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Item Response Theory Analysis of the Scale for the Assessment and Rating of Ataxia in Autosomal Recessive Cerebellar Ataxias

31st PAGE meeting - 28th June 2023

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IRT Analysis of the SARA in ARCAs

Item **R**esponse **T**heory

Item-based analysis

Scale for the **A**ssessment and **R**ating of **A**taxia

Clinical Outcome Assessment (COA)

Autosomal **R**ecessive **C**erebellar **A**taxias

Rare Neurodegenerative Disease (RND)

Keywords

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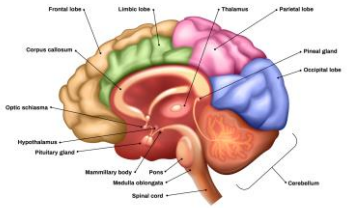
Autosomal Recessive Cerebellar Ataxias (ARCAs)

a heterogenous group of rare and ultra-rare neurodegenerative diseases

Lack of coordination



Affects the cerebellum and associated tracts

Progressive disease
- Loss of ambulation

Genetically defined
>200 disease types

Disease-modifying therapies are on the horizon

Scarcity of robust trial designs in RNDs

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Demonstration of Ataxia patient's gait and stance

Video from: https://www.youtube.com/watch?v=JSyLnt3rLxs

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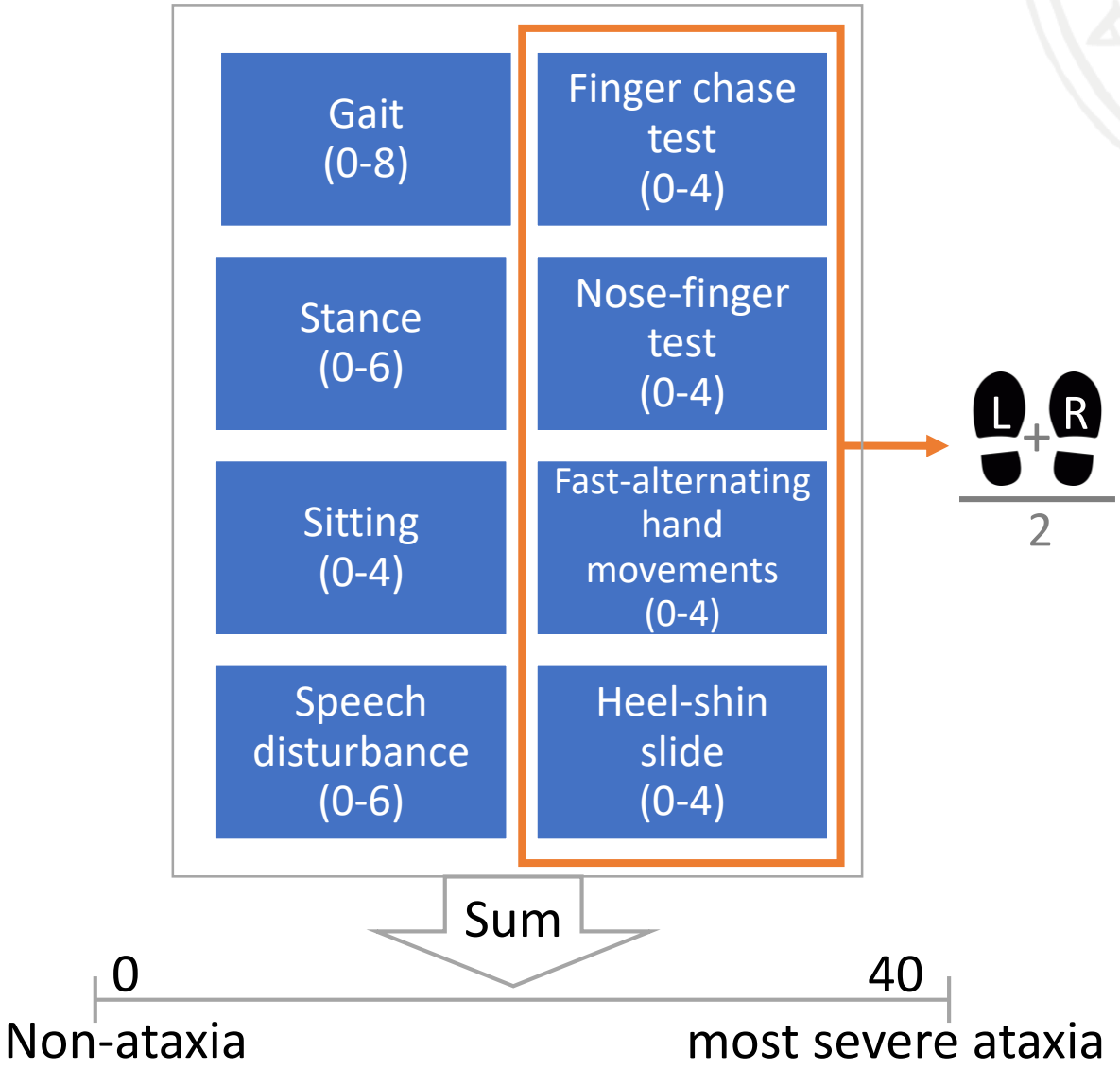
How to measure the ataxia severity?

Scale for the Assessment and Rating of Ataxia (SARA)

- The most widely used outcome measure for ataxias
- Developed in 2004
- Clinician reported outcome



SARA as a primary outcome measure in treatment trials?

