ADAPTIVE HEALTH INTELLIGENCE

EVIDENCE IN ACTION

Modelling immune responses to COVID-19 vaccination with a Bayesian three-level hierarchical model

Michael Dymock

18th October 2023

TELETHON KIDS INSTITUTE
Discover. Prevent. Cure.

WESFARMERS CENTRE OF VACCINES & INFECTIOUS DISEASES

THE UNIVERSITY OF SYDNEY

THE UNIVERSITY OF WESTERN AUSTRALIA

AUSTRALIAN TRIALS METHODOLOGY CONFERENCE 2023

Acknowledgements

- PICOBOO Team
  - Investigators, site staff, participants,…
- Coauthors:
  - **Charlie McLeod**
  - Tom Snelling
  - Peter Richmond
  - **Julie Marsh**

ADAPTIVE HEALTH INTELLIGENCE
EVIDENCE IN ACTION

Overview

- PICOBOO Recap
  - Design
  - Decision rules
- Bayesian model
  - Multivariate responses
  - Hierarchical prior structure
- Simulations
- First scheduled analysis

PICOBOO Recap

- COVID-19 vaccinations in immunocompetent participants
- Participants randomised to receive a booster dose and *may* be rerandomised
- Strata: Primary schedule and age group
- Interventions: Pfizer, Moderna, Novavax, …
- Primary estimand: log10 ancestral SARS-CoV2 anti-spike IgG at 28 days
- Decision rules: Stop recruitment if adequate precision

Notation

- Participant: $i \in \boldsymbol{I} = \{1,2,\ldots,N\}$
- Primary Schedule: $j \in \boldsymbol{J} = \{\mathrm{AZ}, \mathrm{Pf}, \mathrm{Mod}\}$
- Age Group: $l \in \boldsymbol{L} = \{12 -< 18, 18 -< 50, 50 -< 70, \geq 70\}$
- Intervention: $k \in \boldsymbol{K} = \{\mathrm{Pf}, \mathrm{Mod}, \mathrm{Nvx}, \mathrm{Pf\ BA.1}, \mathrm{Mod\ BA.1}, \mathrm{Pf\ BA.4/5}, \mathrm{Mod\ BA.4/5}\}$
- Booster Number: $m \in \boldsymbol{M_i} \subseteq \boldsymbol{M} = \{1,2,3\}$
- Covariates: $\boldsymbol{x_{im}} = \{x_{im1}, x_{im2}, \ldots, x_{imP}\}$
- Outcome: $\boldsymbol{y_{ijk^*l}} \in \mathbb{R}^{|M_i|} \subseteq \mathbb{R}^3 \quad (y_{ijklm} \in \mathbb{R}, \boldsymbol{k^*} \subseteq \boldsymbol{K})$

ADAPTIVE HEALTH INTELLIGENCE
EVIDENCE IN ACTION

Model

$$\boldsymbol{Y}_{\boldsymbol{ijk^*l}} \sim \mathrm{N}\left(\left[\mu_{jklm} + \boldsymbol{x}_{\boldsymbol{im}}\boldsymbol{\beta}\right]^{|M_i|}, \left[\boldsymbol{\Sigma}_{\boldsymbol{l}}\right]^{|M_i|\times|M_i|}\right)$$

Model

$$\boldsymbol{Y}_{\boldsymbol{ijk^*l}} \sim \mathrm{N}\left(\left[\mu_{jklm} + \boldsymbol{x}_{\boldsymbol{im}}\boldsymbol{\beta}\right]^{|M_i|}, \left[\boldsymbol{\Sigma}_{\boldsymbol{l}}\right]^{|M_i|\times|M_i|}\right)$$

Multivariate outcome

ADAPTIVE HEALTH INTELLIGENCE
EVIDENCE IN ACTION

Model

Mean response conditional on covariates

$$\boldsymbol{Y_{ijk^*l}} \sim \mathrm{N}\left(\left[\mu_{jklm} + \boldsymbol{x_{im}\beta}\right]^{|M_i|}, \left[\boldsymbol{\Sigma_l}\right]^{|M_i|\times|M_i|}\right)$$

Multivariate outcome

ADAPTIVE HEALTH INTELLIGENCE

EVIDENCE IN ACTION

Model

Mean response conditional on covariates

$$\boldsymbol{Y_{ijk^*l}} \sim \mathrm{N}\left(\left[\mu_{jklm} + \boldsymbol{x_{im}\beta}\right]^{|M_i|}, \left[\boldsymbol{\Sigma_l}\right]^{|M_i|\times|M_i|}\right)$$

Multivariate outcome

Covariate effects

ADAPTIVE HEALTH INTELLIGENCE

EVIDENCE IN ACTION

Model

Mean response conditional on covariates

Vector is length $|M_i|$

$$\boldsymbol{Y_{ijk^*l}} \sim \mathrm{N}\left(\left[\mu_{jklm} + \boldsymbol{x_{im}\beta}\right]^{|M_i|}, \left[\boldsymbol{\Sigma_l}\right]^{|M_i|\times|M_i|}\right)$$

Multivariate outcome

Covariate effects

ADAPTIVE HEALTH INTELLIGENCE

EVIDENCE IN ACTION

Model

Mean response conditional on covariates

Vector is length $|M_i|$

$$\boldsymbol{Y_{ijk^*l}} \sim \mathrm{N}\left(\left[\mu_{jklm} + \boldsymbol{x_{im}\beta}\right]^{|M_i|}, \left[\boldsymbol{\Sigma_l}\right]^{|M_i|\times|M_i|}\right)$$

