# Quantifying the effect of HD vs SD FluZone vaccination on heterologous immunity

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2024 DIVERsity meeting

# Acknowledgements


- **Coauthors**: Jessica Knight, Wangnan Cao, Amanda Skarlupka, Ye Shen, Justin Bahl, Paul Thomas, Ted Ross, Andreas Handel.
- **Funding**: NIH Grants NIH grants/contracts U01AI150747, R01AI170116, 75N93019C00052, 75N93021C00018, and R35GM146612; USM Start-Up Grant; Georgia Research Alliance; UGA Graduate School.
- **Software**: R Team, Posit PBC, Biorender, R package authors.
- And viewers like you!

# Background: HD is good*

- Induces a stronger homologous antibody response than SD vaccine.
- Also associated with reduced disease severity.

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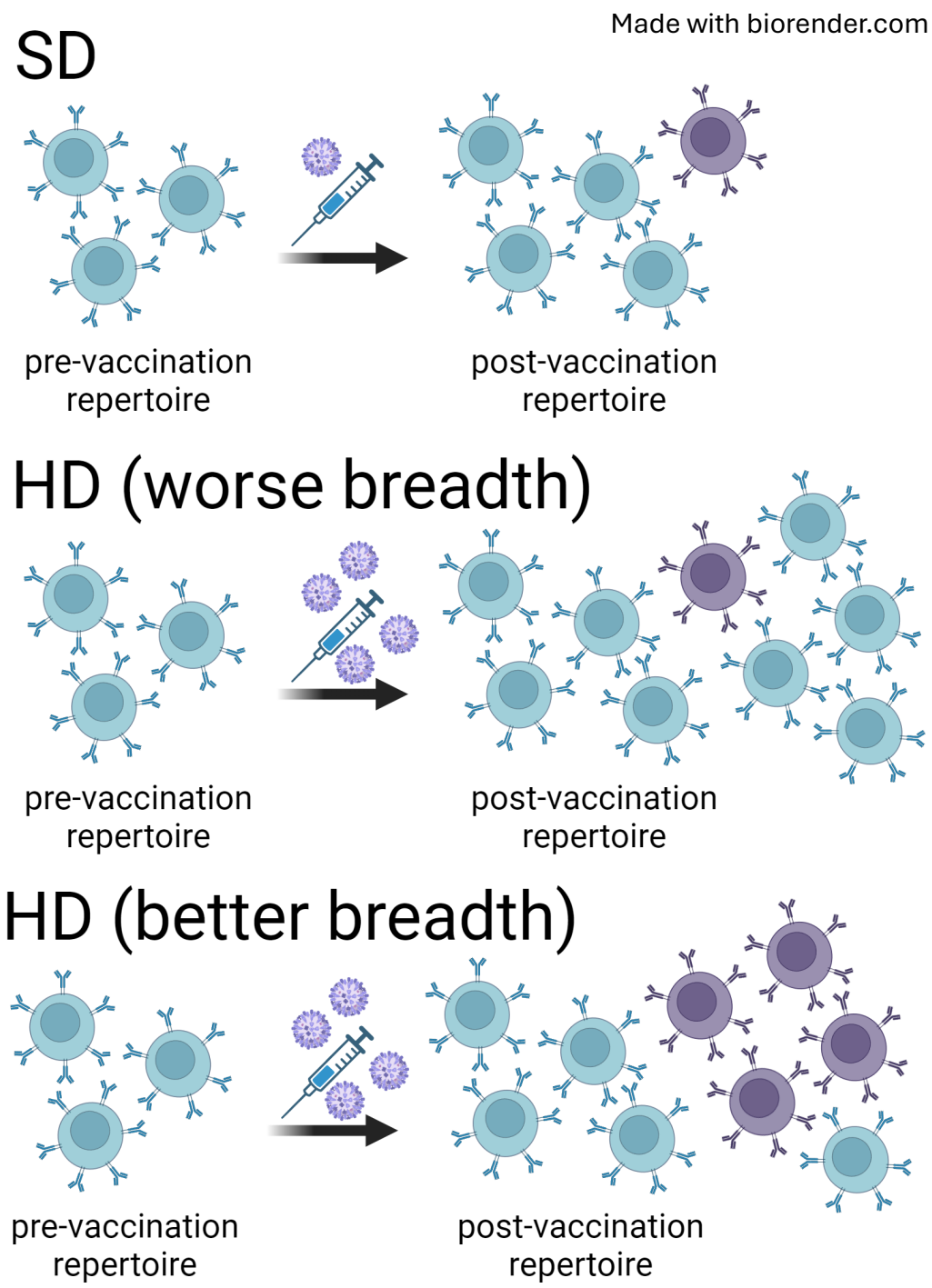
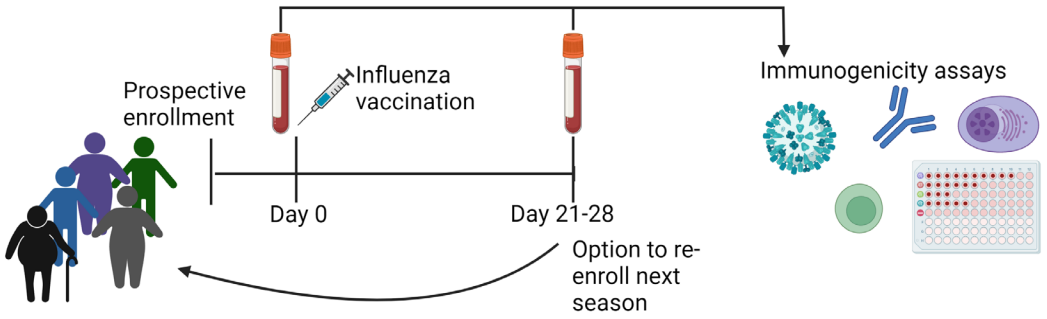
- Induces a stronger homologous antibody response than SD vaccine.
- Also associated with reduced disease severity.
- **BUT** there are viable mechanisms for HD to either reduce or enhance heterologous responses.



