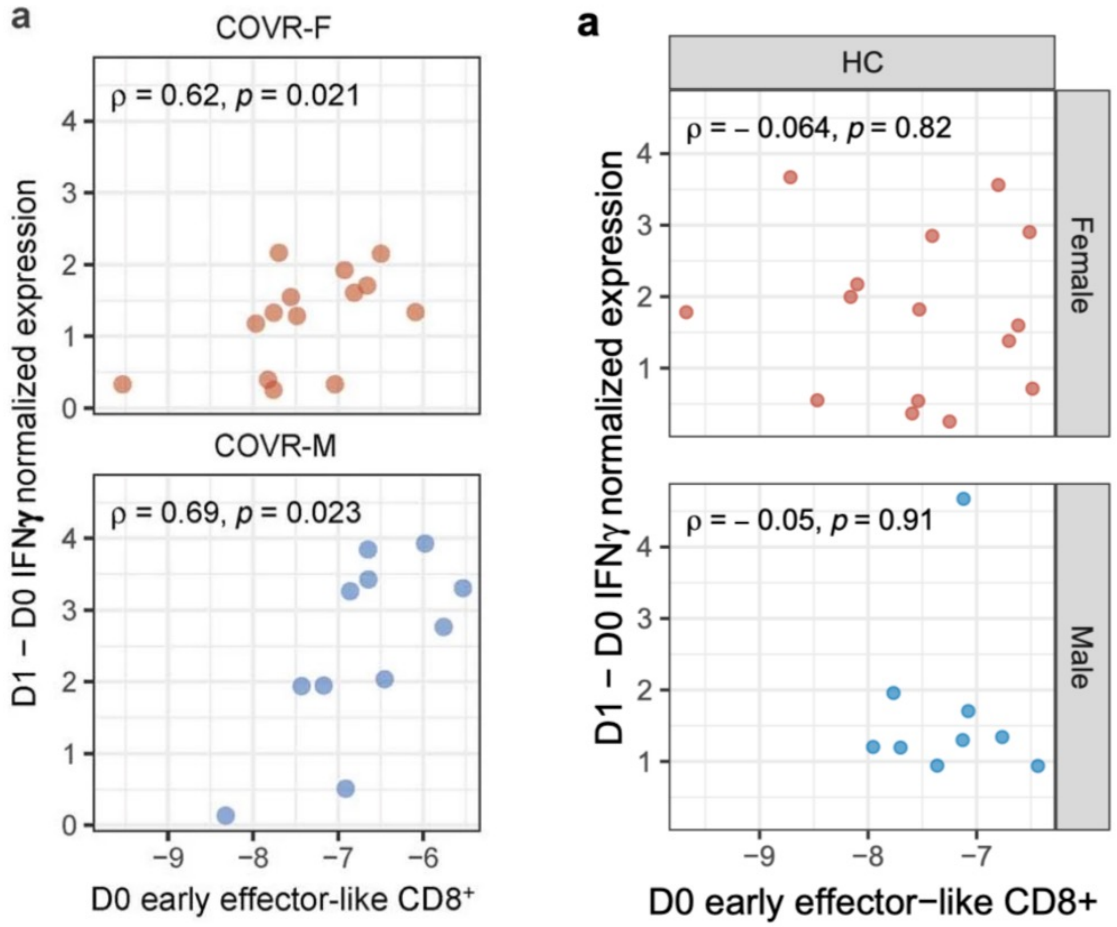
Identification of baseline (D0) immune cells predicting the D1 IFN-related responses

A kind of CD8+ T cells was a top candidate in the COVR-M group
and could therefore be a cellular source of IFNγ after vaccination.

Statistical model: multivariate linear model

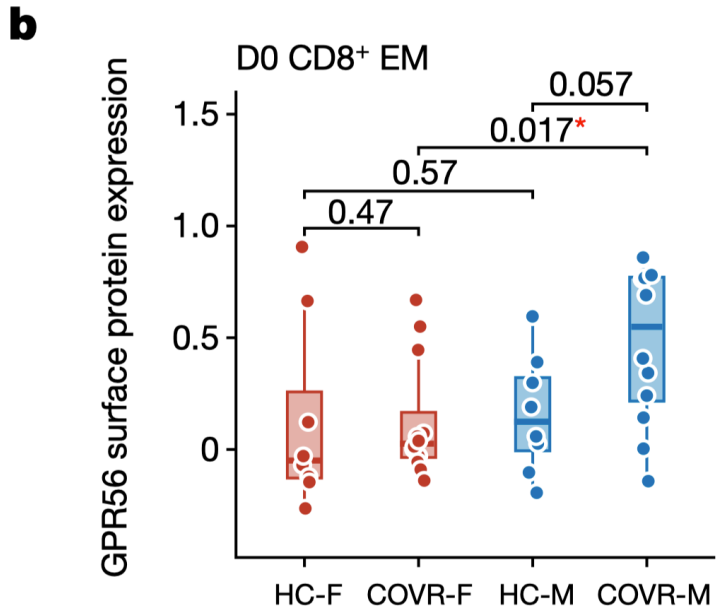
X: $\log_2$ cell frequency of D0 CD8+ T cells