Multivariate outcome

Covariate effects

3x3 variance-covariance matrix

ADAPTIVE HEALTH INTELLIGENCE

EVIDENCE IN ACTION

Model

Mean response conditional on covariates

Vector is length $|M_i|$

Matrix has dimension $|M_i| \times |M_i|$

$$\boldsymbol{Y_{ijk^*l}} \sim \mathrm{N}\left(\left[\mu_{jklm} + \boldsymbol{x_{im}\beta}\right]^{|M_i|}, \left[\boldsymbol{\Sigma_l}\right]^{|M_i| \times |M_i|}\right)$$

Multivariate outcome

Covariate effects

3x3 variance-covariance matrix

ADAPTIVE HEALTH INTELLIGENCE

EVIDENCE IN ACTION

Example: Participant has outcomes for 4th and 5th dose

$$\begin{bmatrix} Y_{ijkl2} \\ Y_{ijk'l3} \end{bmatrix} \sim \mathrm{N}\left(\begin{bmatrix} \mu_{jkl2} + \boldsymbol{x_{i2}\beta} \\ \mu_{jk'l3} + \boldsymbol{x_{i3}\beta} \end{bmatrix}, \begin{bmatrix} \sigma_l^2 & r_{l23}\sigma_l^2 \\ r_{l32}\sigma_l^2 & \sigma_l^2 \end{bmatrix} \right)$$

ADAPTIVE HEALTH INTELLIGENCE
EVIDENCE IN ACTION

Hierarchical prior structure (μ_{jklm})

First level: share between booster doses

$$\mu_{jklm} \sim \mathrm{N}(\mu_{jkl}, \tau^2_{jkl})$$

Hierarchical prior structure (μ_{jklm})

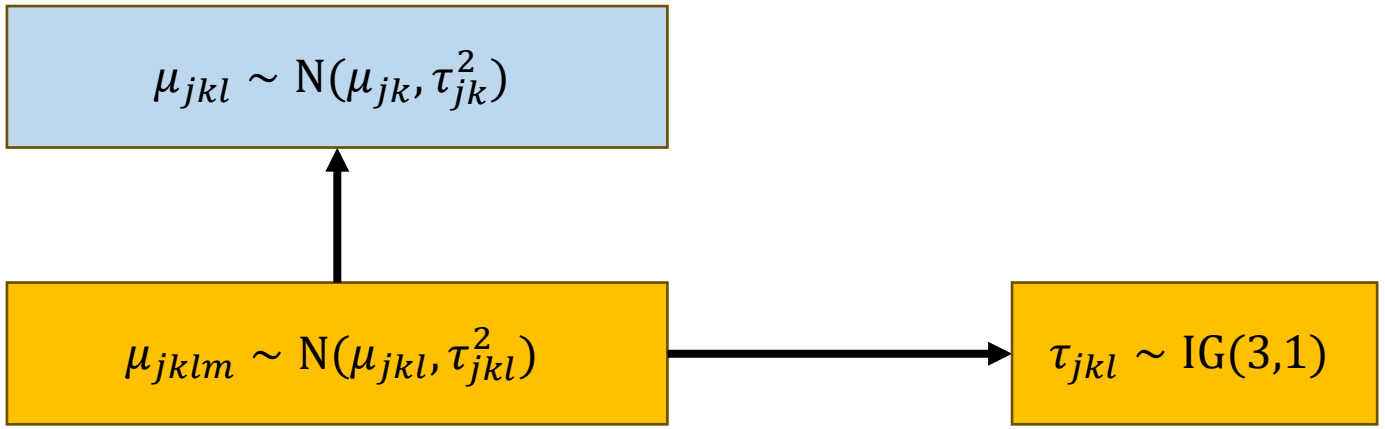
First level: share between booster doses

$$\mu_{jklm} \sim \mathrm{N}(\mu_{jkl}, \tau^2_{jkl}) \rightarrow \tau_{jkl} \sim \mathrm{IG}(3,1)$$

Hierarchical prior structure (μ_{jklm})

Second level: share between age groups

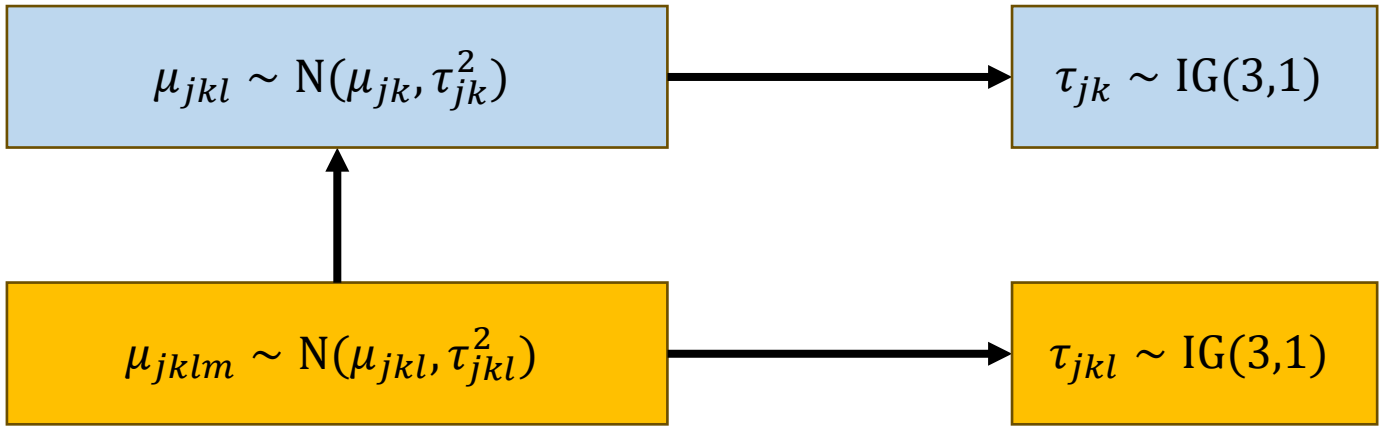
First level: share between booster doses



