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Modeling a Composite Score in Parkinson's Disease using Item Response Theory

PAGE - 2015

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Parkinson's Disease

- Parkinson's disease is a progressive neurodegenerative brain disorder characterized by
  - loss of neurons in substantia nigra
  - decrease in the dopamine levels

- Parkinson's disease is known to affect approximately 6.3 million people worldwide[1]

- Movement Disorder Society (MDS) - sponsored revision[2] of the Unified Parkinson's Disease Rating Scale (UPDRS)

1. European Parkinson's Disease Association (http://www.epda.eu.com/en/)
2. Goetz et al. Move Disord. 2007; 22(1) 41-7

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MDS-UPDRS

Composite Scale

Part I
- Non-motor aspects of experiences of daily living
  - *e.g. cognitive impairment*

Part II
- Motor aspects of experiences of daily living
  - *e.g. tremors*

Part III
- Motor examination
  - *e.g. finger tapping – right & left hands*

Part IV
- Motor complications
  - *e.g. functional impact of dyskinesias*

- Overall, there are 68 items – 66 ordered categorical and 2 binary
- ***Higher total score*** *(range: 0 – 267) indicates* ***more severe disease***

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Data

- Parkinson Progression Markers Initiative (PPMI) Database:
  - Longitudinal MDS-UPDRS data:
    at baseline(0), up to 12 visits (60 months) ➔ 255023 observations

Healthy Controls	De Novo Parkinson's Disease Subjects	Subjects With Scans Without Evidence of Dopaminergic Deficit (SWEDD)
(n = 196)	*(n = 423)*	*(n = 64)*
Age ≥ 30 years	*Diagnosed ≤ 2 years*	*Consented as Parkinson's patients*
No first degree blood relative with Parkinson's disease	***Not** taking any medications for Parkinson's disease*	

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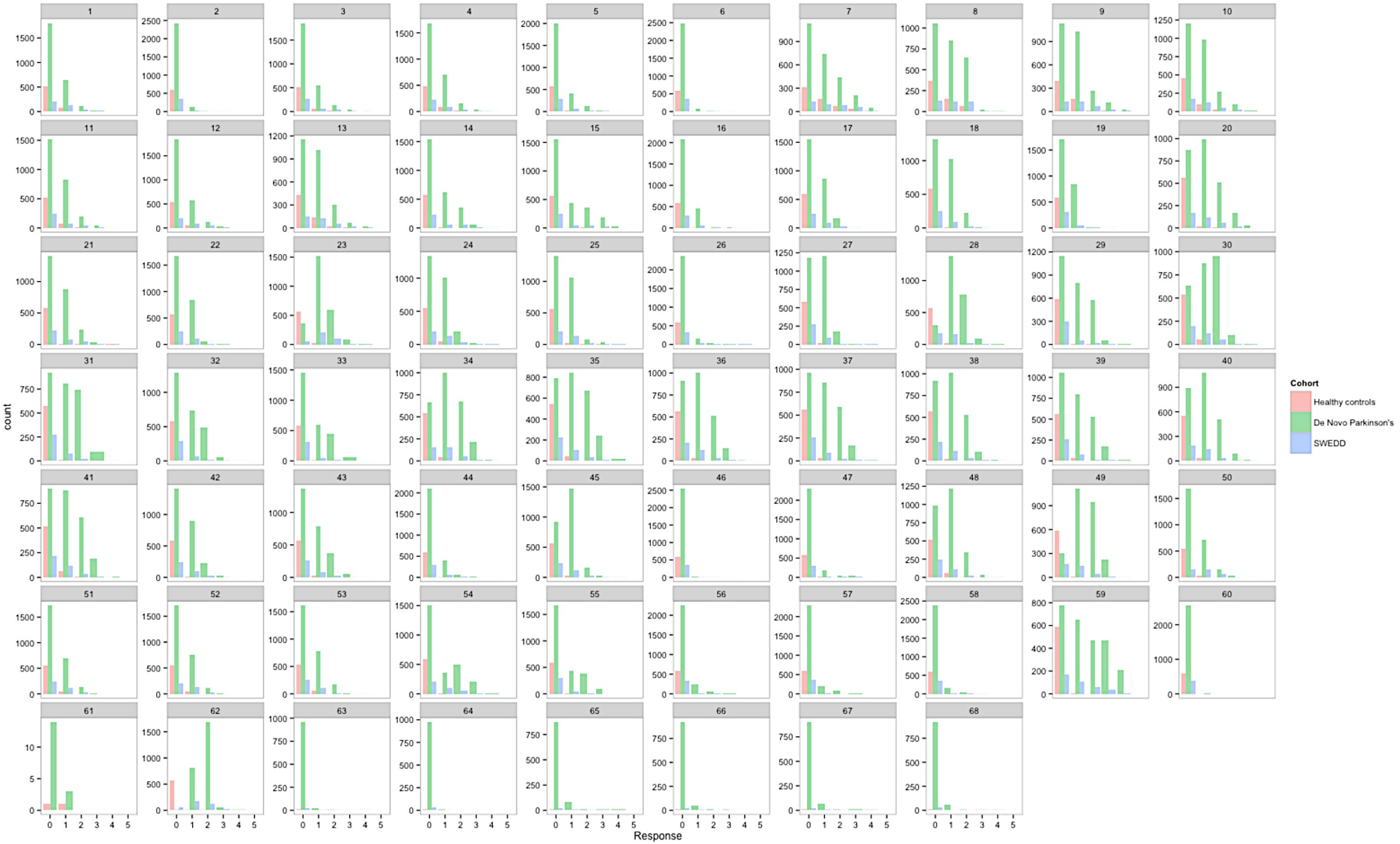
PPMI – Item Responses



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Item 23

Over the past week, have you usually had a shaking or tremor?

0: Normal	Not at all. I have **no shaking** or tremor
1: Slight	Shaking or tremor occurs but **does not cause problems** with any activities
2: Mild	Shaking or tremor cause problems with only a **few** activities
3: Moderate	Shaking or tremor cause problems with **many** of my daily activities
4: Severe	Shaking or tremor cause problems with **most** of my activities

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Item 23

Over the past week, have you usually had a shaking or tremor?