Problem

- Concerns about SARA metric properties from regulatory agencies and recent studies
- Modifications to optimize the SARA
- Scarce data evidence and validation
- Analysis based on SARA total score

Aim

Evaluate the **metric properties and performance** of the SARA using **Item Response Theory (IRT)**

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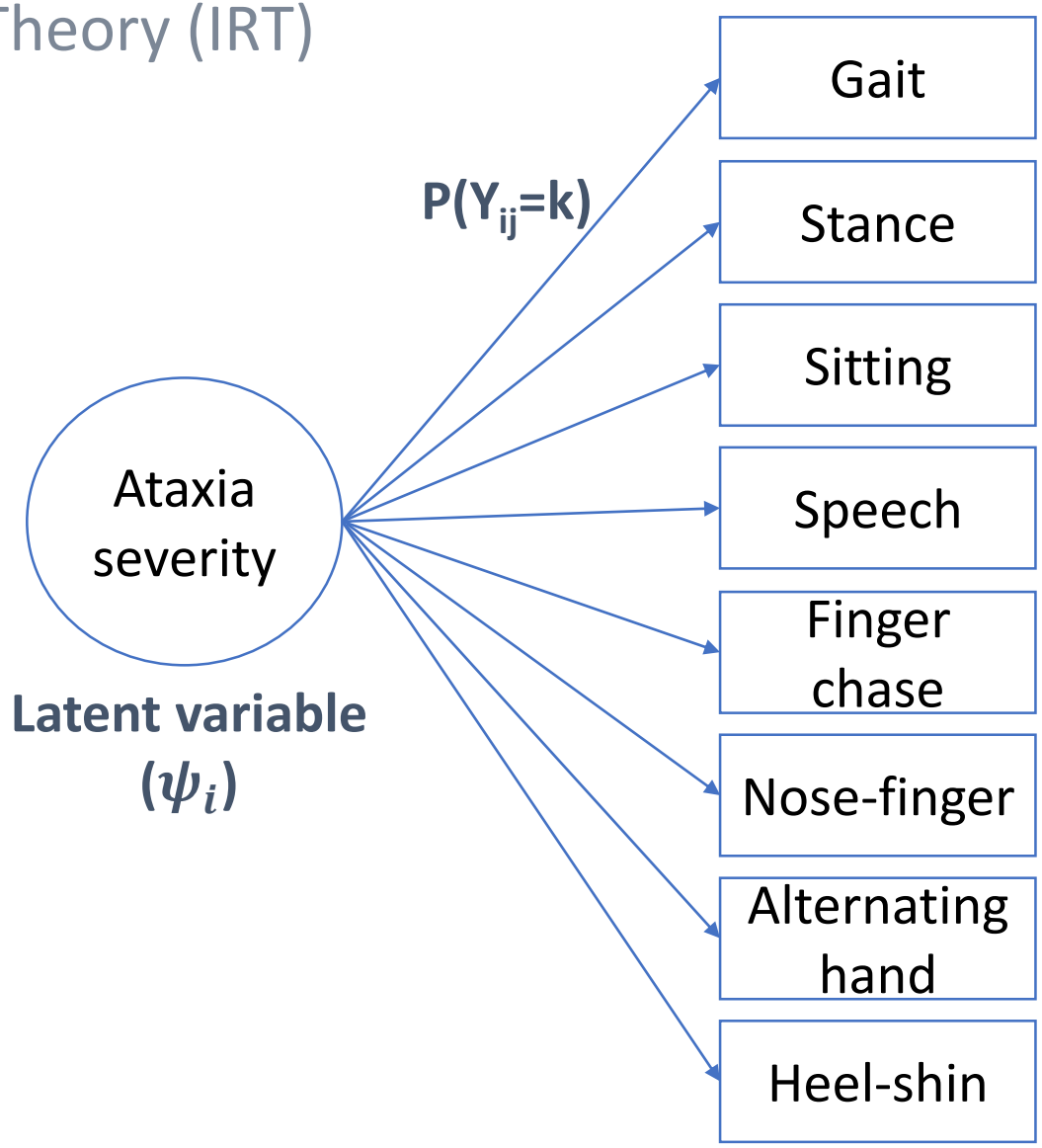
Sub-scores analysis
using Item Response Theory (IRT)

IRT model of SARA



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Sub-scores analysis
using Item Response Theory (IRT)

2-parameters logit functions

$$P(Y_{ij} \geq k) = \frac{e^{(a_j(\psi_i - b_{j,k}))}}{1 + e^{(a_j(\psi_i - b_{j,k}))}}$$

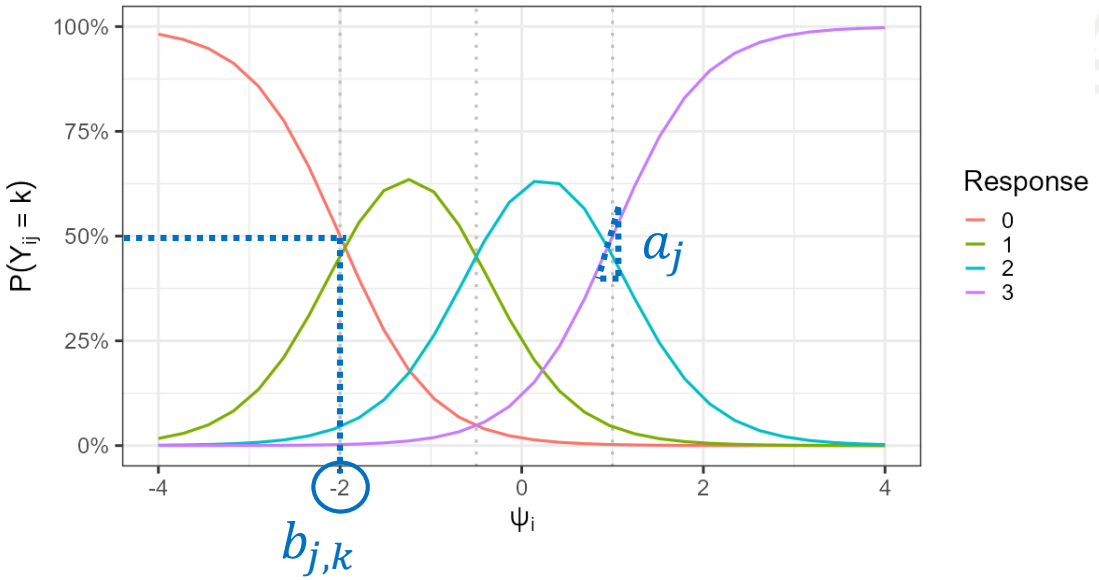
$$P(Y_{ij} = k) = P(Y_{ij} \geq k) - P(Y_{ij} \geq k+1)$$