Y: change (D1-D0) in IFNγ levels

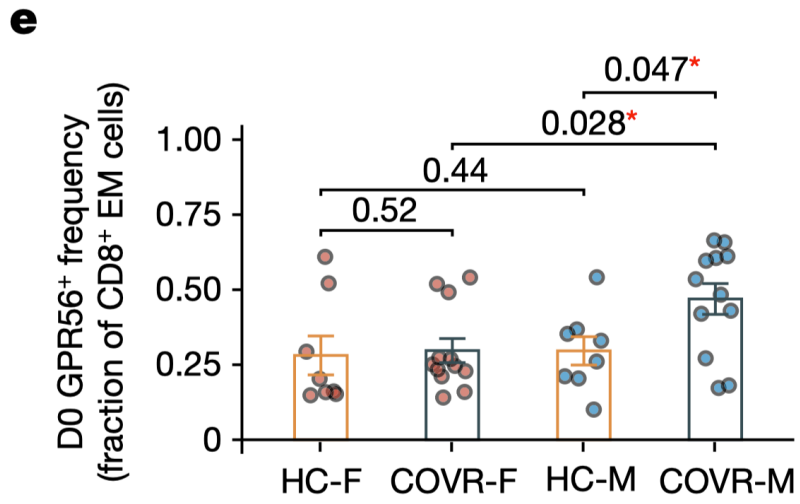


Identification of differentially-expressed genes in CD8+ T cells

GPR56 is the top differentially expressed marker in CD8+ T cells with increased expression in the male recoverees relative to the healthy control and female recoverees



GPR56 protein expression



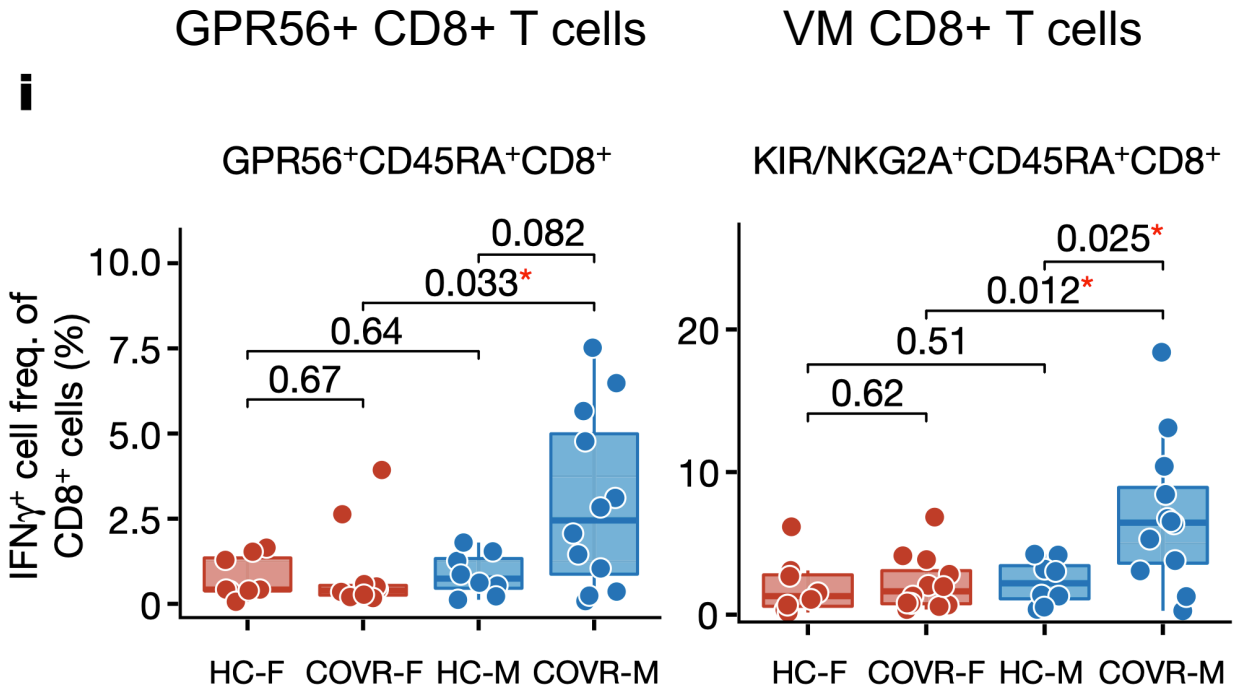
GPR56+ CD8+ T cell frequency

GPR56+ CD8+ T cells from the COVR-M group produced more IFNγ after IL-15 stimulation in vitro