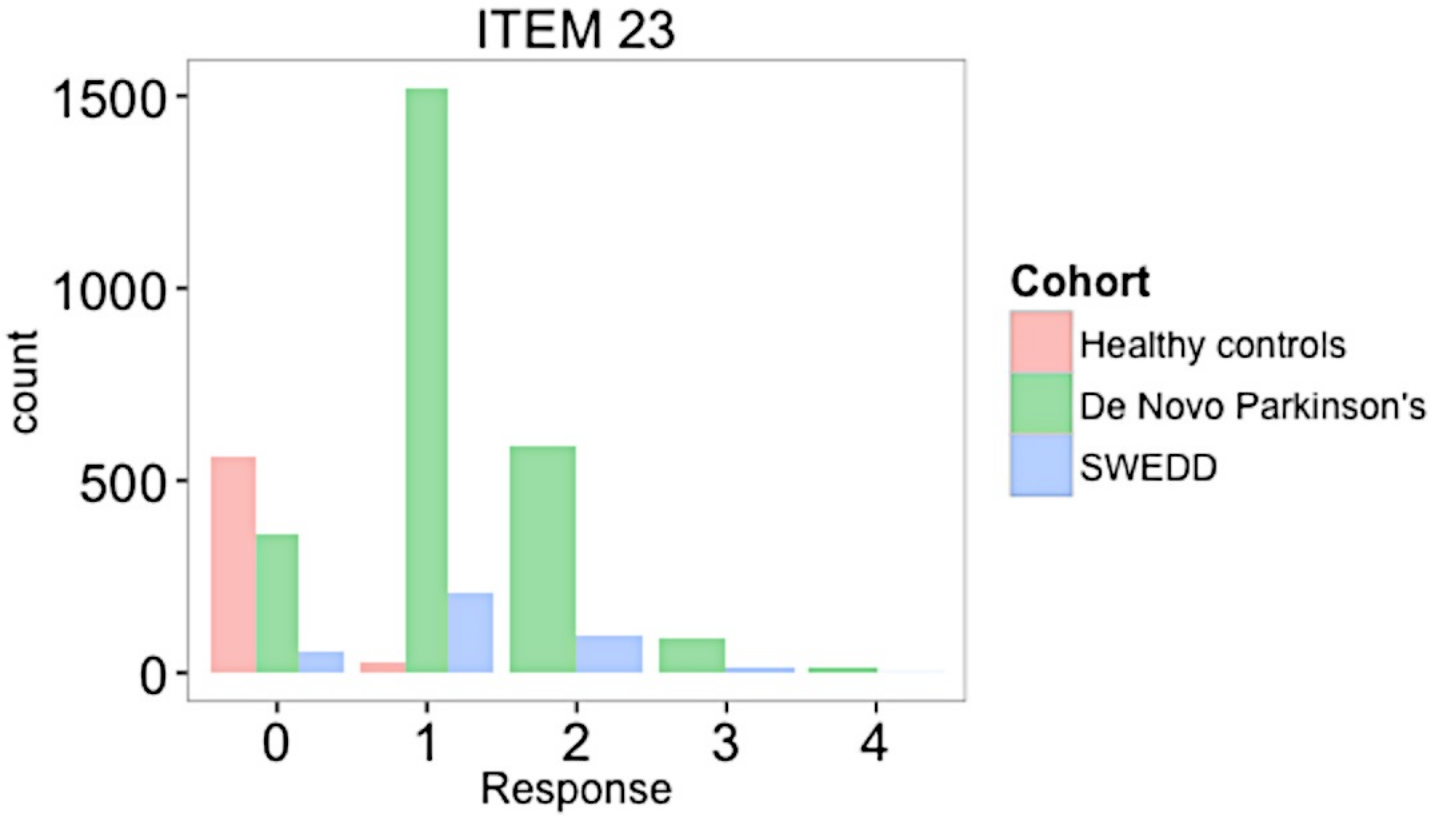
0: Normal

1: Slight

2: Mild

3: Moderate

4: Severe



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Item Response Theory

It relates the probability of responses to items in an assessment to an underlying latent (hidden) variable

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Item Response Theory

It relates the probability of responses to items in an assessment to an underlying latent (hidden) variable

It has been applied in

- Alzheimer's[1] (ADAS-cog)
- Multiple Sclerosis[2] (EDSS)
- Schizophrenia[3] (PANSS)

1. Ueckert S., et al, Pharmaceutical Research 2014; 31(8):2152-2165.
2. Kalezic A., et al, PAGE 22 (2013) Abstract 2903
3. Krekels E., et al, PAGE 23 (2014) Abstract 3145

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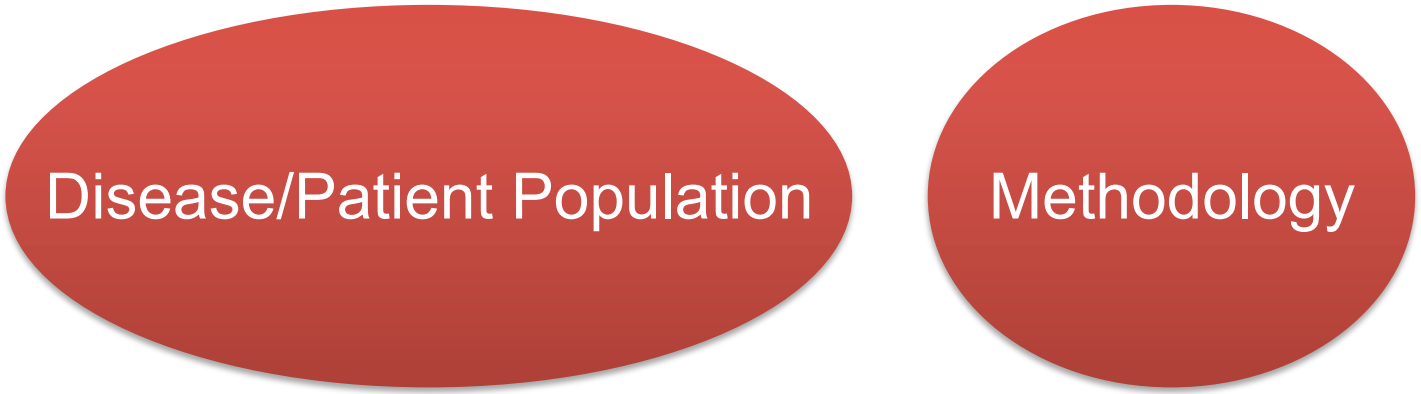
Aims of the project



- To explore IRT model components and investigate MDS-UPDRS features
- To describe MDS-UPDRS longitudinal changes
- To provide a model for future design and analysis of trials in Parkinson's Disease
- To explore model building strategies and diagnostics for IRT

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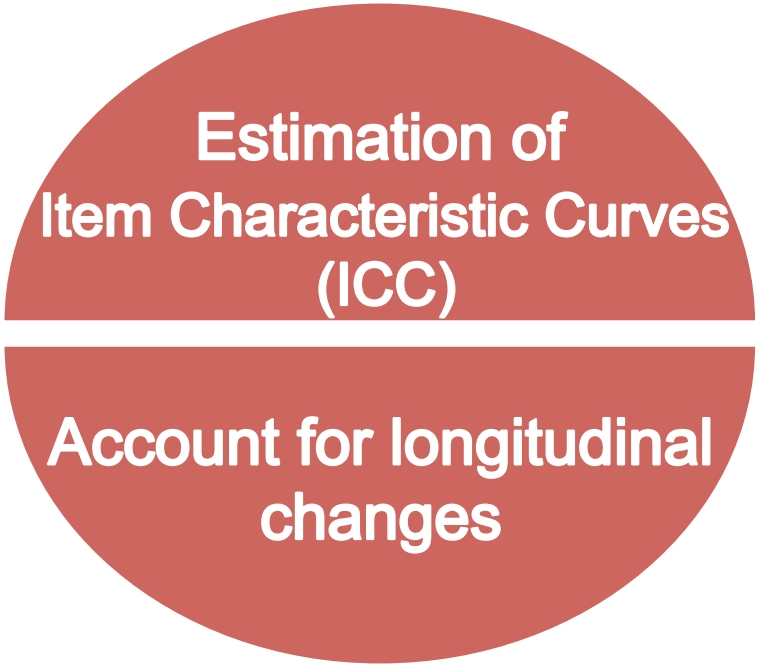
Model building strategy