# Do the benefits of HD vaccination extend to heterologous Abs?

# UGAFluVac data



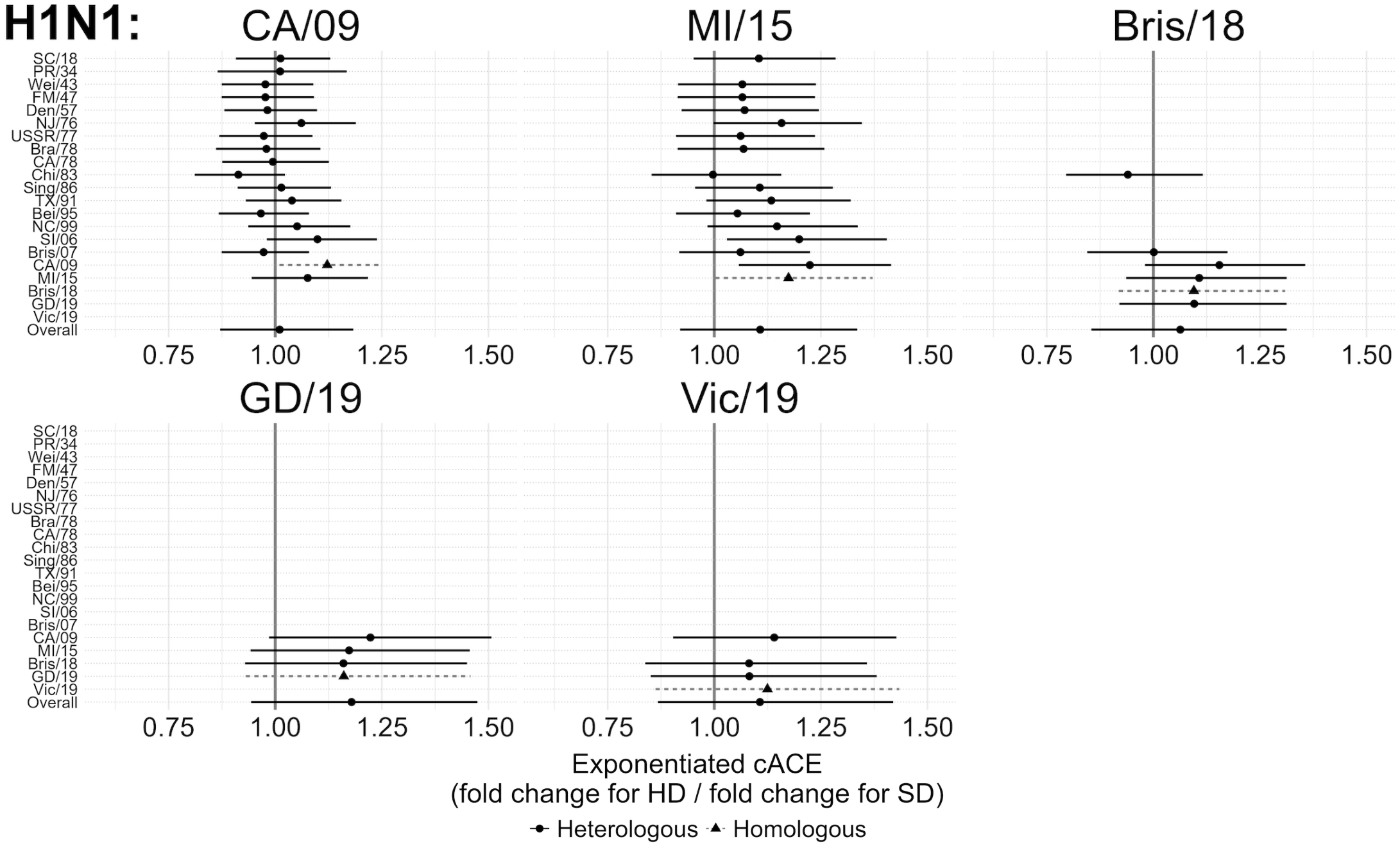

- Prospective open cohort design where individuals could repeat.
- Age 65+ offered choice of HD or SD vaccine.
- Large panel of heterologous HAI

| **Characteristic** | **FL**, N = 123 | **PA**, N = 219 | **UGA**, N = 326 | **Overall**, N = 668 |
|---|---|---|---|---|
| Season, n (%) | | | | |
| 2013 - 2014 | 20 (16) | 36 (16) | 0 (0) | 56 (8.4) |
| 2014 - 2015 | 35 (28) | 57 (26) | 0 (0) | 92 (14) |
| 2015 - 2016 | 35 (28) | 63 (29) | 0 (0) | 98 (15) |
| 2016 - 2017 | 33 (27) | 63 (29) | 15 (4.6) | 111 (17) |
| 2017 - 2018 | 0 (0) | 0 (0) | 38 (12) | 38 (5.7) |
| 2018 - 2019 | 0 (0) | 0 (0) | 19 (5.8) | 19 (2.8) |
| 2019 - 2020 | 0 (0) | 0 (0) | 90 (28) | 90 (13) |
| 2020 - 2021 | 0 (0) | 0 (0) | 83 (25) | 83 (12) |
| 2021 - 2022 | 0 (0) | 0 (0) | 81 (25) | 81 (12) |
| Dose, n (%) | | | | |
| SD | 82 (67) | 73 (33) | 79 (24) | 234 (35) |
| HD | 41 (33) | 146 (67) | 247 (76) | 434 (65) |
| Age, Median (Range) | 70 (65 - 82) | 70 (65 - 85) | 70 (65 - 86) | 70 (65 - 86) |
| Birth year, Median (Range) | 1945 (1933 - 1951) | 1945 (1931 - 1951) | 1950 (1934 - 1956) | 1947 (1931 - 1956) |

# Methods outline

- Bayesian hierarchical / mixed-effects model with **titer increase** (log2 fold change) as the outcome.
- Controlled for confounders using smoothing splines and multiple hierarchical effects.
- From model predictions, estimate the posterior **Average Causal Effect**, the predicted change in titer increase of switching from SD to HD in the study sample (with all other factors staying the same).