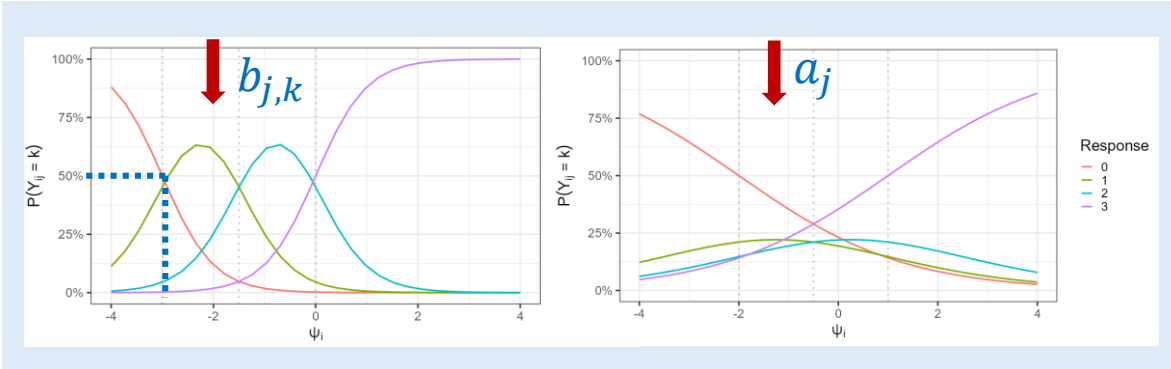
Y_{ij}: observed item score for individual i and item j

k: item response score

- Scale characteristics
  - a_j: Item discrimination
  - $b_{j,k}$: Item difficulty
- Subjects characteristics
  - ψ_i: Latent variable

Item characteristic curves (ICCs)





Dataset

Autosomal Recessive Cerebellar Ataxias Registry

- 1932 visits
- 990 patients
- 69% of patients have genetically defined diagnosis
- 115 ARCA genetic subpopulations
- SARA sub-scores data

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The questions we want to answer in this IRT analysis

- Do all SARA items share one common underlying latent variable?
- What are the characteristics (and performance) of each SARA item?
- Is one IRT model applicable to all ARCA genetic subpopulations?

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The questions we want to answer in this IRT analysis, **and how**

	Methods
Do all SARA items share one common underlying latent variable? (*i.e.*, unidimensional)	• Data correlations • Residuals correlations
What are the characteristics (and performance) of each SARA item?	• Item parameters • Item characteristics curves • Fisher information
Is one IRT model applicable to all ARCA genetic subpopulations?	• Model fit for each subpopulation

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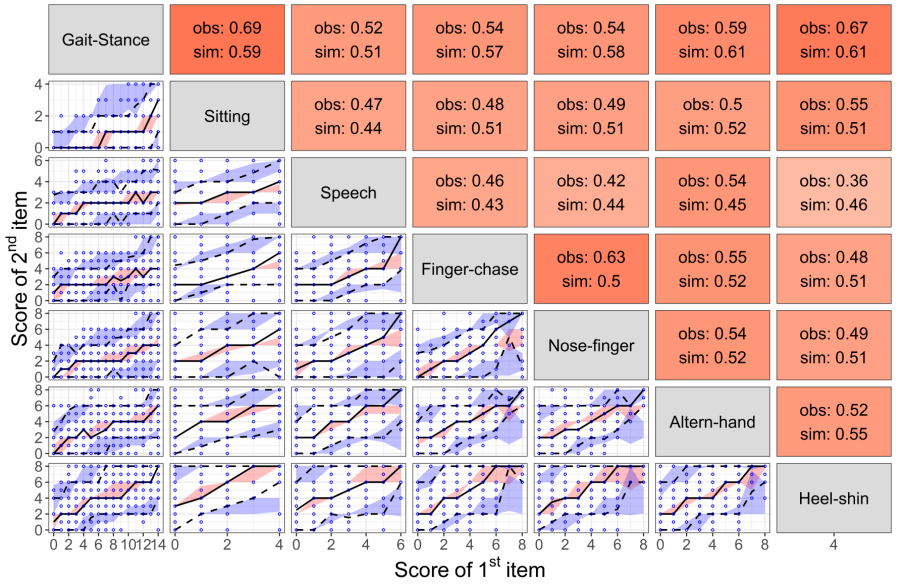
Item-pairs correlations to evaluate SARA dimensionality

Upper matrix

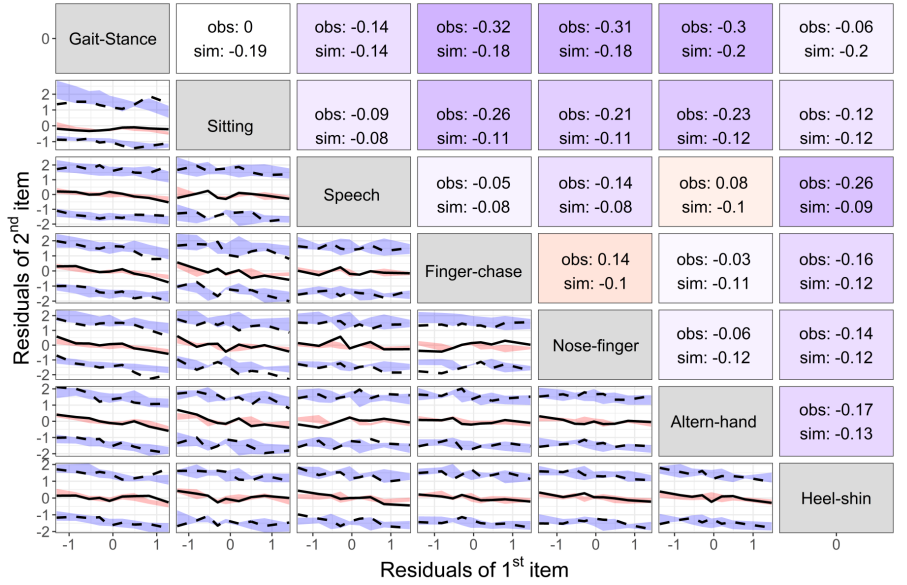
1. Data correlations → before modelling
2. Residual correlations → after modelling
3. Average correlations for 100 simulations