- Subjects of De Novo cohort was used as reference population
  - Healthy controls and SWEDD cohort modeled by shift in (distribution of) disability



- Estimation of ICC with shifts
  - Fix the ICC
  - Estimate the longitudinal changes
- Simultaneous estimation of ICC and longitudinal changes

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Structural IRT model

Model parameters divided into

- Item specific parameters – a_j, b_j ... (discrimination and difficulty)
- Subject specific parameters – D_i (disability)

66x

$D_i = \eta_i$

2x

$D_i(t) = D_{i,0} + Slope_i * t$

De Novo cohort: $D_{i,0} \sim N(0, 1)$

Other cohorts:
Shift in baseline
Different slopes

Ordered categorical (0 - 4/5)

$$P(Y_{ij} \geq k) = f_j(D_i) = \frac{e^{aj(Di - bj)}}{1 + e^{aj(Di - bj)}}$$

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

Binary (0/1)

$$P(Y_{ij} = 1) = f_j(D_i) = \frac{e^{aj(Di - bj)}}{1 + e^{aj(Di - bj)}}$$

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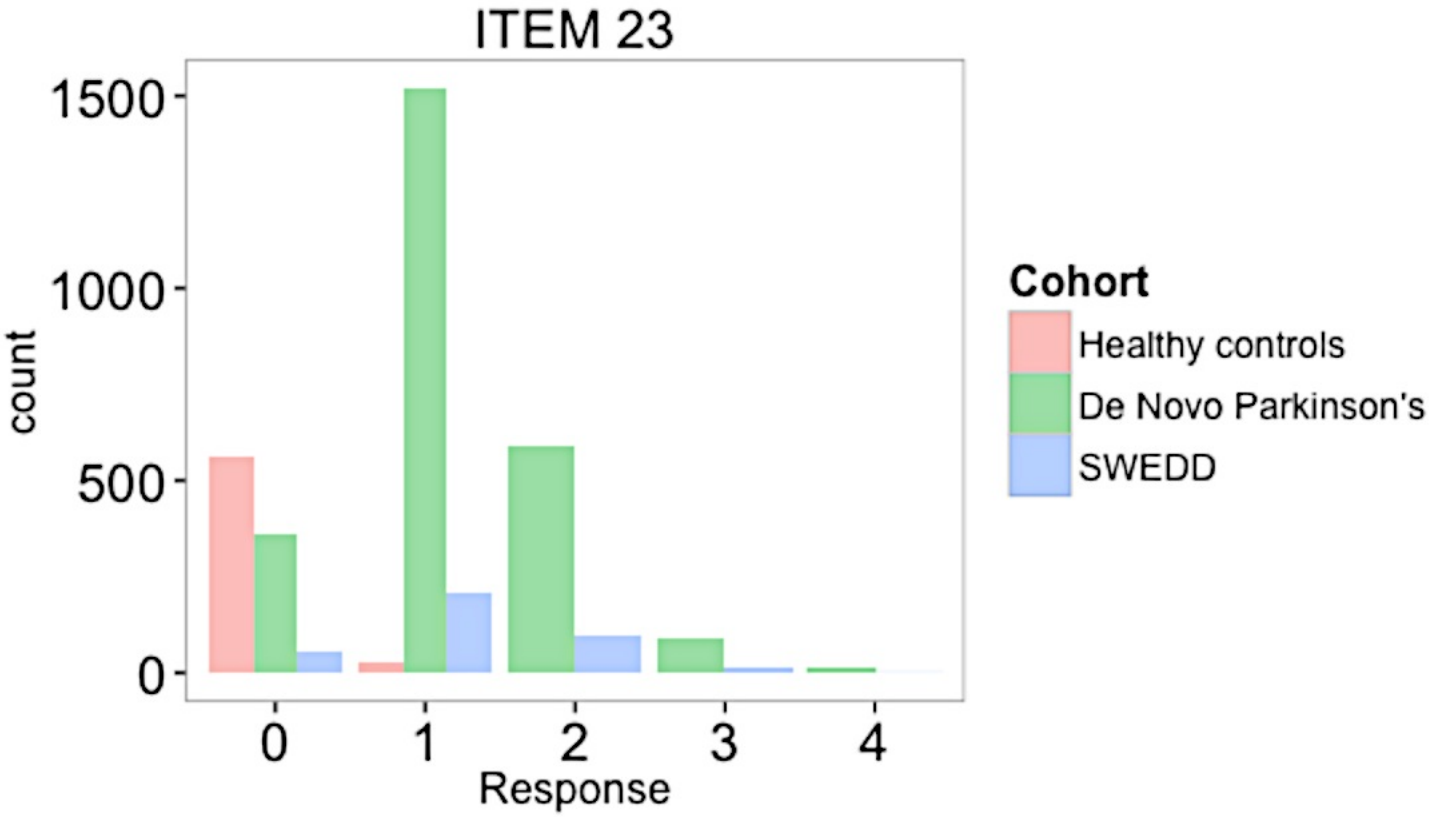
Item Characteristic Curve

Item 23 – Distribution of item responses



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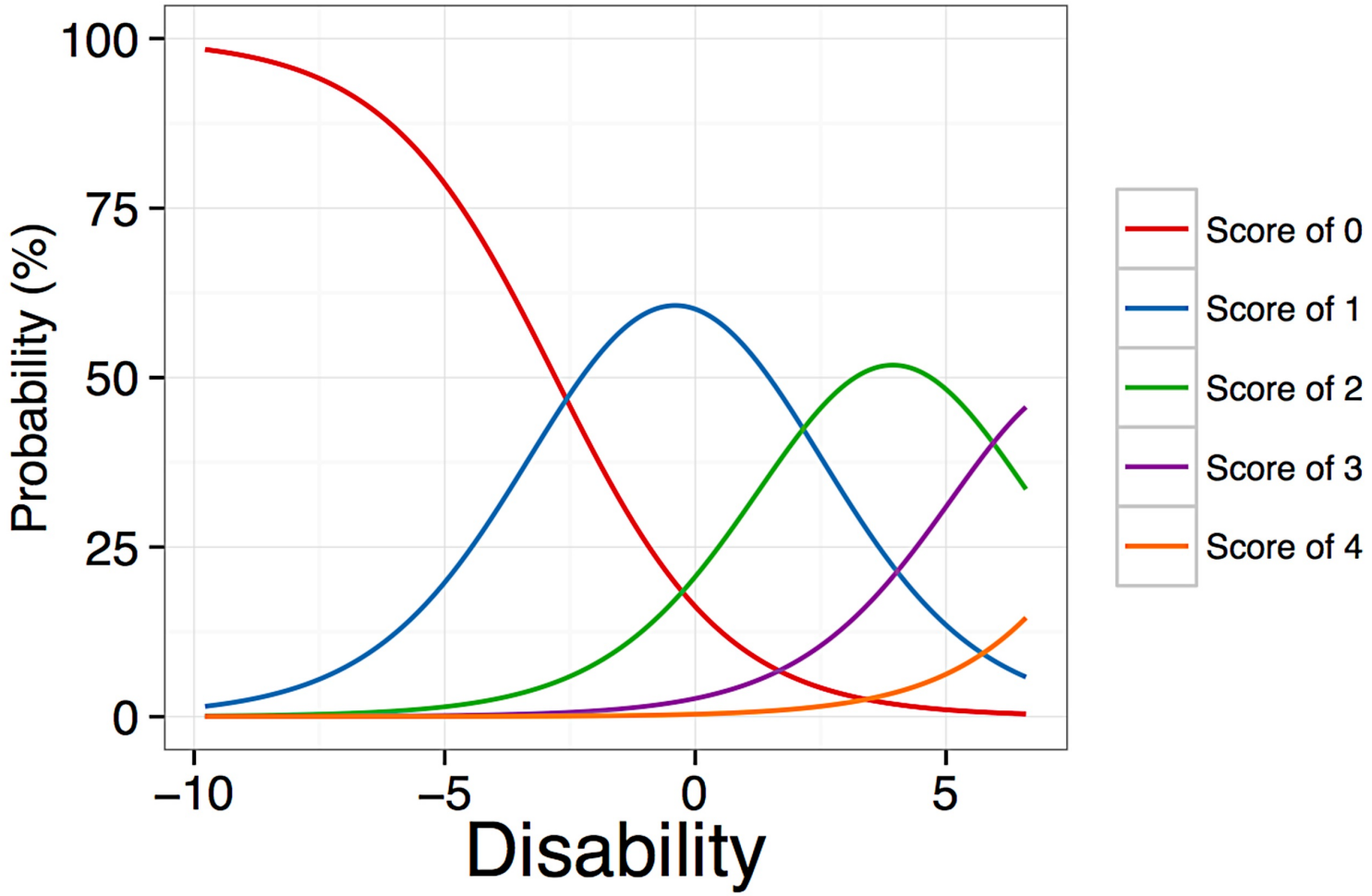
Item Characteristic Curve