# cACE conditional on assay strain and vaccine strain



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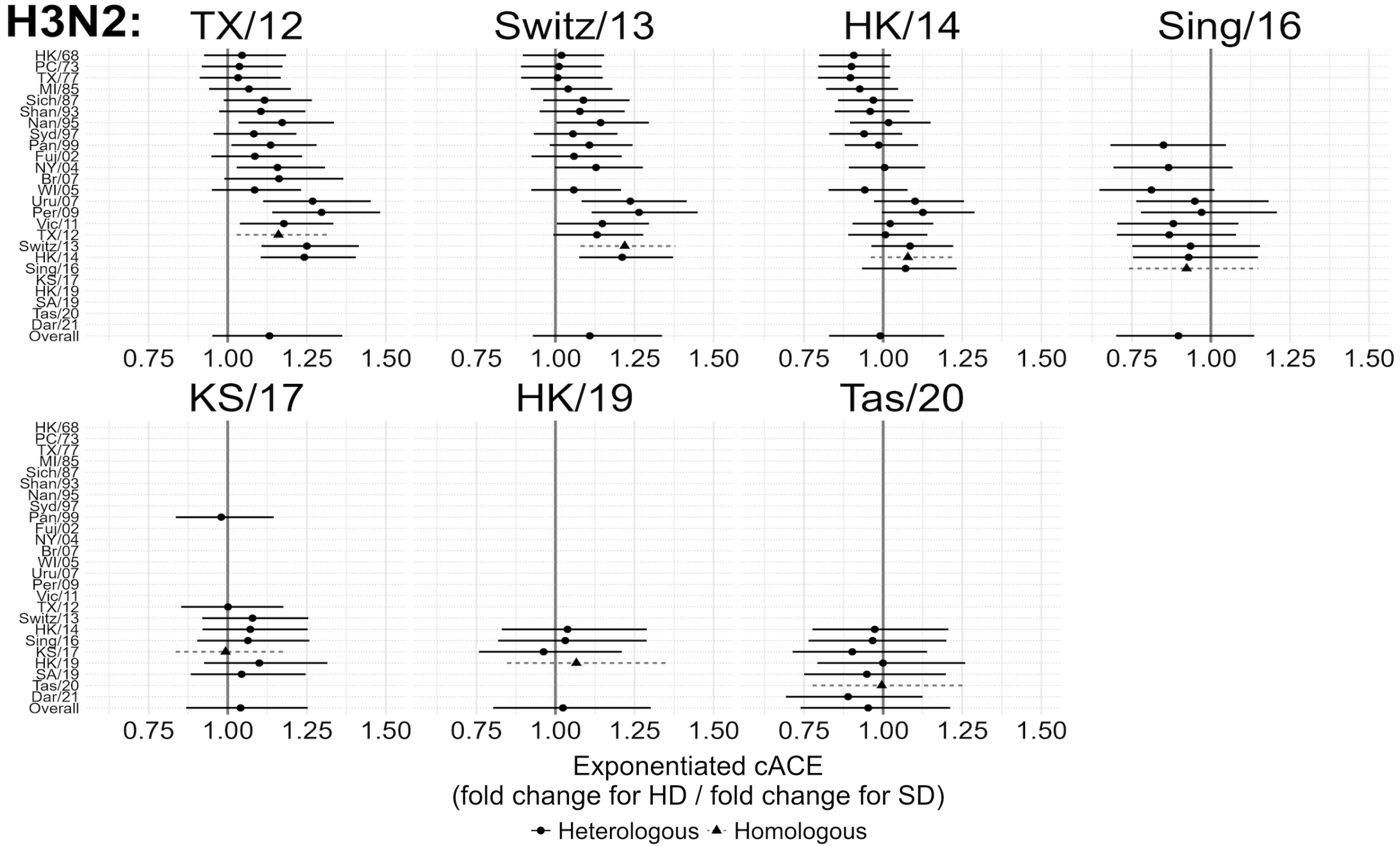