Lower matrix

4. VPC-like diagnostic
   - The 5th, 50th, and 95th percentiles (lines)
   - 95% confidence intervals of the corresponding percentiles (shaded areas)



Item scores



Residuals

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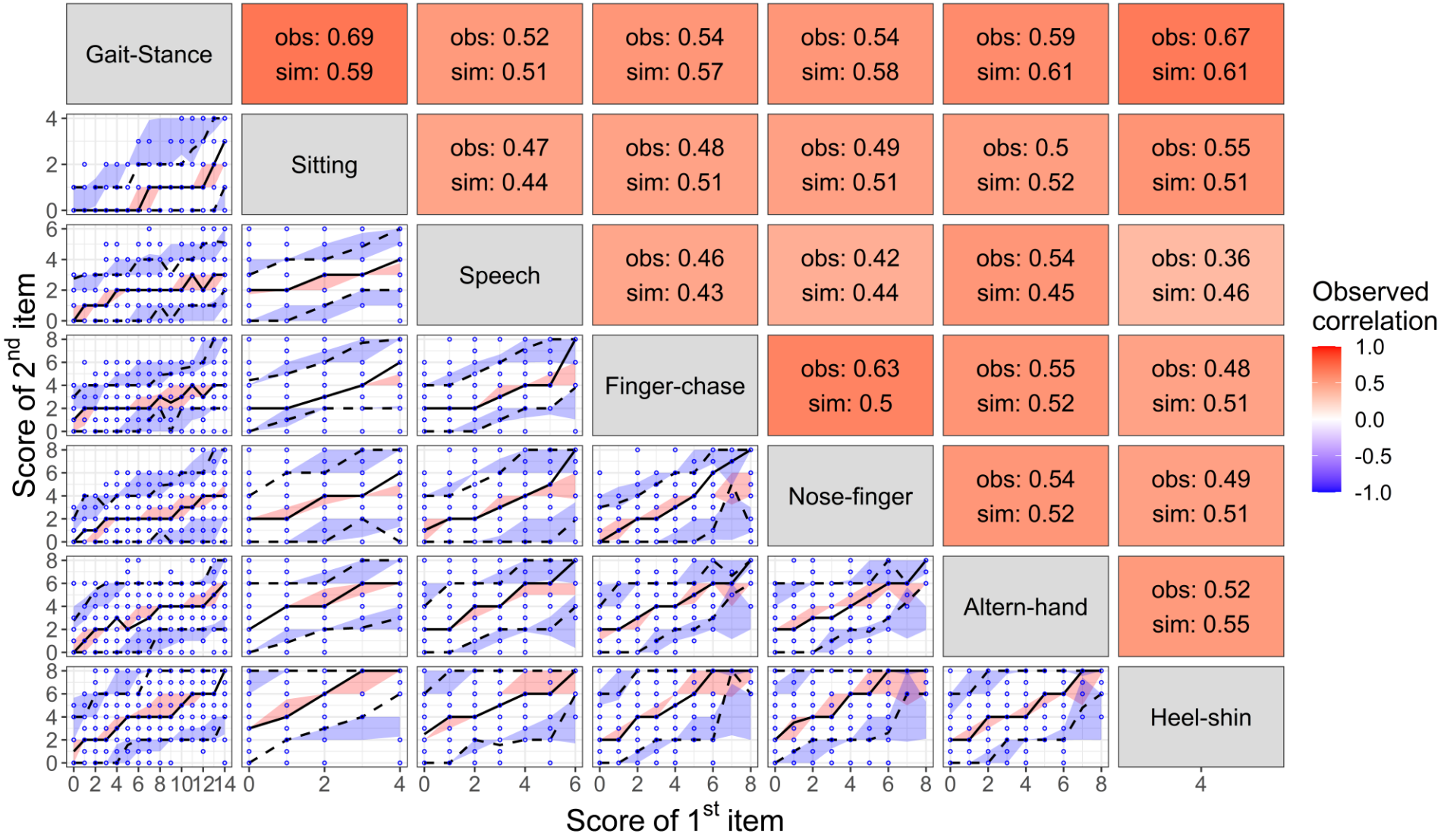
1. High (and similar) levels of correlations indicate unidimensionality
2. Data correlation patterns of simulated datasets mimic the original dataset