Item 23 – Individual probabilities



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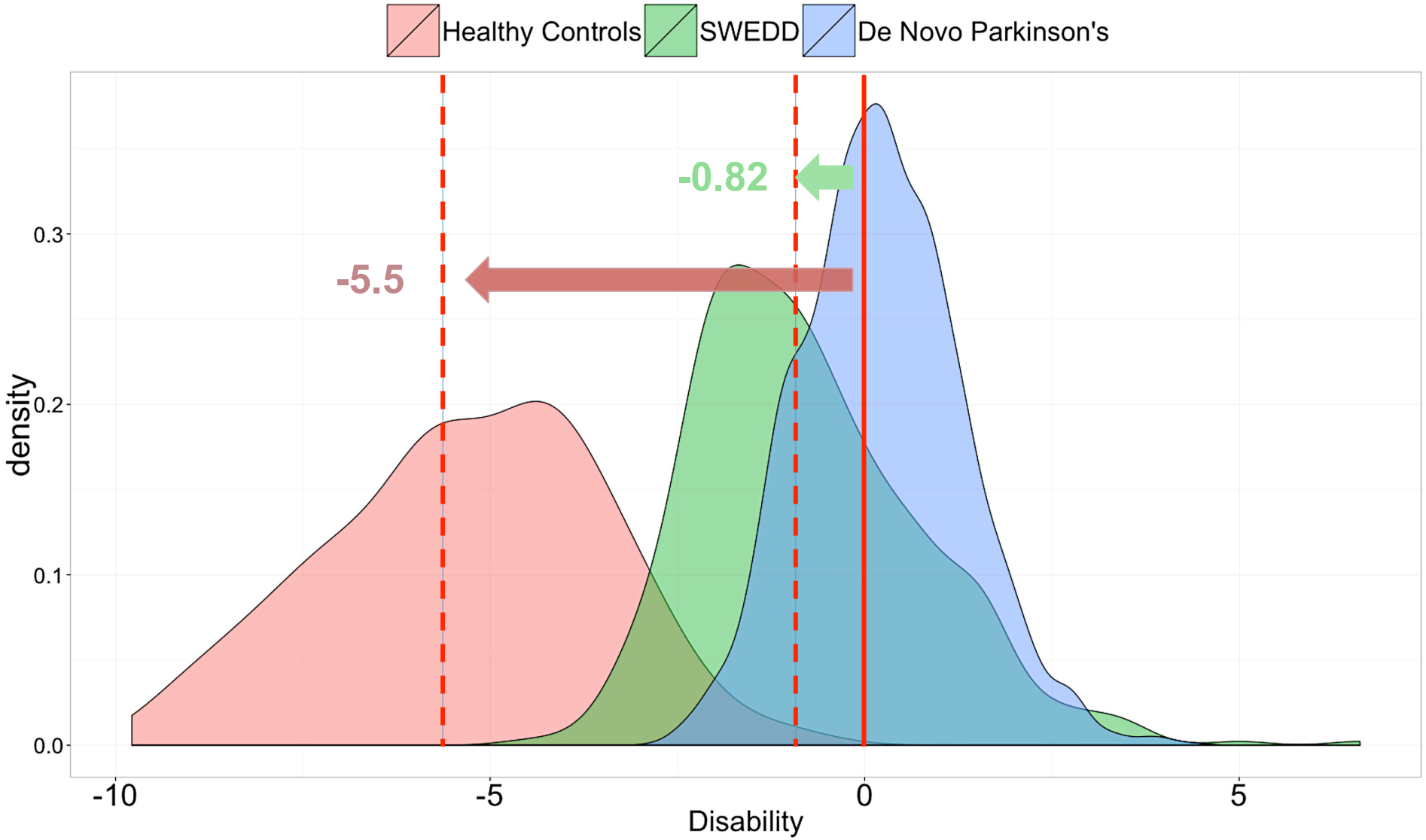
Results