Hierarchical prior structure (μ_{jklm})

Second level: share between age groups

First level: share between booster doses

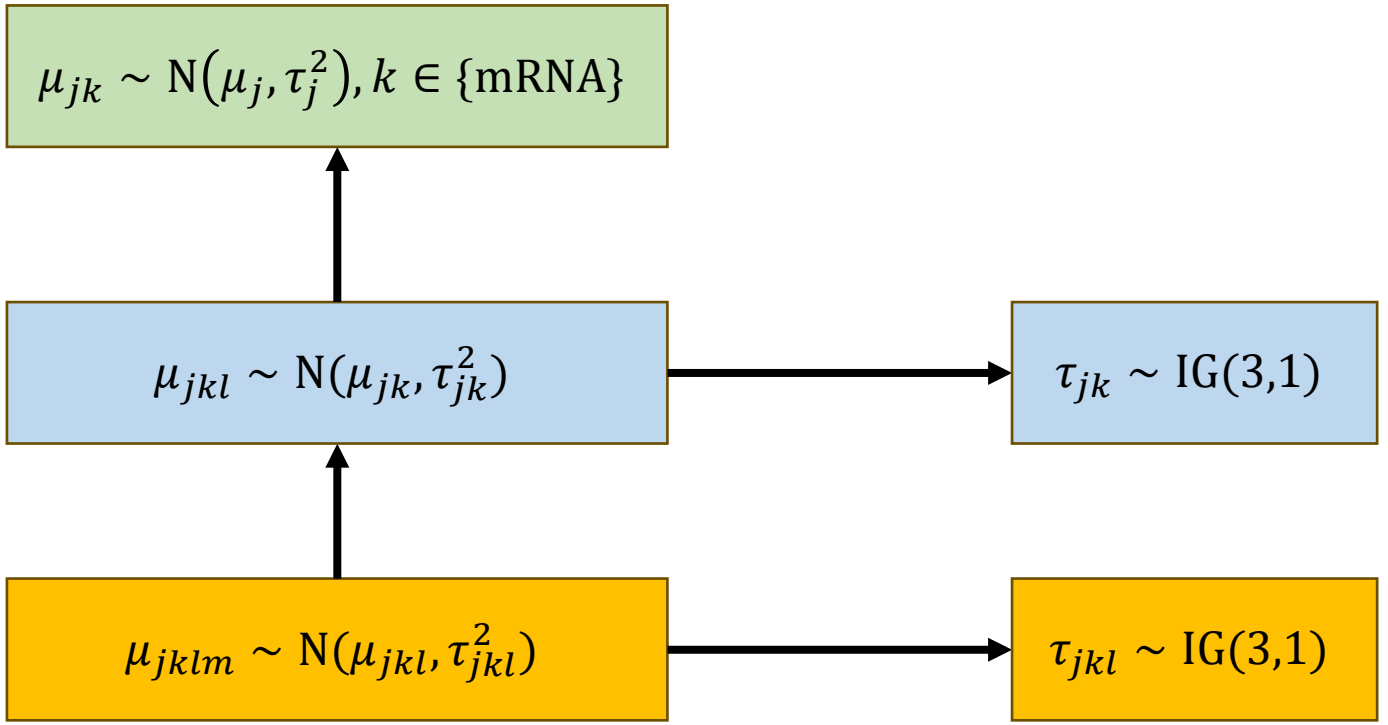


Hierarchical prior structure (μ_{jklm})