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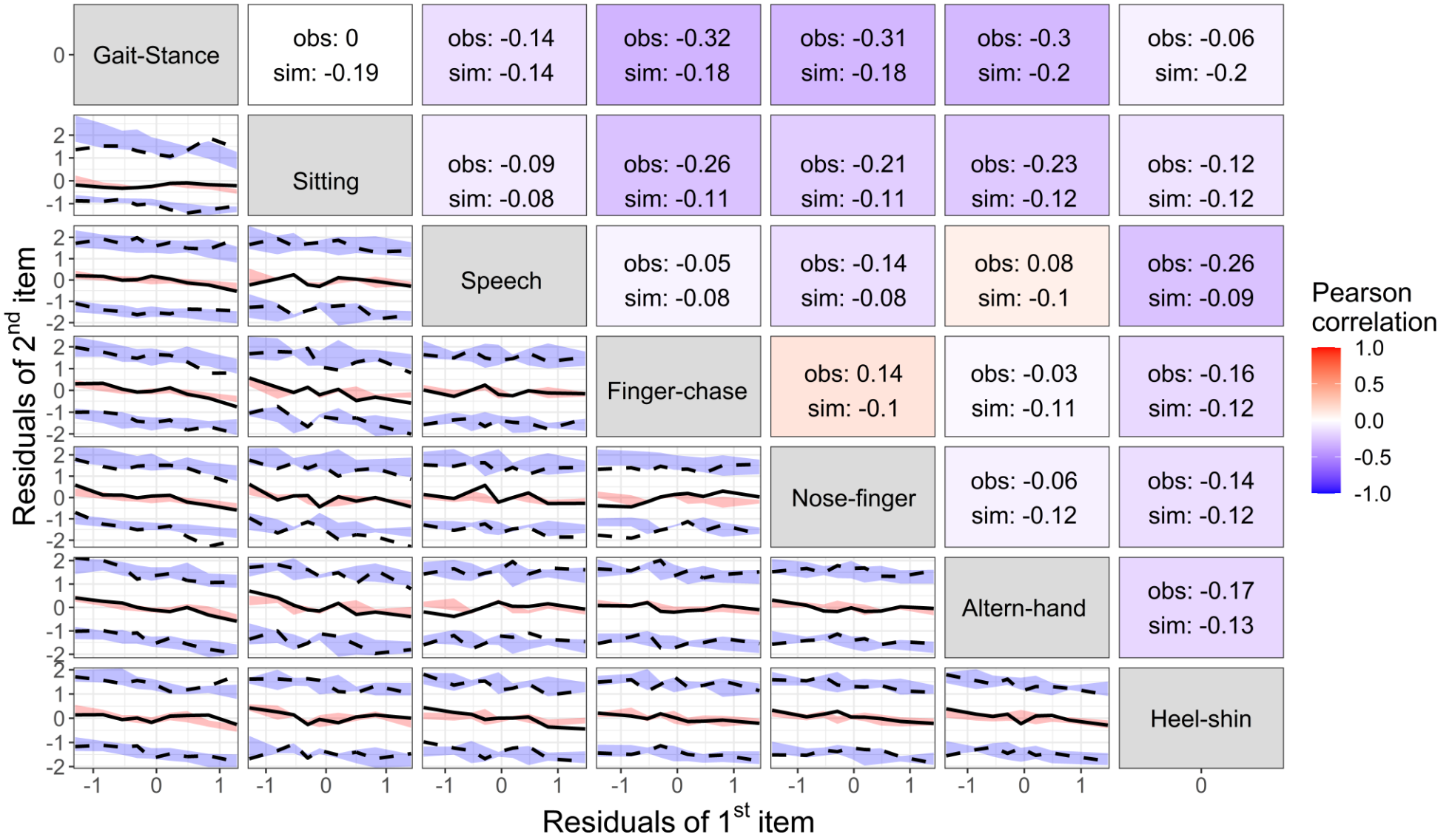
1. Low negative residual correlations indicate a good fit of the unidimensional model
2. Correlation patterns were mimicked in the simulations



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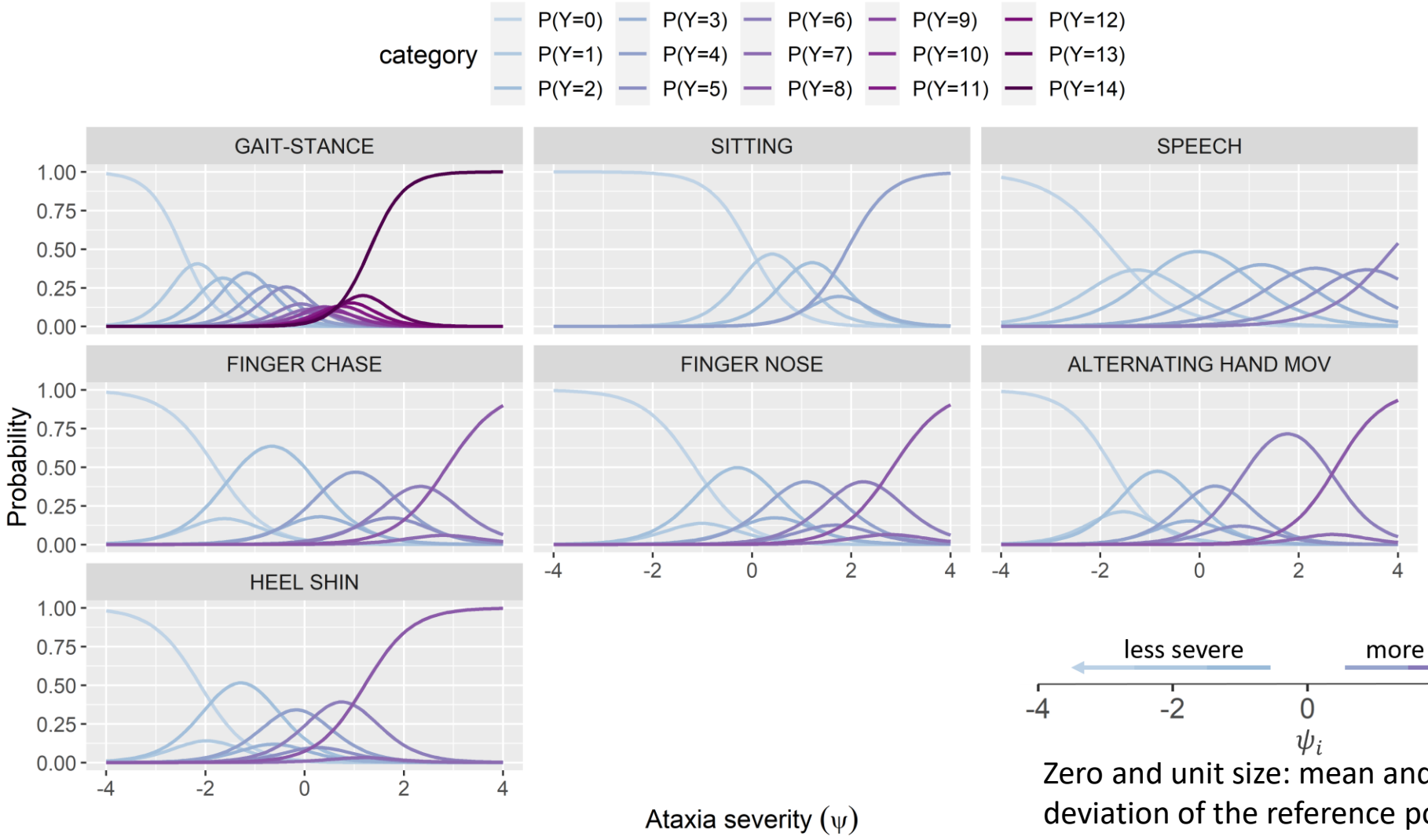
Good ICCs indicating the high discrimination ability of SARA items and properly designed response categories