Background

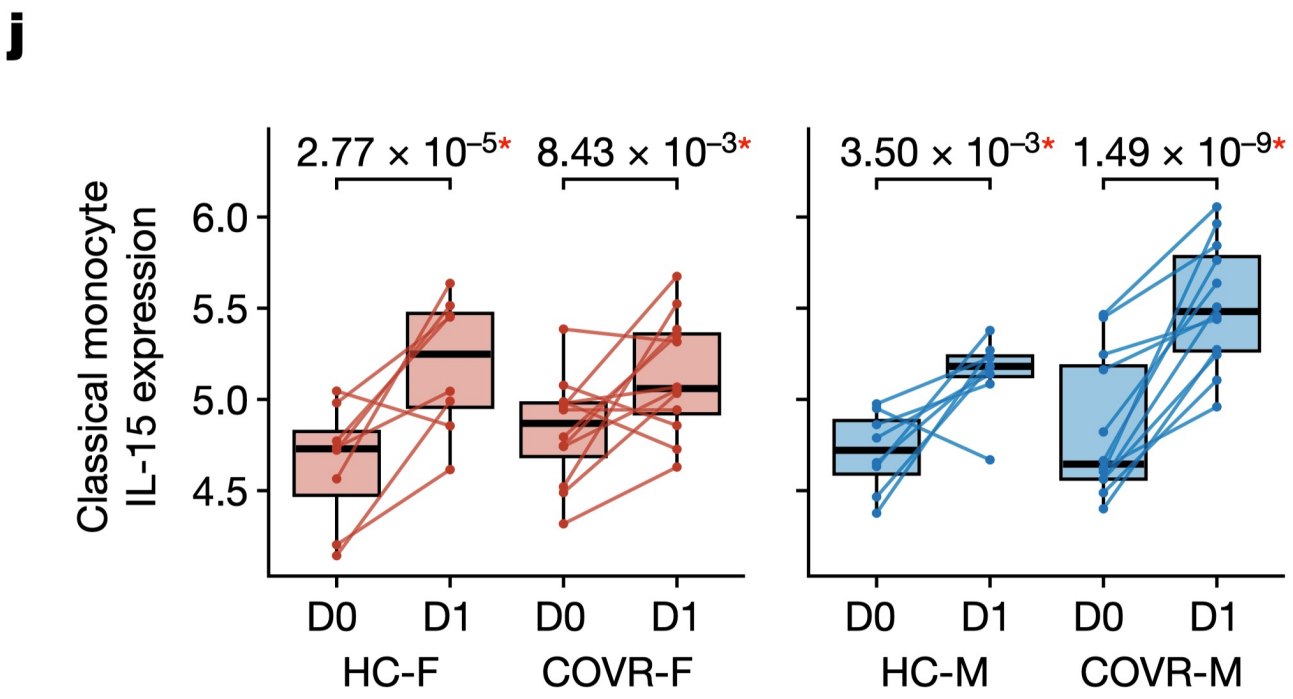
The manner of GPR56+ CD8+ T cells is similar to that of virtual memory (VM) CD8+ T cells.

VM CD8+ T cells can expand and produce IFNγ through cytokine stimulation (e.g., IL-15) without T cell receptor stimulation.



Cellular source of IL-15

Classical monocytes from the COVR-M group showed the most significant increases in IL15 mRNA levels on day 1 after influenza vaccination.



Brief summary

The increased IFNγ response in the COVR-M group after vaccination could be attributed to elevated IL-15 produced by classical monocytes and VM-like CD8+ T cells that produce more IFNγ after IL-15 stimulation.