Shift in baseline disability for a typical individual



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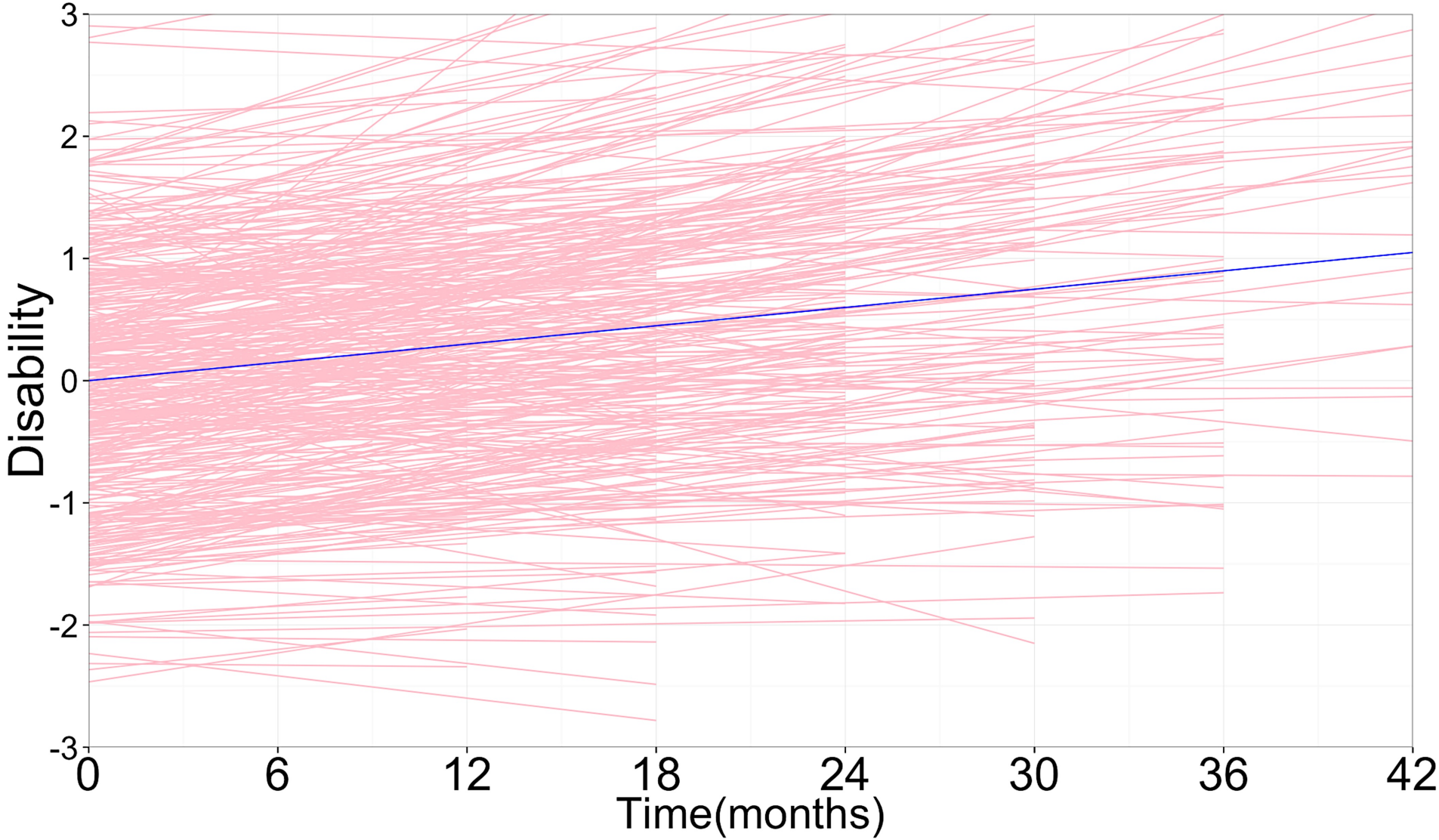
Results

*Longitudinal changes – **De Novo cohort***



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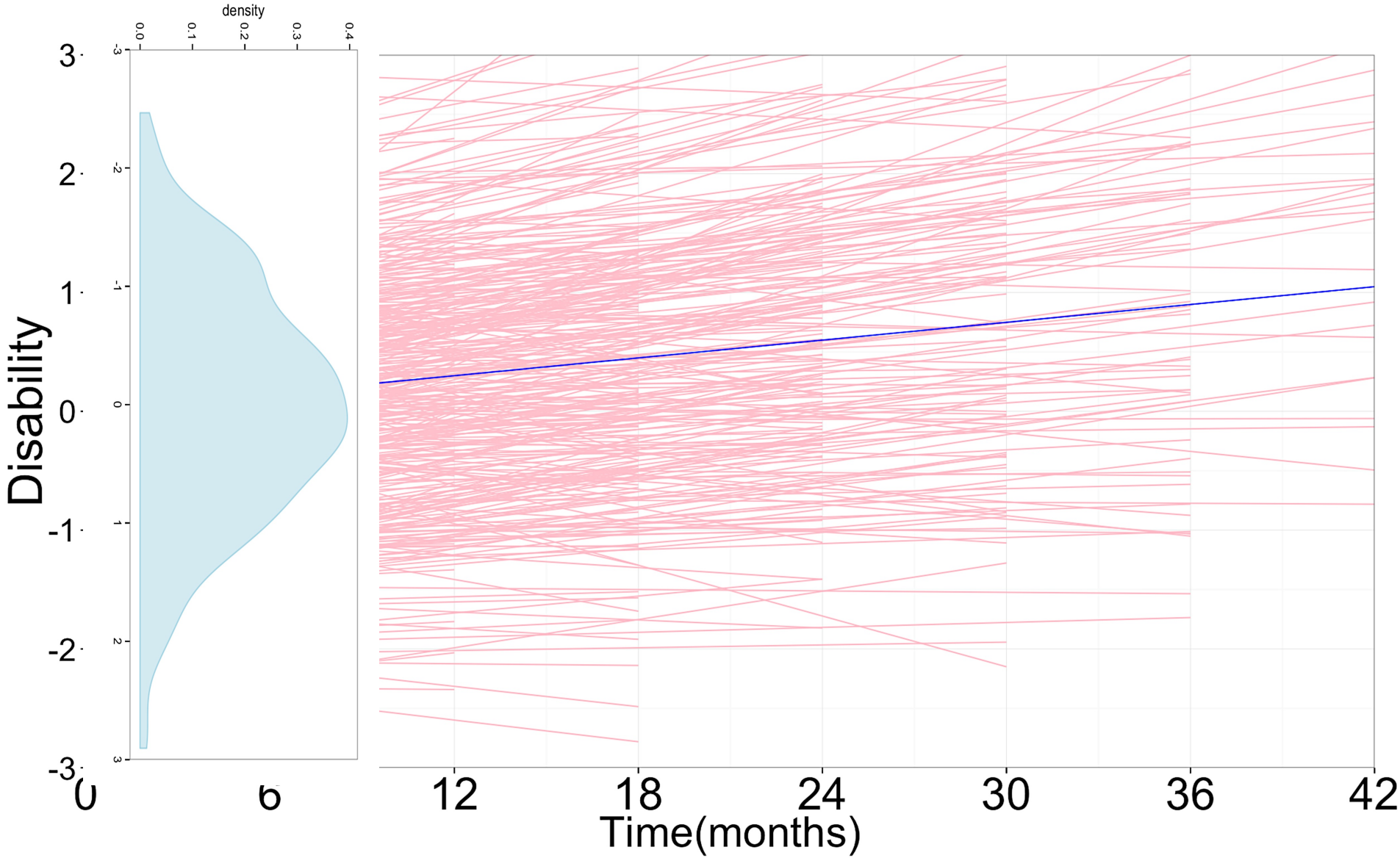