Zero and unit size: mean and standard deviation of the reference population

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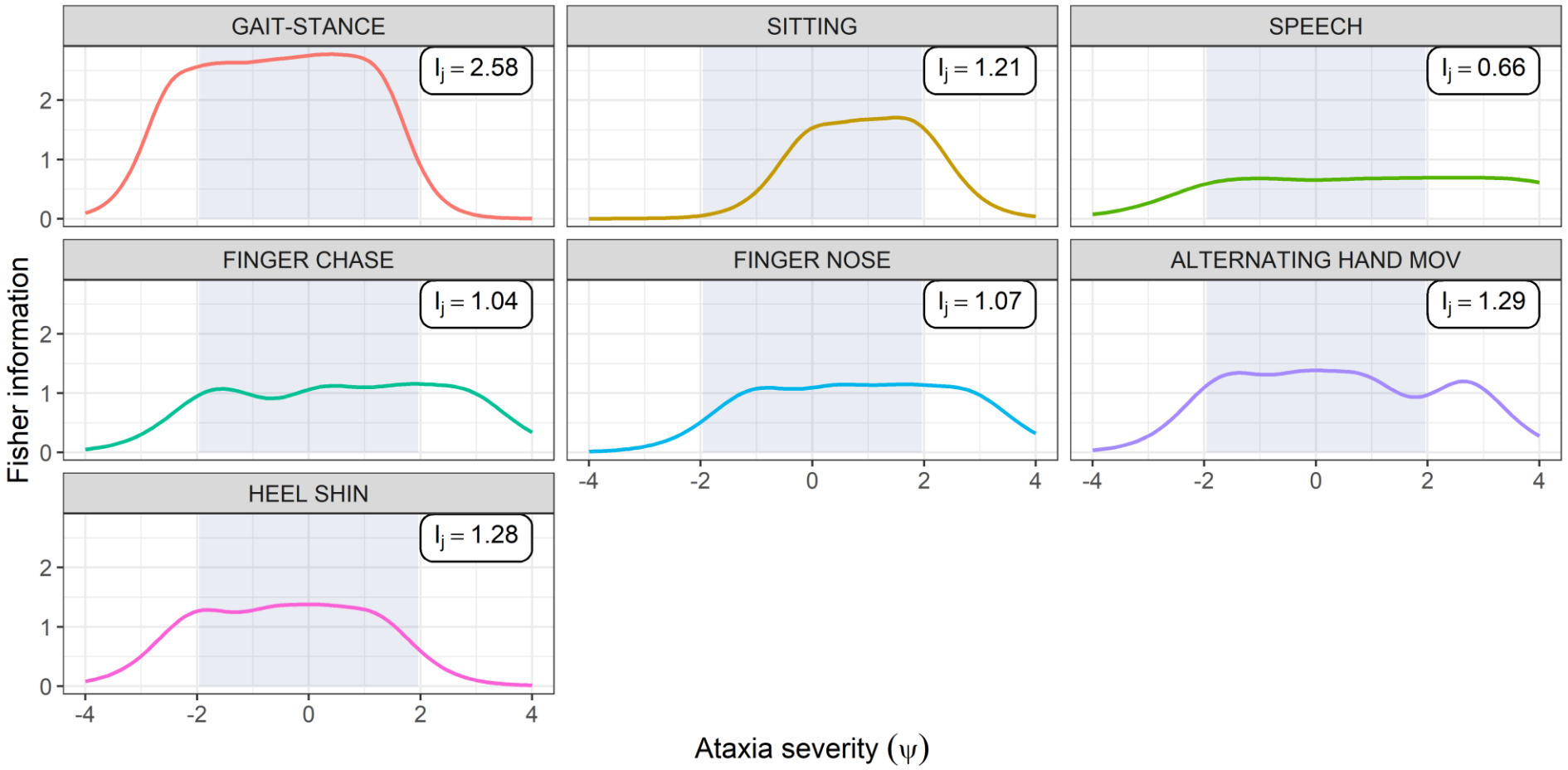
All SARA items are informative with varying importance at different disease severity levels