Third level: share between mRNA interventions

Second level: share between age groups

First level: share between booster doses

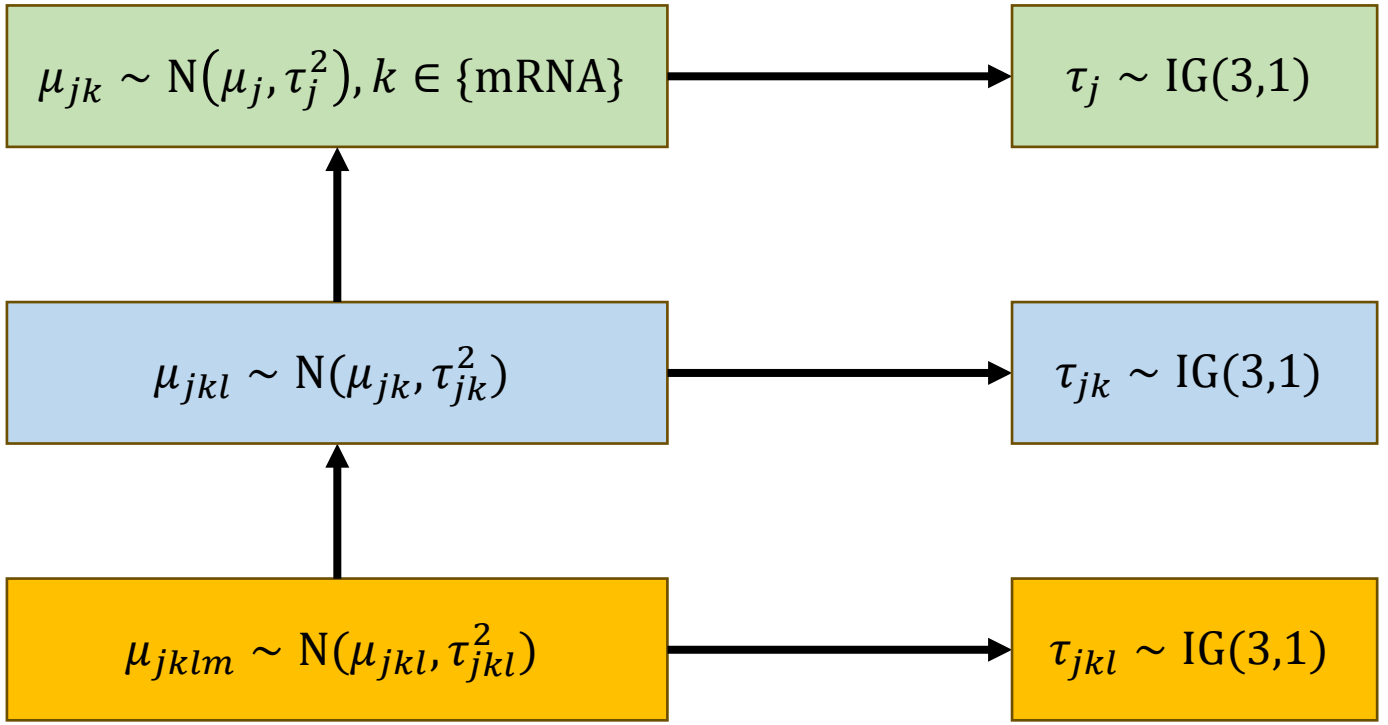


Hierarchical prior structure (μ_{jklm})

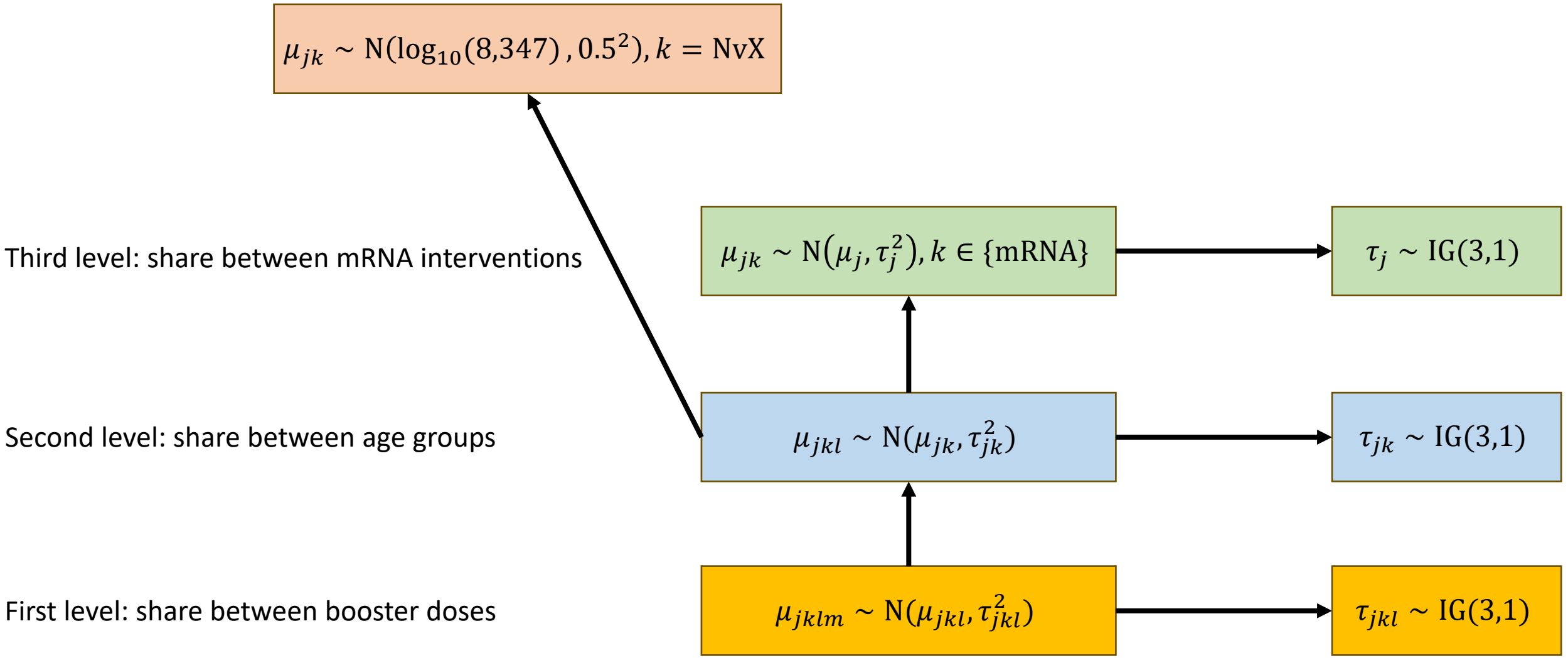
Third level: share between mRNA interventions