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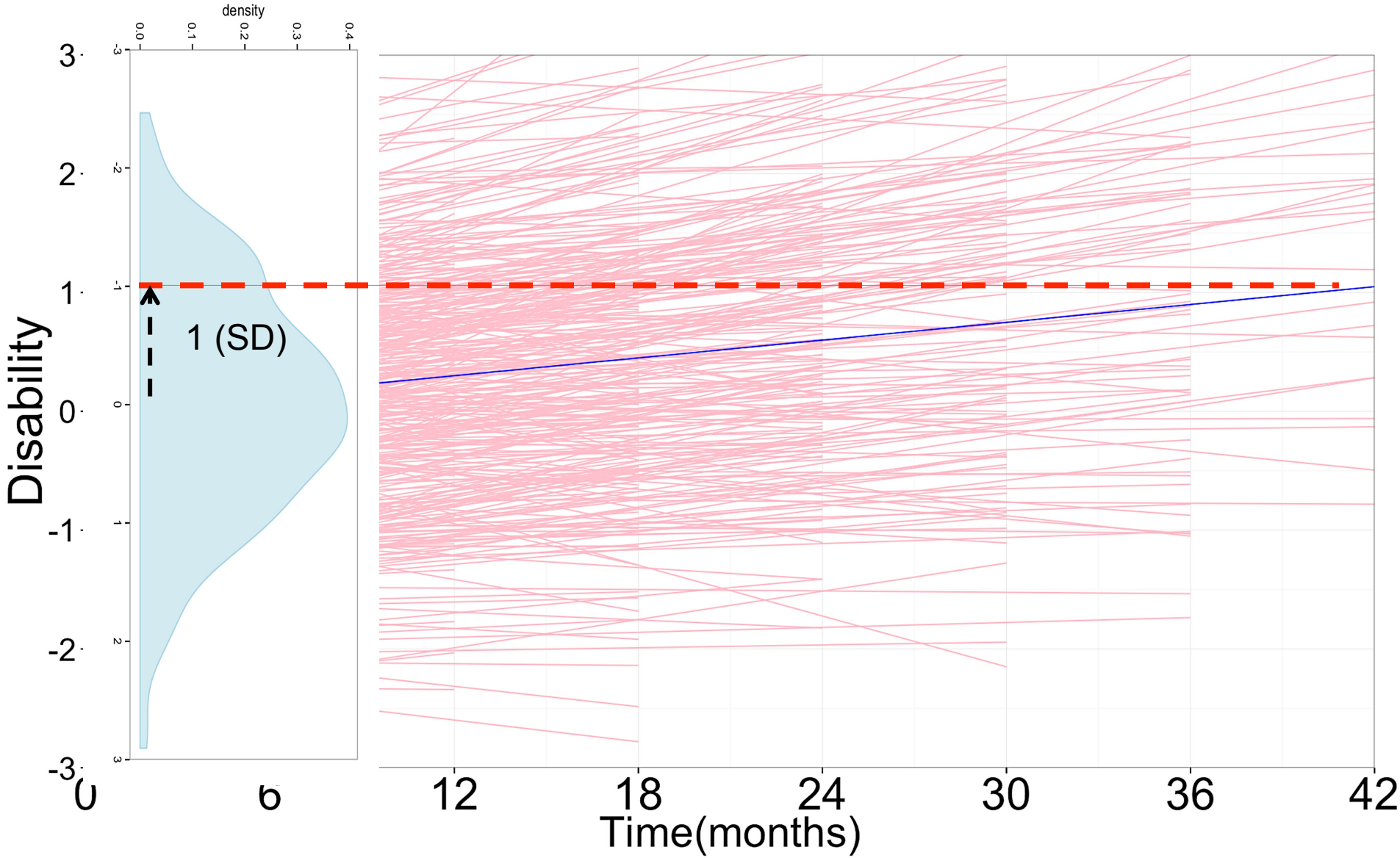

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Results

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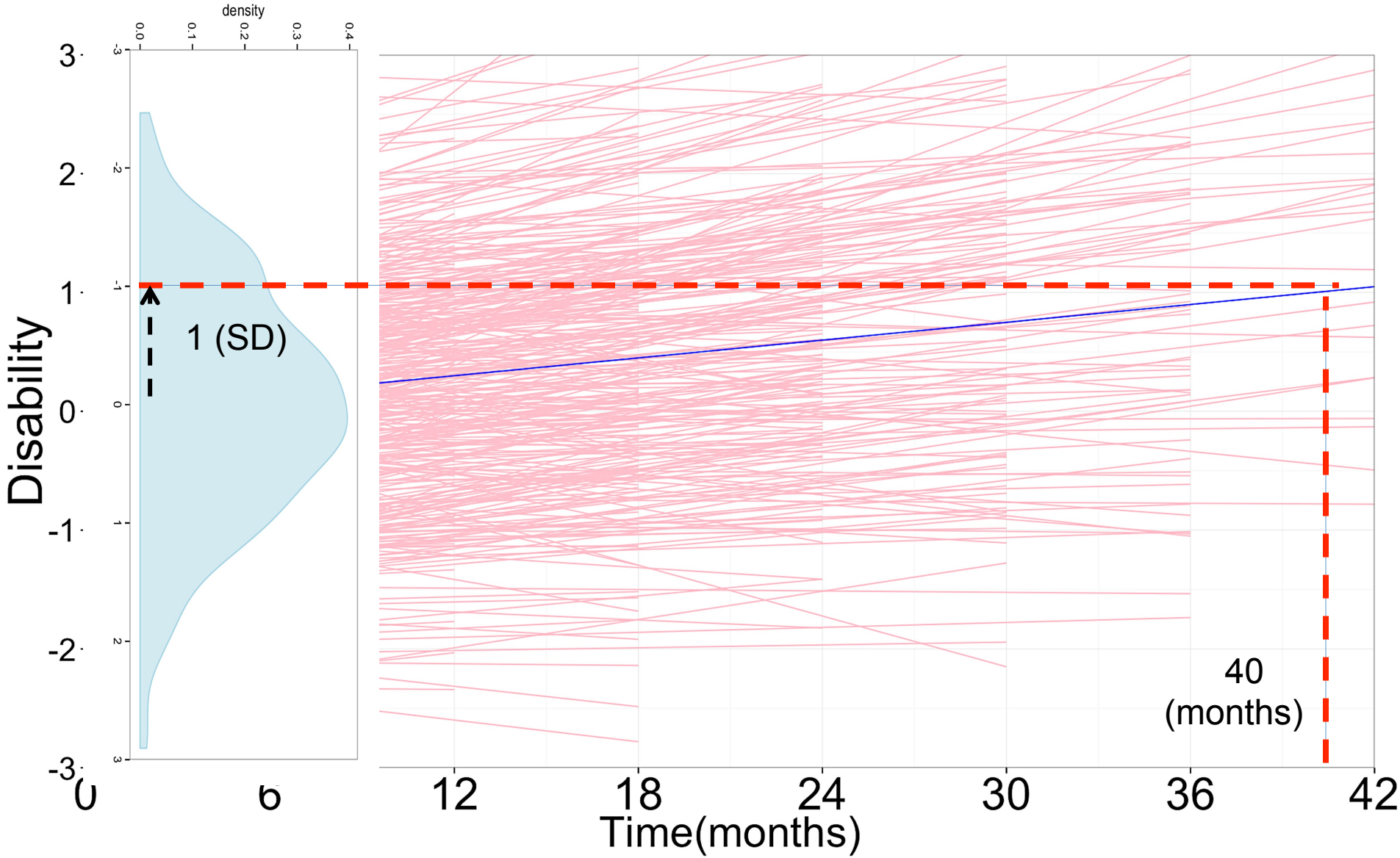