Shaded areas: the ataxia severity interval for 95% of the studied population

I_j: total item information in the population

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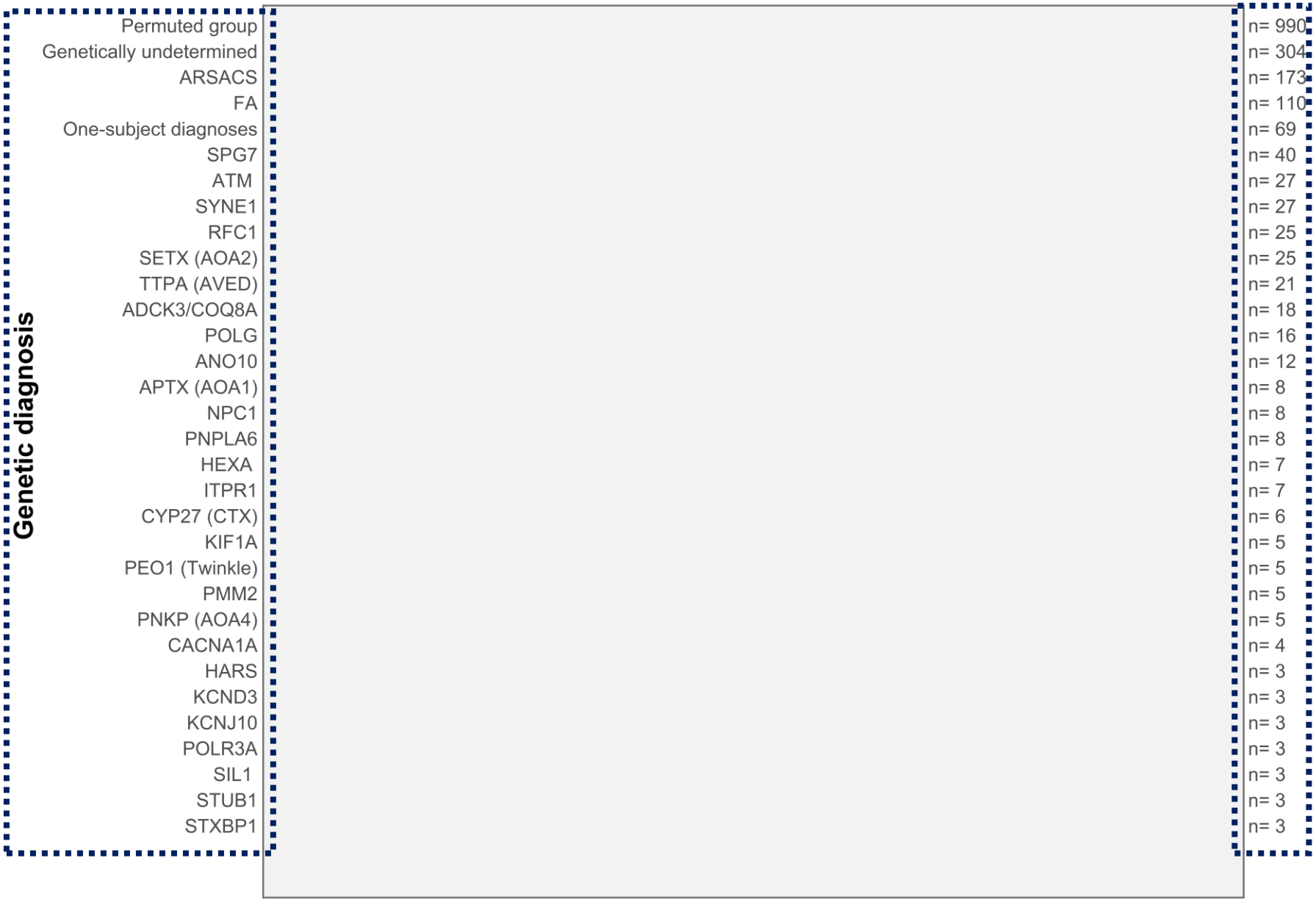
Analysis of ARCA genetic subpopulations



→ Number of subjects in each subpopulation

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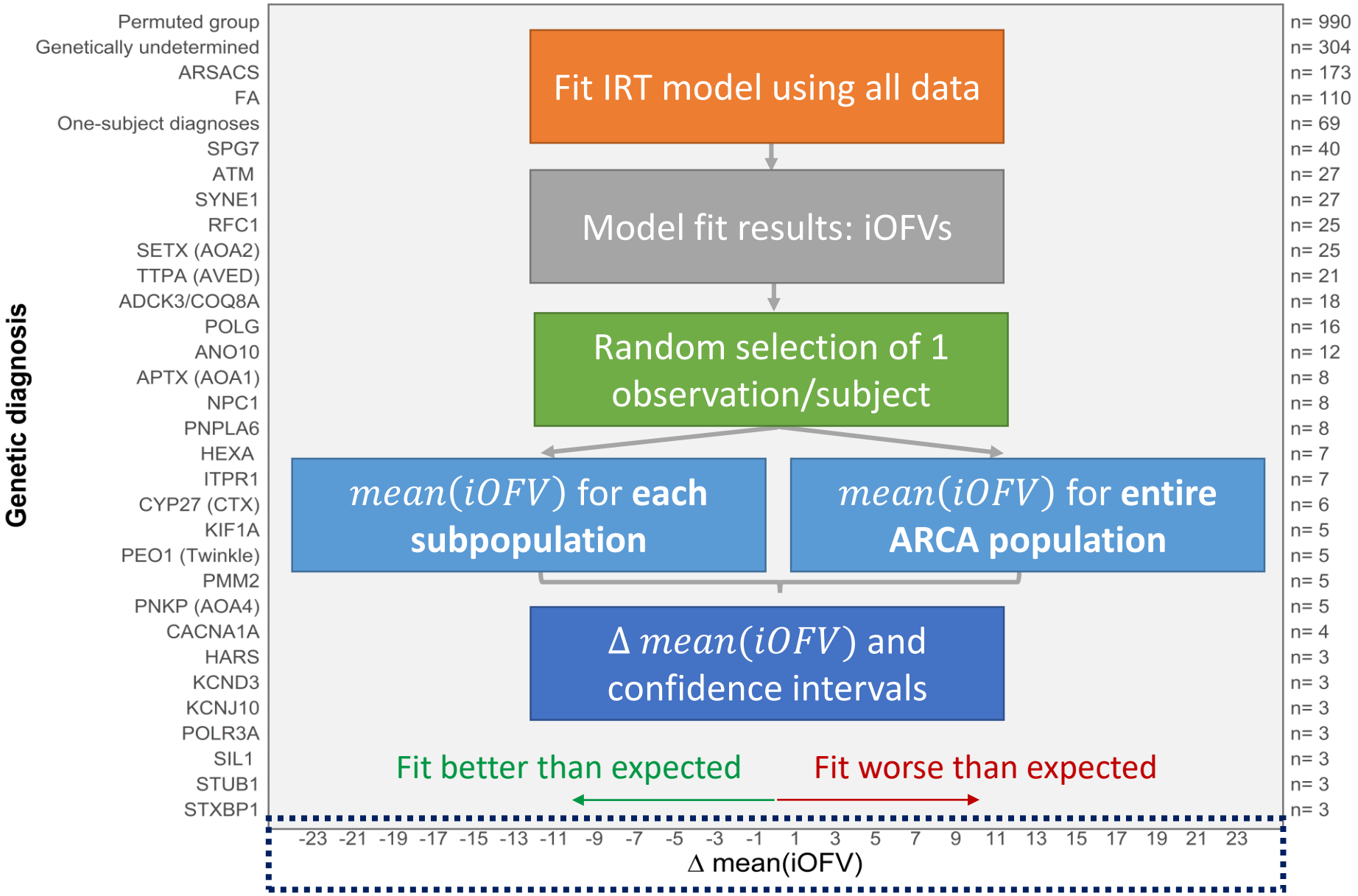
Analysis of ARCA genetic subpopulations