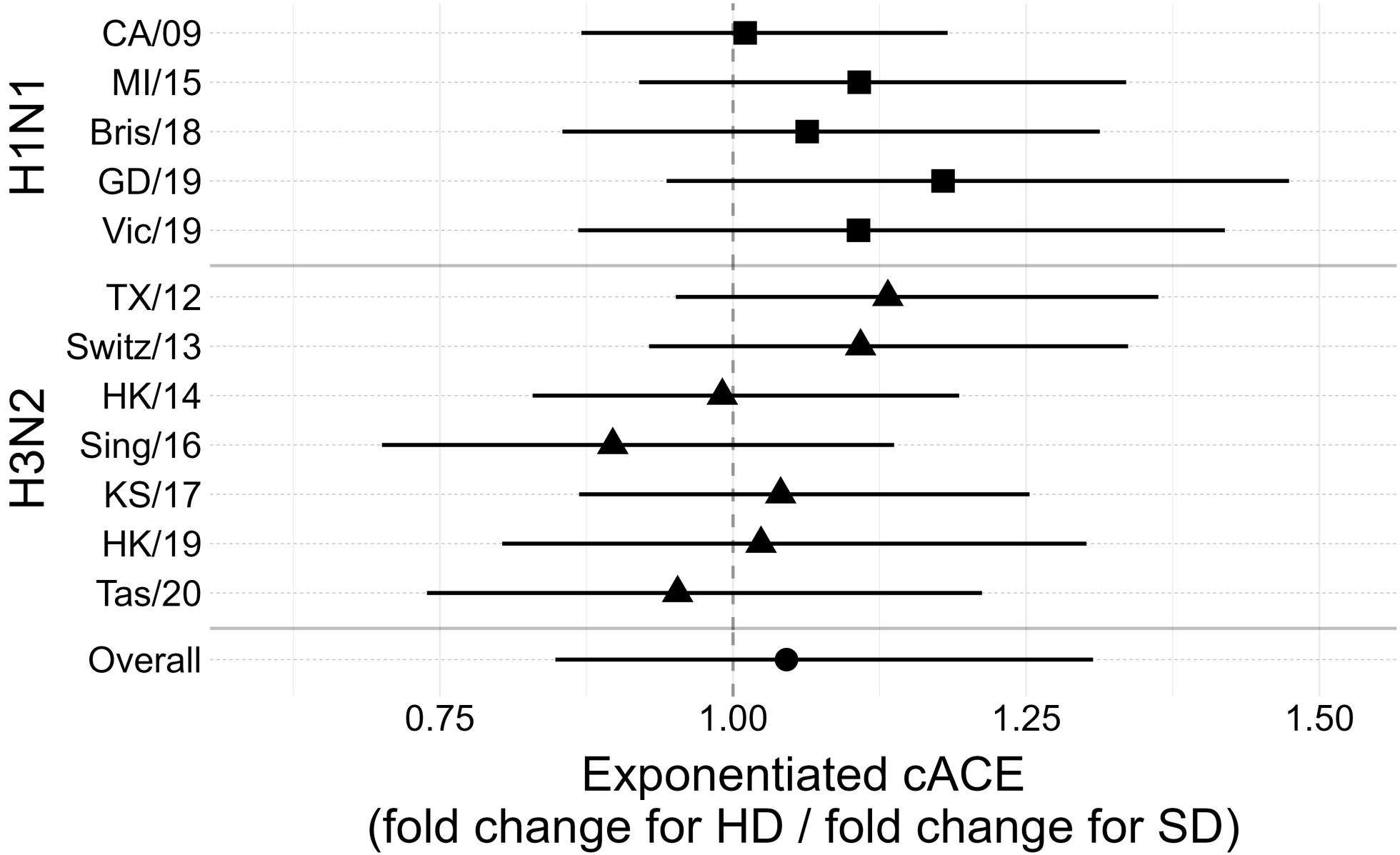
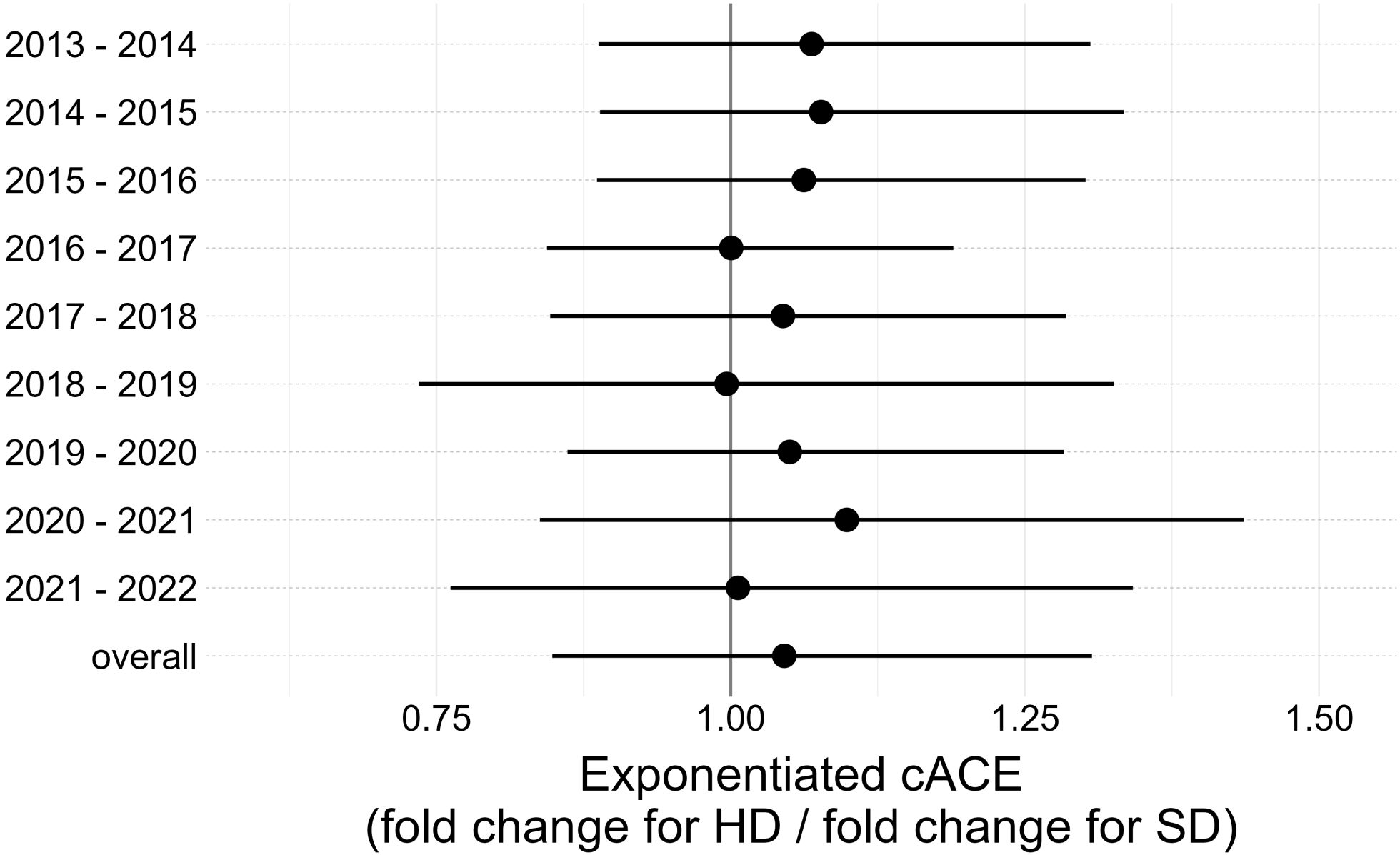