Second level: share between age groups

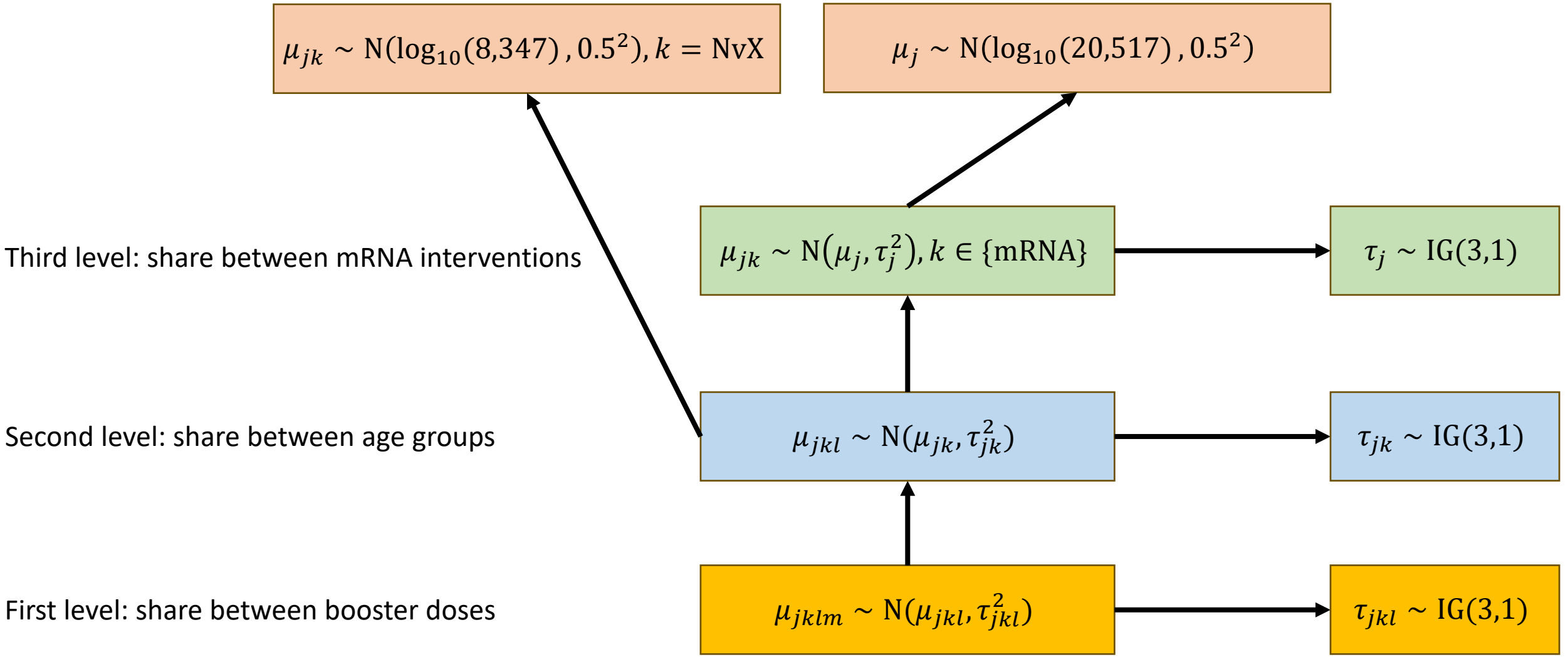
First level: share between booster doses



Hierarchical prior structure (μ_{jklm})



Hierarchical prior structure (μ_{jklm})



Other prior distributions

$$\beta_p \sim \mathrm{N}(0,1)$$

$$\boldsymbol{\Sigma_l} = \boldsymbol{Q_l R_l Q_l}$$

$$\boldsymbol{Q_l} = \sigma_l \boldsymbol{I_3}$$

$$\boldsymbol{R_l} = \begin{pmatrix} 1 & r_{l12} & r_{l13} \\ r_{l21} & 1 & r_{l23} \\ r_{l31} & r_{l32} & 1 \end{pmatrix}$$

$$\sigma_l \sim \mathrm{Exponential}(0.5)$$

$$\boldsymbol{R_l} \sim \mathrm{LKJcorr}^{1}(2)$$

[1]Lewandowski, et. al. (2009) – Cholesky decomposition

ADAPTIVE HEALTH INTELLIGENCE
EVIDENCE IN ACTION

Simulated example

Assume:

$$i \in \boldsymbol{I} = \{1,2,\ldots,300\}$$

$$j \in \boldsymbol{J} = \{\mathrm{Pf}\}$$

$$l \in \boldsymbol{L} = \{12 -< 18, 18 -< 50, 50 -< 70, \geq 70\}$$

$$k \in \boldsymbol{K} = \{\mathrm{Pf}, \mathrm{Mod}, \mathrm{Nvx}\}$$

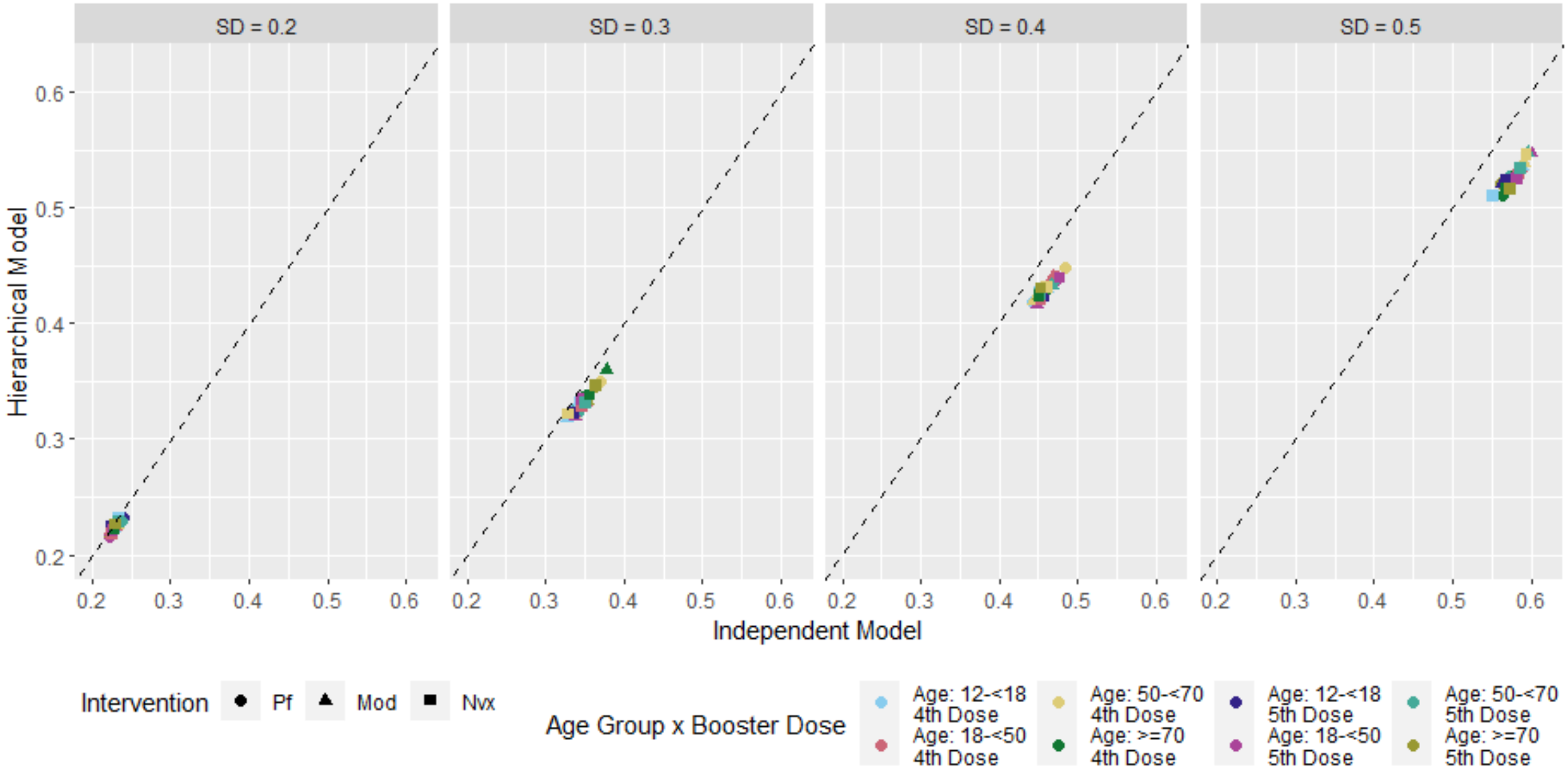
$$m \in \boldsymbol{M_i} = \boldsymbol{M} = \{2,3\}$$

Scenarios:

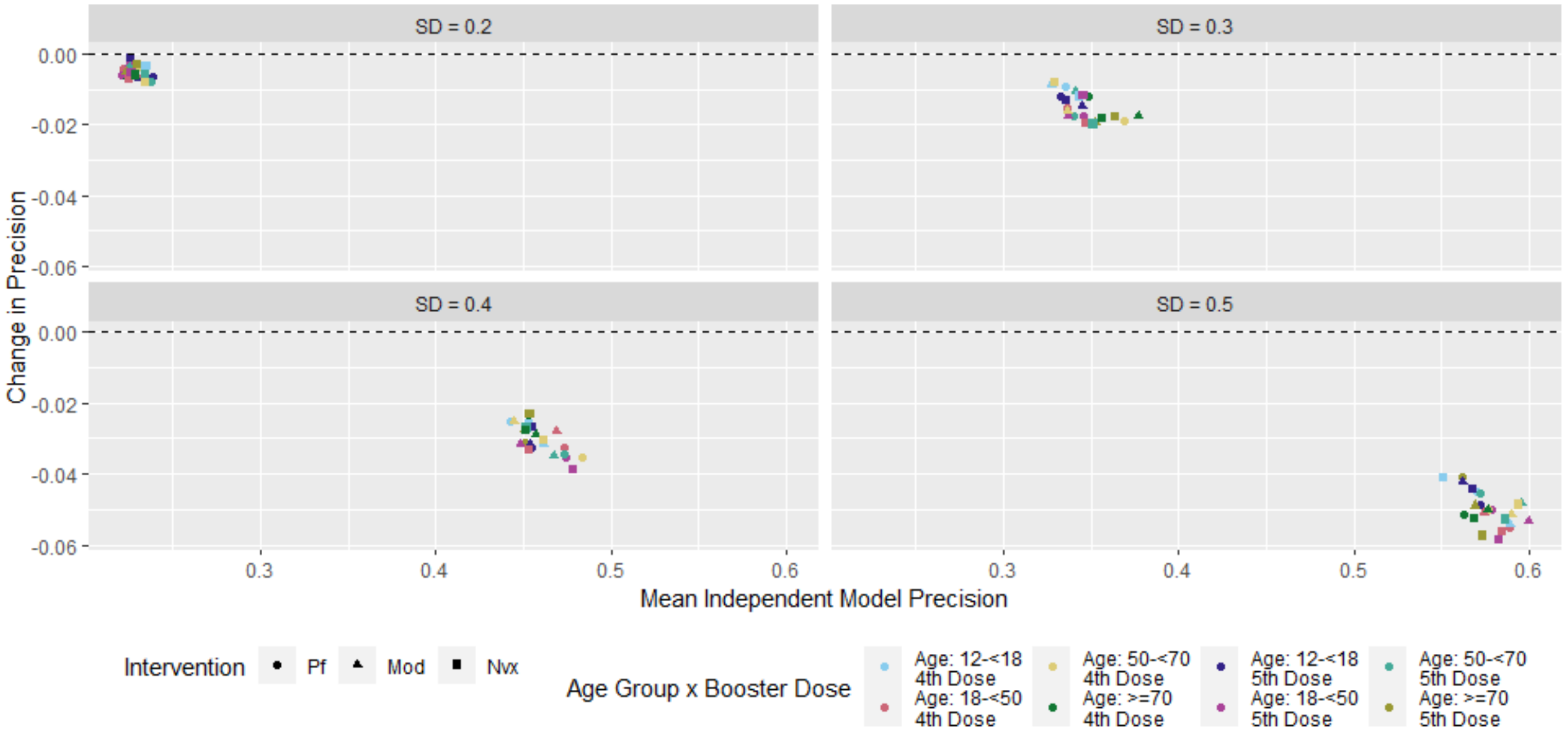
1) SD = 0.2
2) SD = 0.3
3) SD = 0.4
4) SD = 0.5