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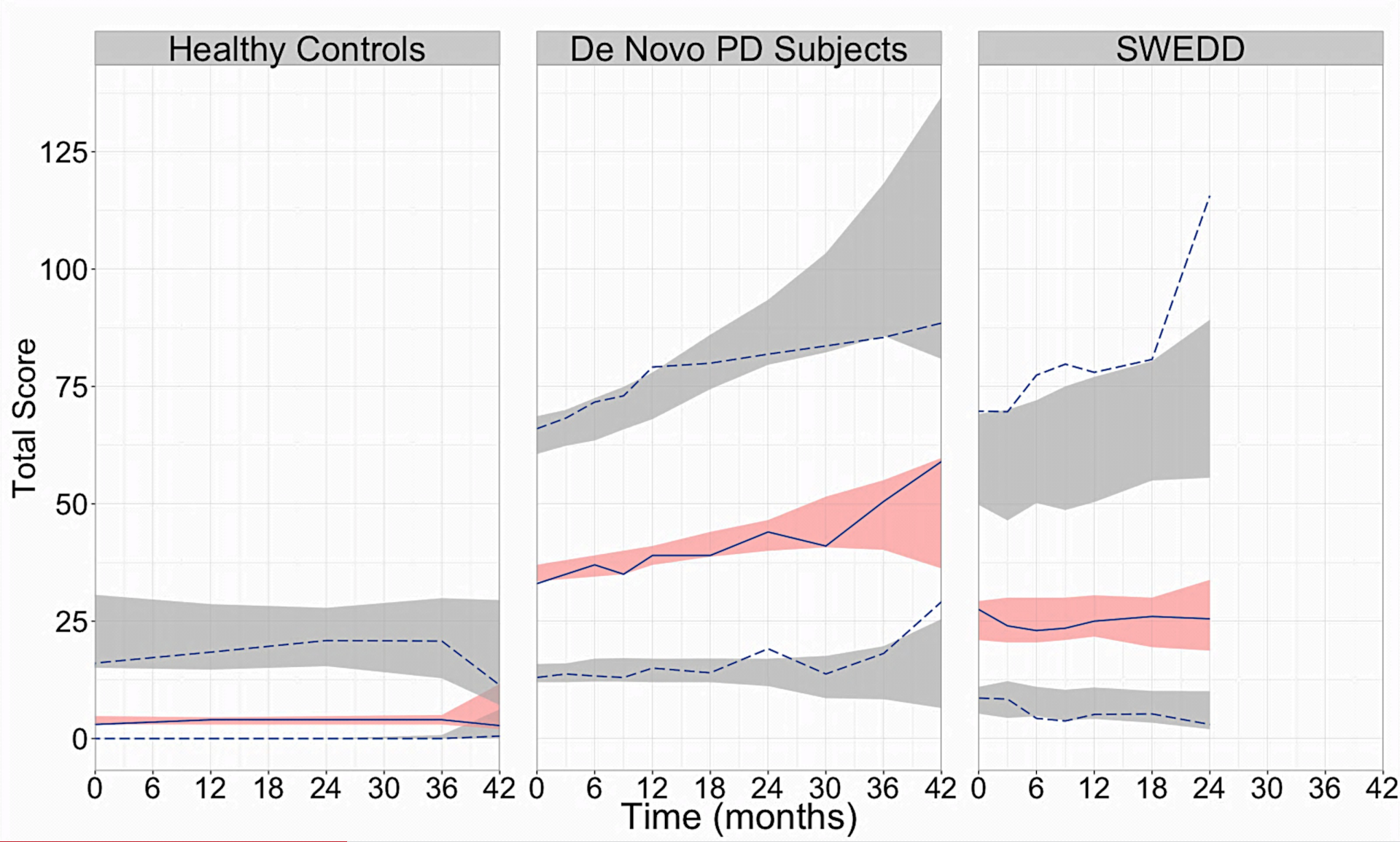
Diagnostics

VPC of longitudinal model – All cohorts



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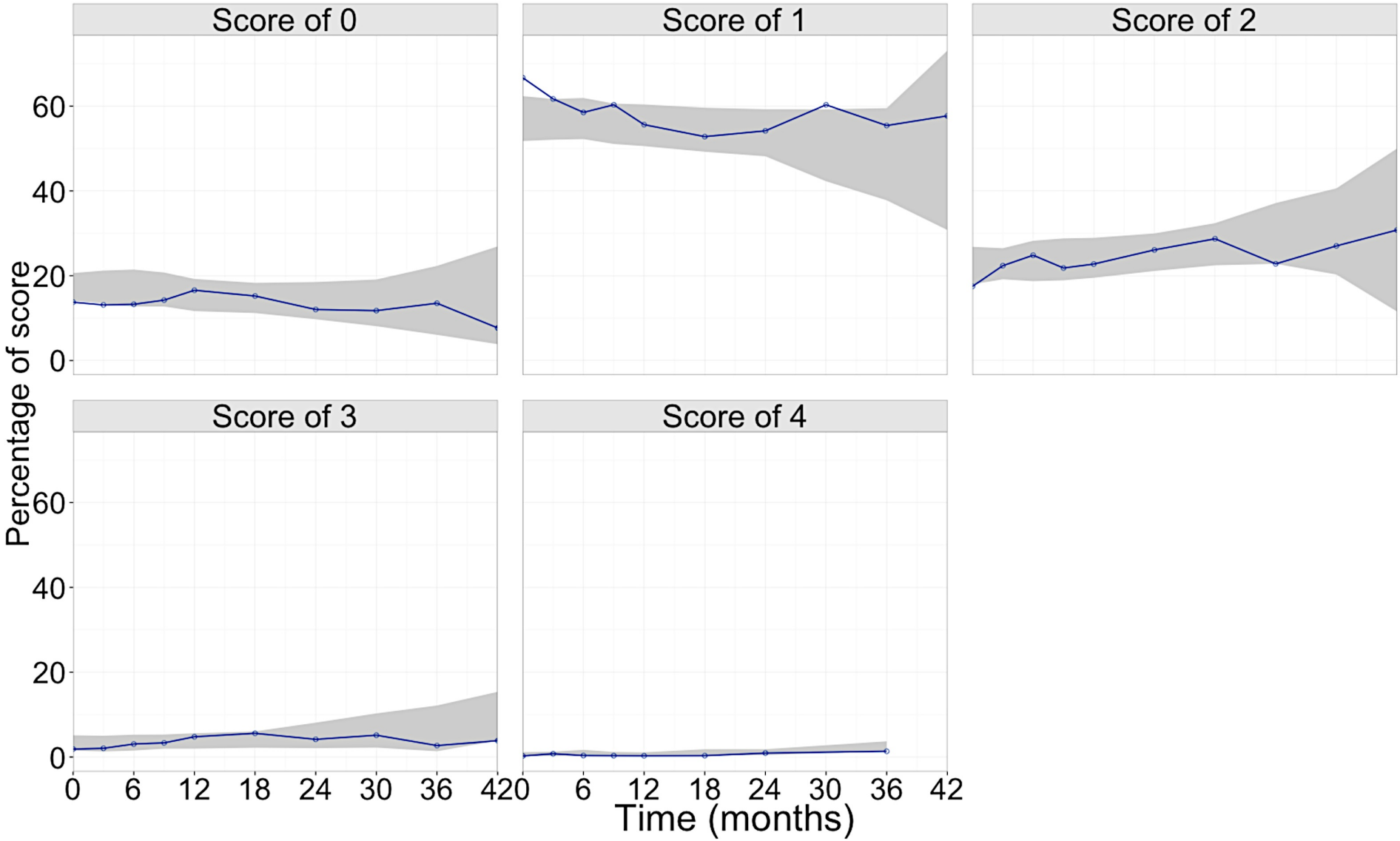
Diagnostics