# cACE conditional on vaccine strain (averaged over assay strains)



# cACE conditional on season
# (averaged over all vaccine/assay strains in season)



# Conclusions

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# Conclusions

- Our results are consistent with a small positive effect of HD on heterologous antibody response.
- The effect is small and variable – potentially some subset of people get a better result.
- Some strains have a worse response with HD – we don’t understand why.
- If HD is better, maybe higher dose is even better?

# Future work

- Examine distribution of ICEs (instead of summarizing with ACE) for more granular detail.
- Incorporating flu B data.
- Using antigenic distance as a continuous predictor rather than using a strain-specific model.

# Thank you!

Contact info: https://wzbillings.com/

Code/manuscript draft: https://github.com/ahgroup/Billings-2024-HD-Heterologous

# Methods outline

- For each outcome, we fit a separate linear mixed-effects model using the R package **brms**.
- We create two **counterfactual samples** and get the model predictions for each individual.

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| ID | Age | Titer increase | Dose |
|---|---|---|---|
| 1 | 65 | 4 | HD |
| 2 | 67 | 2 | SD |
| 3 | 66 | 8 | HD |
| 4 | 80 | 2 | SD |
| 5 | 74 | 1 | HD |

“real” study sample

# Methods outline

- For each outcome, we fit a separate linear mixed-effects model using the R package **brms**.
- We create two **counterfactual samples** and get the model predictions for each individual.

| ID | Age | $\widehat{TI}$ | Dose |
|---|---|---|---|
| 1 | 65 | 3.2 | **SD** |
| 2 | 67 | 1.6 | **SD** |
| 3 | 66 | 6.5 | **SD** |
| 4 | 80 | 3.2 | **SD** |
| 5 | 74 | 4.1 | **SD** |

| ID | Age | $\widehat{TI}$ | Dose |
|---|---|---|---|
| 1 | 65 | 4.4 | **HD** |
| 2 | 67 | 2.1 | **HD** |
| 3 | 66 | 6.8 | **HD** |
| 4 | 80 | 2.9 | **HD** |
| 5 | 74 | 4.1 | **HD** |

counterfactual study samples

# Methods outline

- For each outcome, we fit a separate linear mixed-effects model using the R package **brms**.
- We create two **counterfactual samples** and get the model predictions for each individual.

| ID | Age | $\widehat{\text{ICE}}$ |
|---|---|---|
| 1 | 65 | 1.2 |
| 2 | 67 | 0.5 |
| 3 | 66 | 0.3 |
| 4 | 80 | -0.3 |
| 5 | 74 | 0.0 |

counterfactual contrasts (**ICE** estimate)

# Methods outline

- For each outcome, we fit a separate linear mixed-effects model using the R package **brms**.
- We create two **counterfactual samples** and get the model predictions for each individual.
- The **ACE (Average Causal Effect)** is our measure of the effect of dose after controlling for confounding (average of all of the ICEs over the study sample)**.**
- We calculate **conditional ACE (cACE)** for various strata by averaging over within-stratum ICEs.

# Model formula

```
outcome ~
    dose +
    s(birth_year_c, k = 5) +
    s(age_c, k = 5) +
    s(log_pretiter, k = 5) +
    s(year_c, k = 5, by = study) +
    (1 | id) +
    (1 | study) +
    (1 + dose | strain_type) +
    (1 + dose | strain_type:strain_name) +
    (1 + dose | vaccine_name) +
    (1 + dose | vaccine_name:strain_type)
```

## Model likelihood and priors

For the post-vaccination titer and titer increase outcomes, we used a Gaussian (Normal distribution) likelihood function for the model. Letting the outcome be $y$, we assumed that

$$y_i \sim \text{Normal}\left(\mu_i, \sigma\right),$$

where $\sigma$ is the residual variance, and $\mu_i$ is described by the `brms` equation above, which builds a model for the conditional mean of `y_i` given the predictor data.