ADAPTIVE HEALTH INTELLIGENCE
EVIDENCE IN ACTION

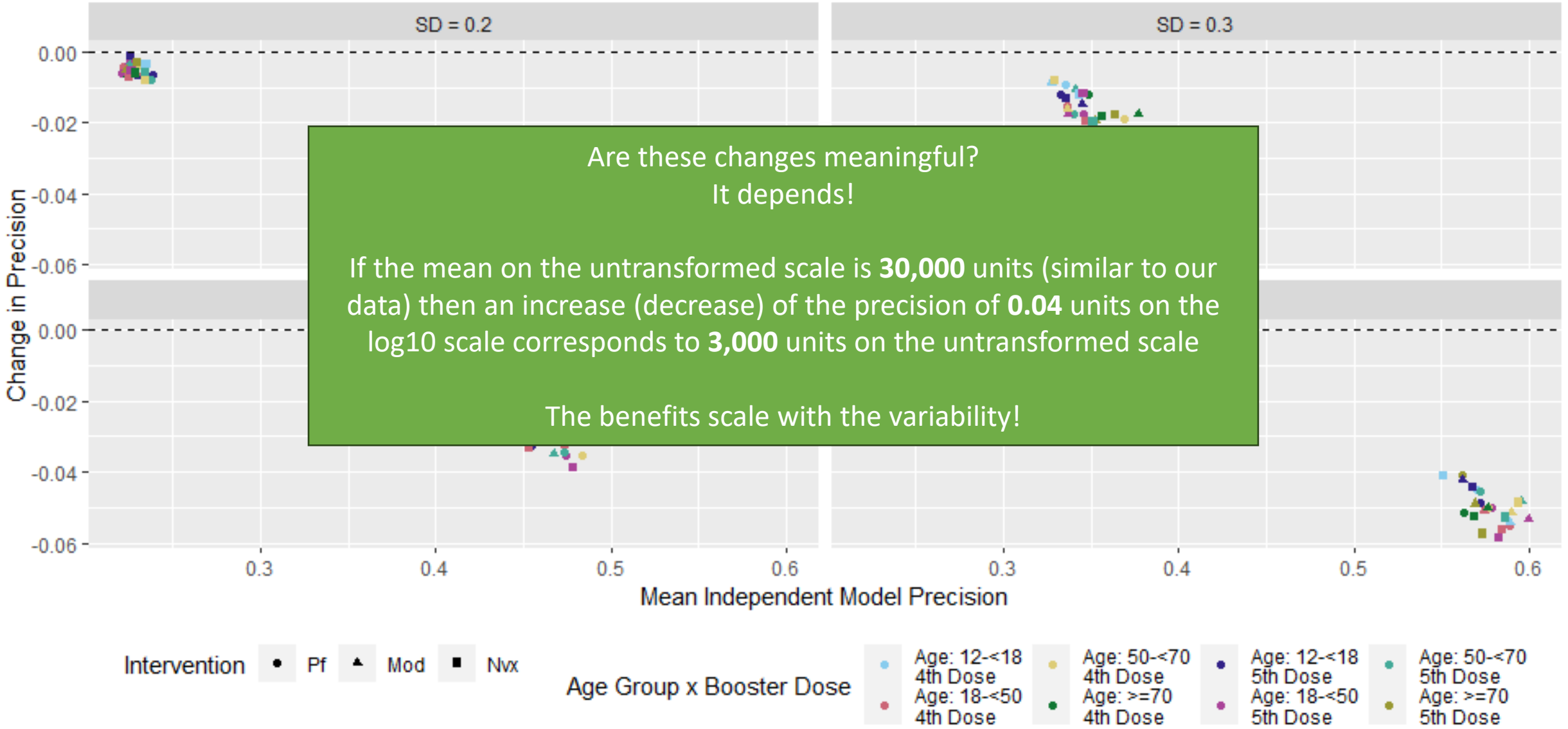
Precision comparison



Change in precision



Change in precision



First Scheduled Analysis

$$i \in \boldsymbol{I} = \{1,2,\ldots,266^{*}\}$$

$$j \in \boldsymbol{J} = \{\mathrm{AZ}, \mathrm{Pf}\}$$

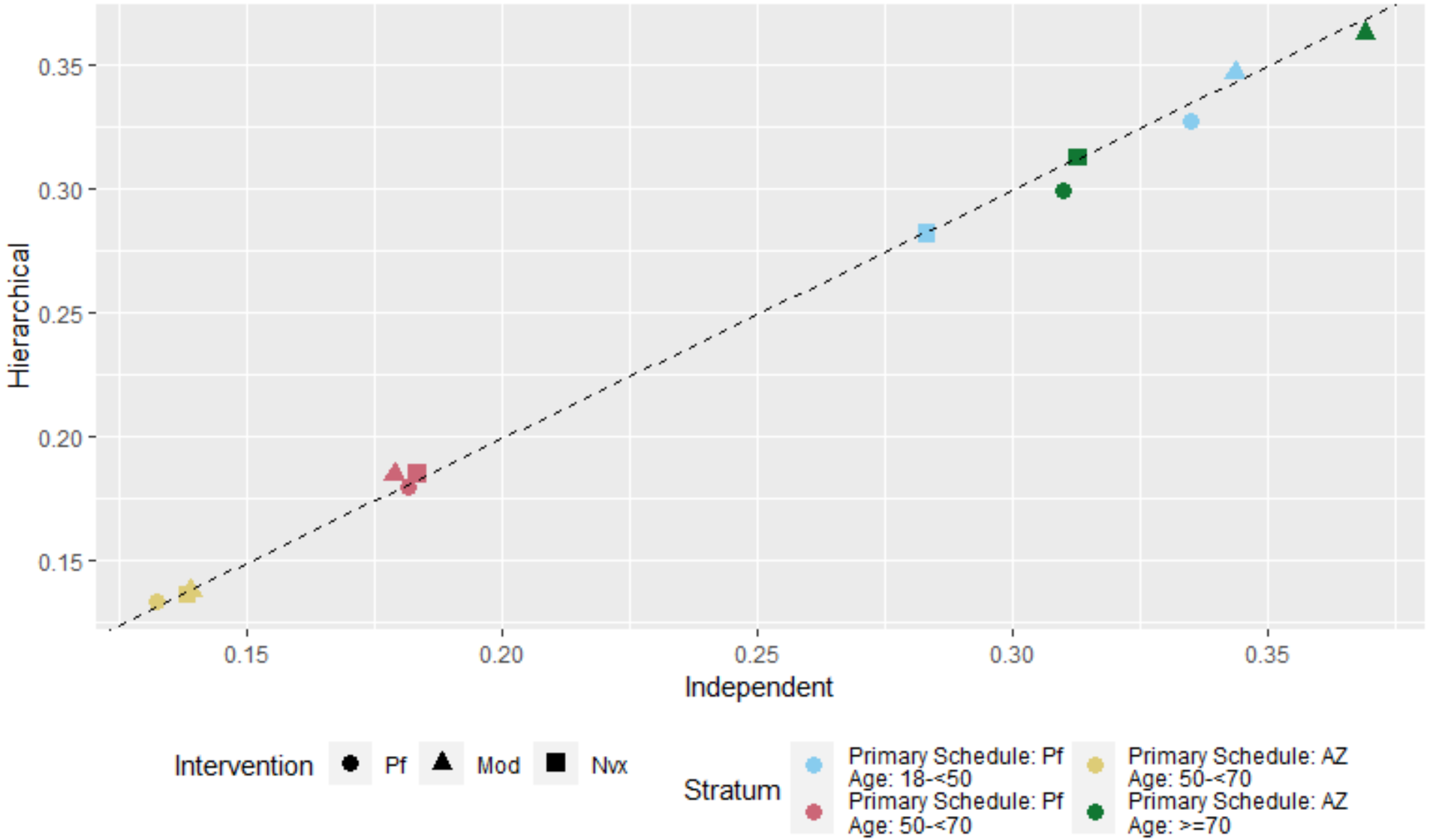
$$l \in \boldsymbol{L} = \{12 -< 18, 18 -< 50, 50 -< 70, \geq 70\}$$

$$m \in \boldsymbol{M} = \{1,2\}$$ **but no rerandomised participants**

*Analysis scheduled for 300 but only 266 “eligible” samples due to missed visit windows, exclusion due to COVID-19 infection, etc.

ADAPTIVE HEALTH INTELLIGENCE
EVIDENCE IN ACTION

First Scheduled Analysis – Precision Comparison



Discussion

- Bayesian hierarchical model efficiently estimates parameters by allowing for *information borrowing* between subgroups
- Gains in precision scale with data variability (perhaps not surprisingly)
- Is the additional statistical machinery worthwhile?
- Will the gains (or lack of gains) in precision vary as PICOBOO progresses?