Results

1. Baseline of mild COVID-19 recoverees
2. Contrasting influenza vaccination responses
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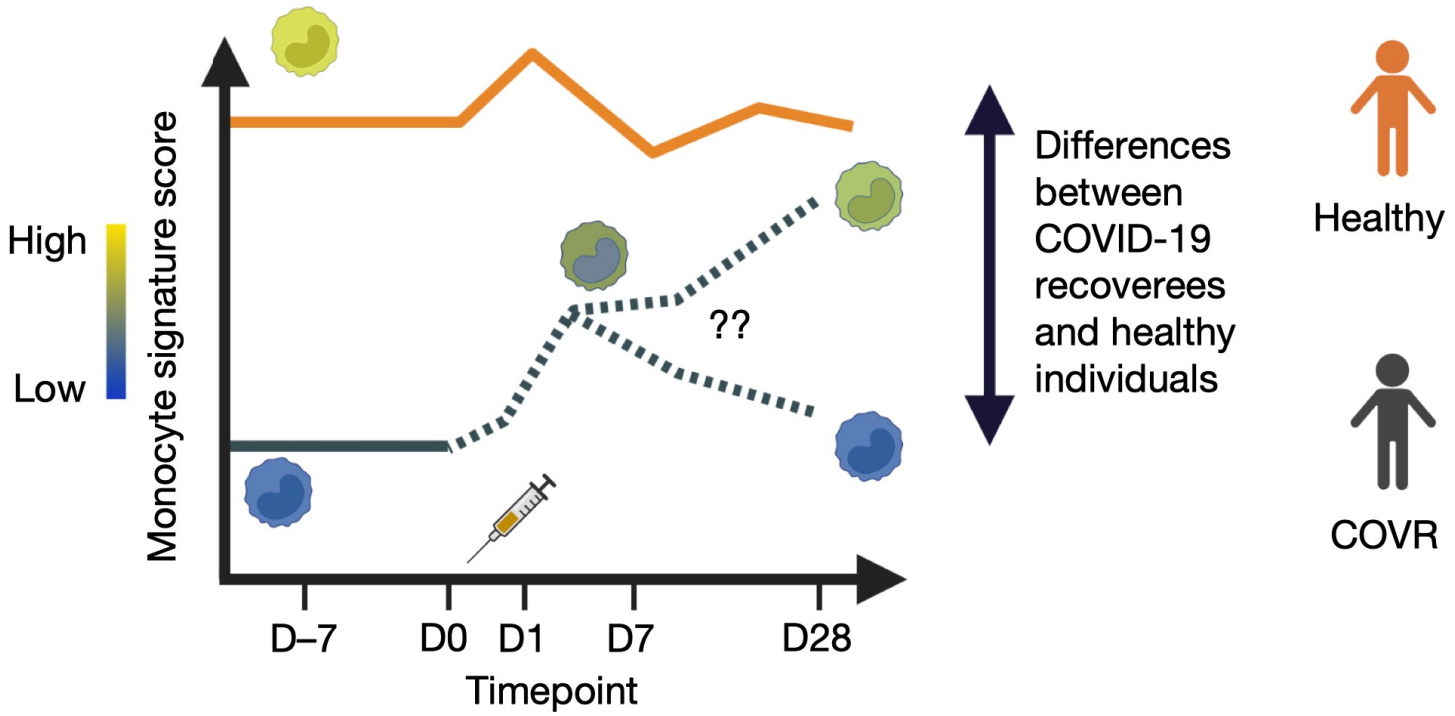
4. Vaccination shifts monocyte imprints

Can influenza vaccination help to shift the immune baseline of COVID-19 recoverees towards a healthy state?