$$\Delta\, mean(iOFV) = mean\left(iOFV_{subpop}\right) - mean\left(iOFV_{all\ pop}\right)$$

iOFV: individual objective function value

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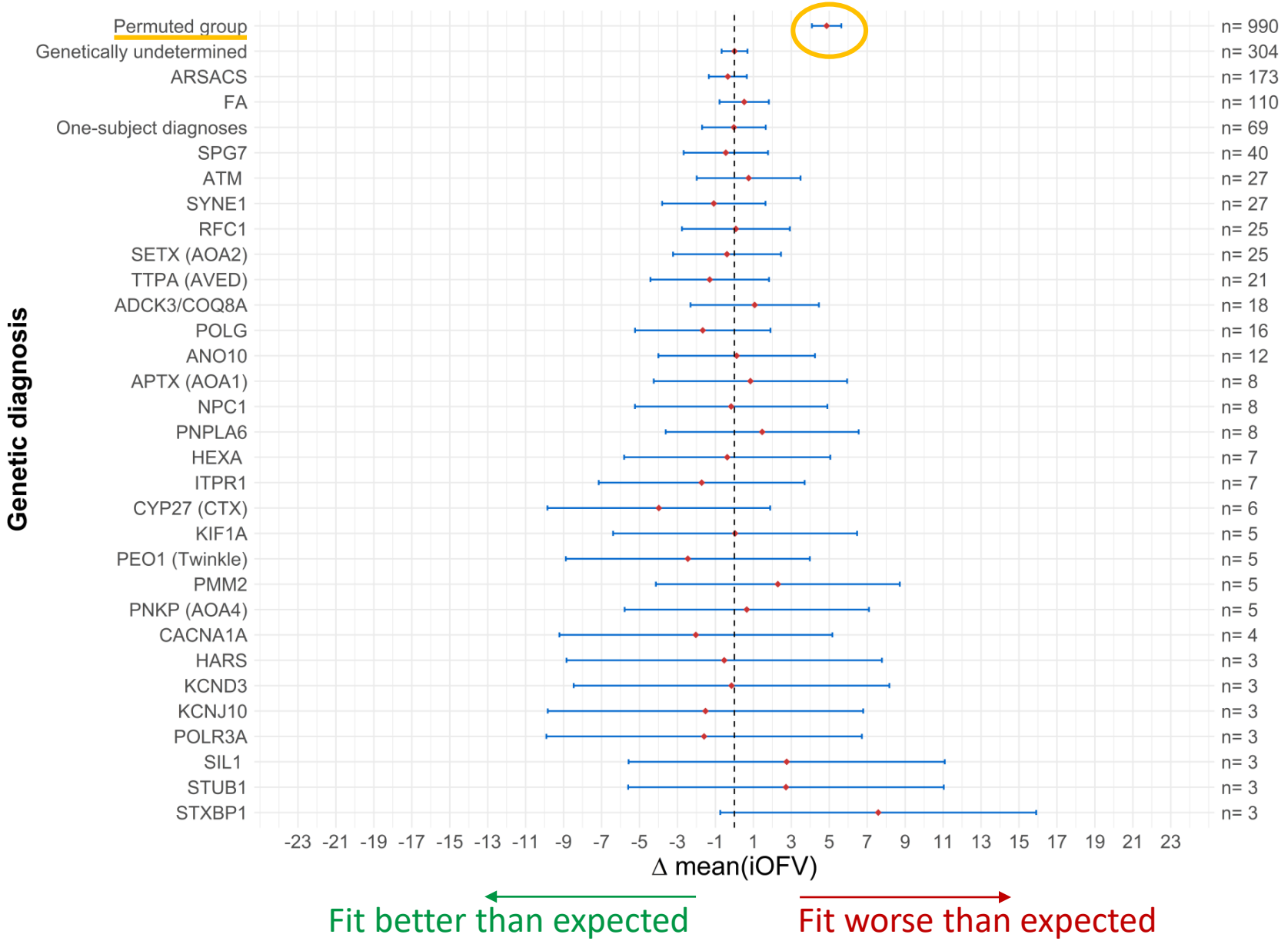
Absence of evidence for differences between ARCA subpopulations



Permuted group:
a hypothetical subpopulation created by permuting the sub-scores of each item across individuals.

- Red points: difference in means of iOFVs
- Error bars: 95% confidence intervals (based on pooled two-sampled t-test assuming equal variances)
- n: number of subjects in each group

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Conclusions

- Unidimensional- captures one single latent variable
- SARA is well-performing with high discrimination values
- All items are informative with varying importance at different disease severity levels
- IRT model is applicable across all genetic subpopulations and no item patterns differences

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Contributions

- Evidence of the adequacy of SARA using IRT analysis
- IRT framework that describes
  - SARA on the item level
  - Disease severity of ataxia patients (cross-sectional)

Acknowledgments

Evidence-RND consortium

- Matthis Synofzik
- Andreas Traschütz
- Rebecca Schüle
- Thomas Klockgether
- France Mentré
- Emmanuelle Comets
- Niels Hendrickx
- Ralf-Dieter Hilgers
- Nicole Maria Heussen
- Alex Sverdlov
- Yevgen Ryeznik

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Poster session IV-15
Thursday 15:25-16:55

Predicting individual disease progression including parameter uncertainty in rare neurodegenerative diseases: the example of Autosomal-Recessive Spastic Ataxia Charlevoix Saguenay (ARSACS)

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Thank you for listening!

Questions?

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