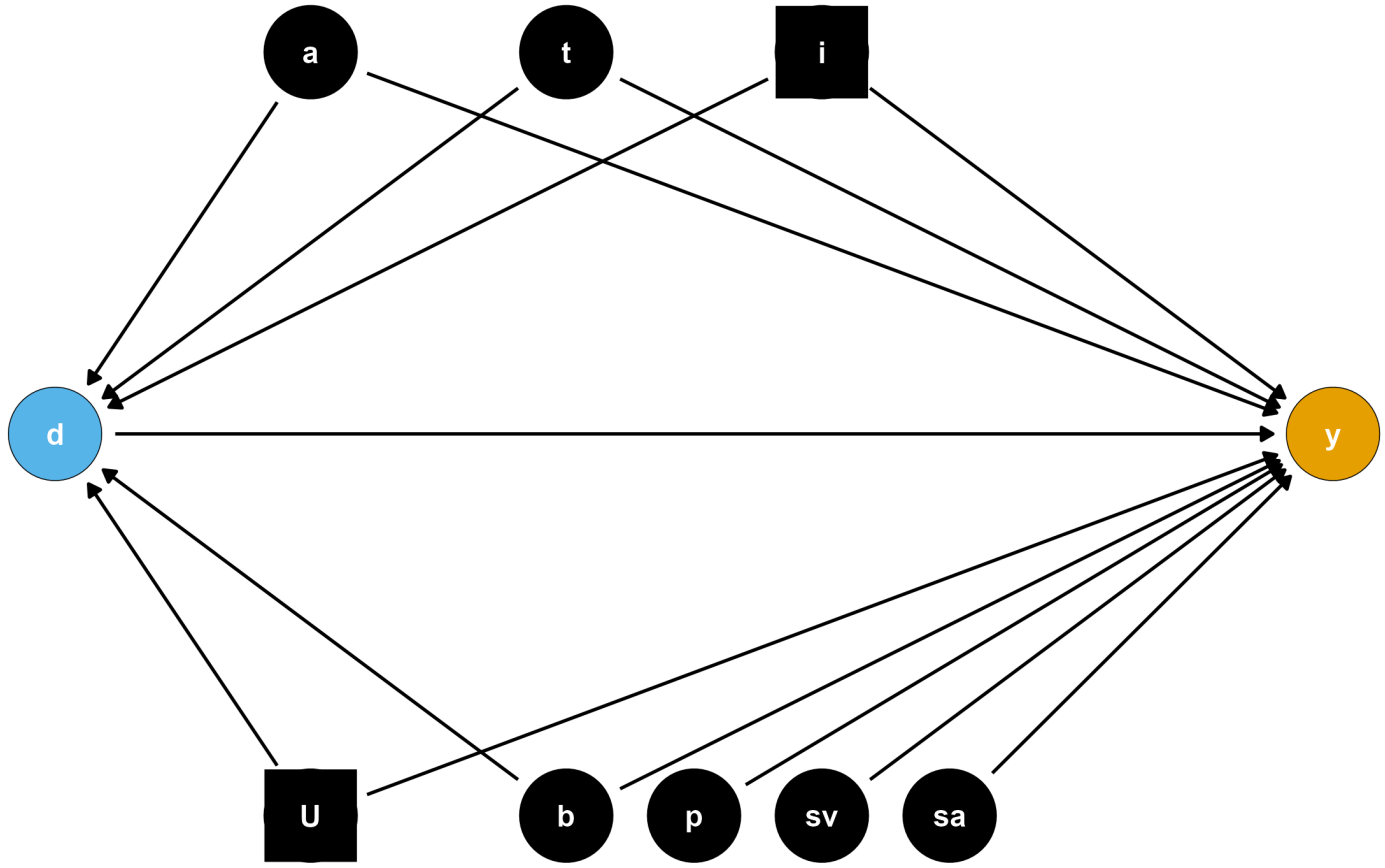
For the linear models, we used the following priors:

$$\begin{aligned}
\alpha_{(\cdot)} &\sim \text{Normal}(0, 5) \\
\beta_{(\cdot)} &\sim \text{Normal}(0, 5) \\
\sigma &\sim t^{+}(\nu = 3, 0, 1) \\
L_{(\cdot)} &\sim \text{LKJ}(1)
\end{aligned}$$

# Model fitting details and diagnostics

- brms to Stan (via cmdstanr).
- Sampled using NUTS.
- 16 parallel chains with 500 warmup, 1250 sampling iterations per chain (20k samples total).
- Target Metropolis proposal acceptance rate of 0.99.
- Post warmup divergent transitions: **7/20000.**
- Minimum E-BFMI across chains: **0.552**.
- Min. ESS (tail) across all parameters: **2808**.
- Min. ESS (bulk) across all parameters: **1623**.
- Max. $\hat{R}$ across all parameters: **1.009**.

# DAG for confounder identification




| Abbreviation | Variable |
|---|---|
| d | Vaccine dose |
| y | Immunological outcome |
| a | Age |
| t | Calendar time |
| i | Other individual effects |
| U | Other unobserved confounders |
| b | Birth year |
| p | Pre-vaccination titer |
| sv | Strain included in vaccine |
| sa | Strain used for assay |