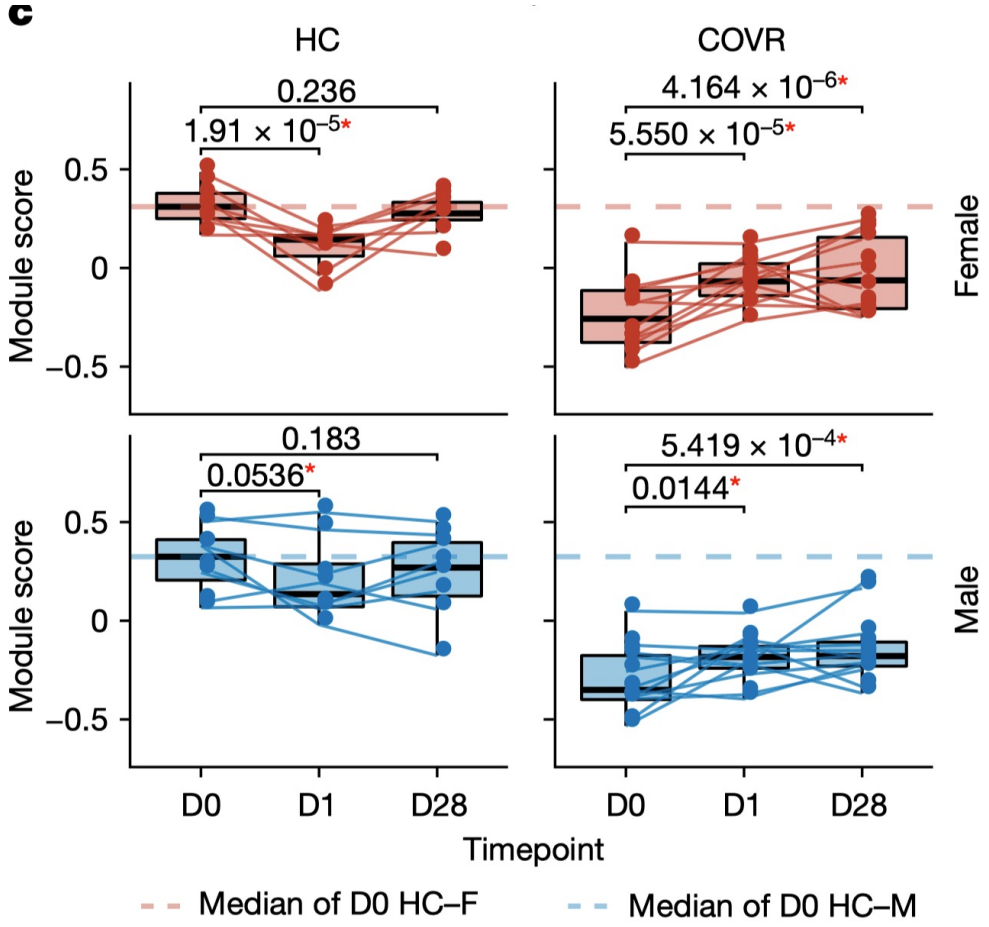
Examine whether the influenza vaccine shifts immune states towards normal

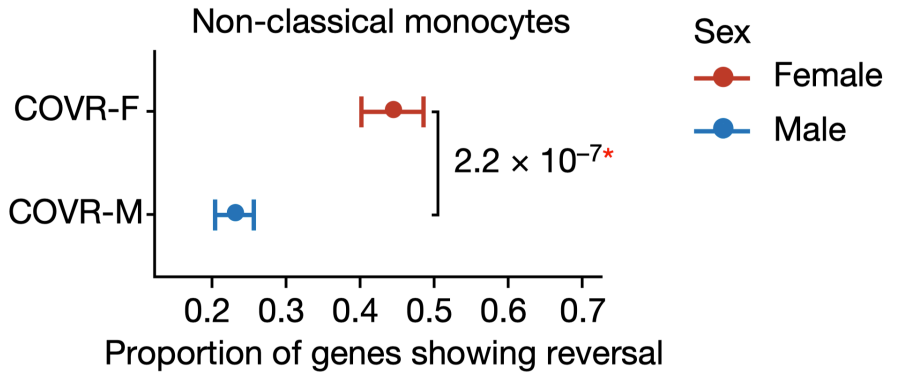


1. Using monocyte status as an example of immune baseline.

2. Focusing on the monocytes owing to the robustly depressed innate immune receptor (IIR) signature (reported in Fig. 1f,g).

Influenza vaccination can help to shift the immune state of recoverees towards the healthy state (monocytes), especially in female recoverees





The results for classical monocytes are similar.

Summary

1. Even mild, non-hospitalized COVID-19 infections may establish new, sex-dependent immunological imprints detectable months after clinical recovery.

2. Male recoverees have stronger inflammatory responses compared with the healthy control and female recoverees.

3. The increased IFNγ response in the COVR-M group after vaccination could be attributed to elevated IL-15 produced by classical monocytes and VM-like CD8+ T cells that produce more IFNγ after IL-15 stimulation.

4. Influenza vaccination can help to shift the immune state of recoverees towards the healthy state (monocytes), especially in female recoverees.

Discussion

Published: 22 August 2016

Sex differences in immune responses

Sabra L. Klein & Katie L. Flanagan

Nature Reviews Immunology **16**, 626–638 (2016) | Cite this article

Healthy female individuals tend to have stronger inflammatory responses to infections and vaccines (previous studies, non-COVID-19 related).

1. It was therefore surprising to find that male COVID-19 recoverees have a more unstable immune status at the baseline and stronger innate and adaptive responses to influenza vaccination.

2. Future research could assess whether some of the sex-specific imprints are associated with long-term COVID-19 effects.

Thanks for you attention!