*Item 23 - Longitudinal model – **De Novo cohort***



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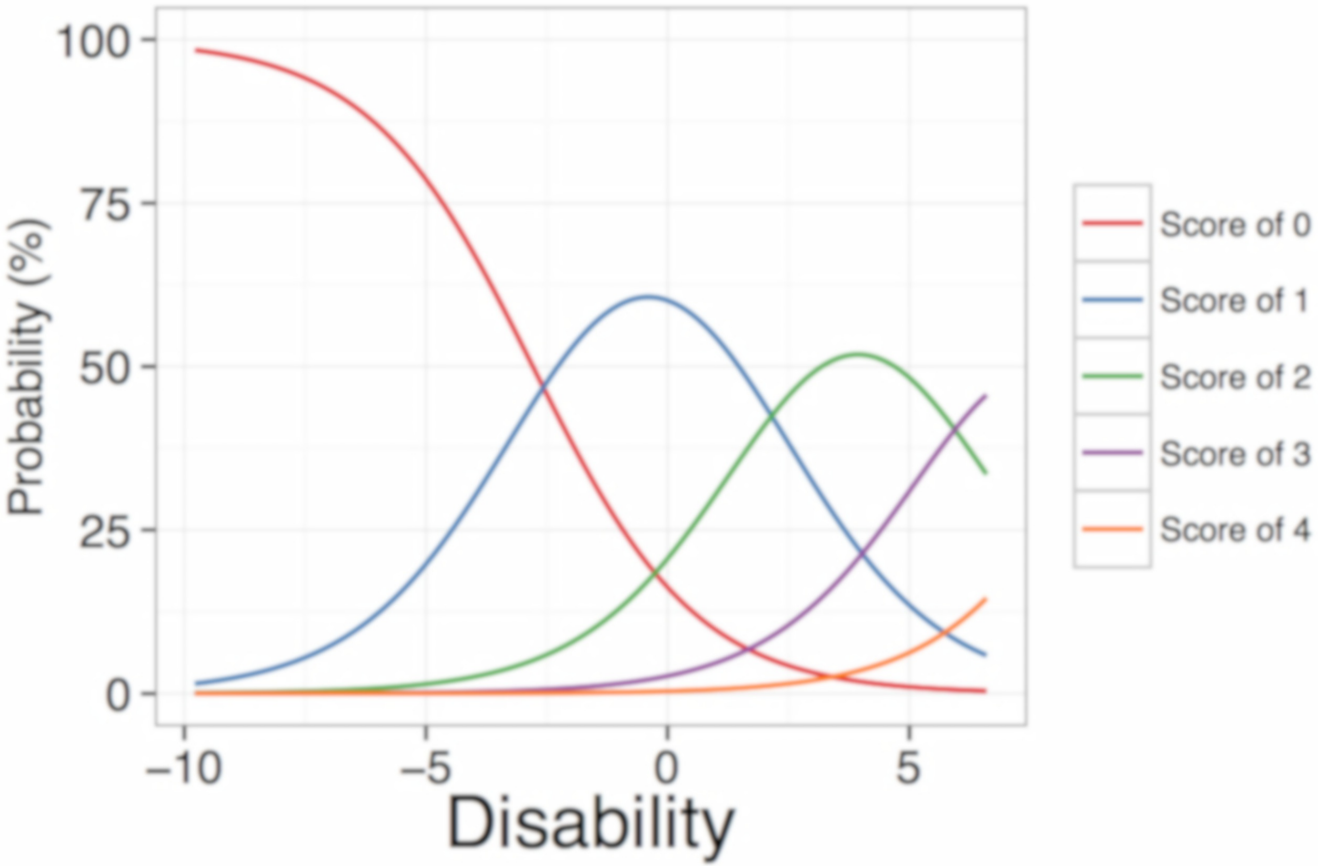
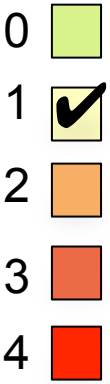
Item Characteristic Curve

Item 23 – Individual probabilities

For i[th] subject, j[th] (23[rd]) item, **DV = 1**

Based on ICC





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Item Characteristic Curve

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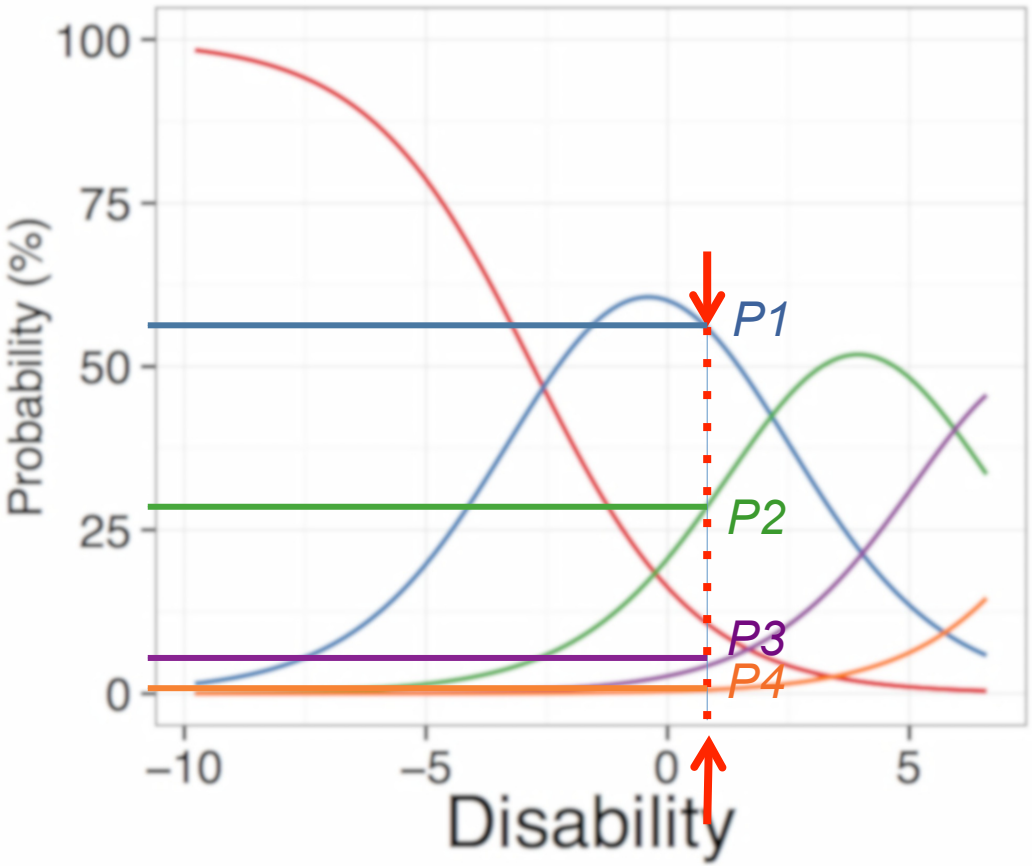

0
1 ✔
2
3
4

$\mathbf{E_{ij}}$ (weighted prediction)

= P1*1 +
P2*2 +
P3*3 +
P4*4

RES = DV – $\mathbf{E_{ij}}$

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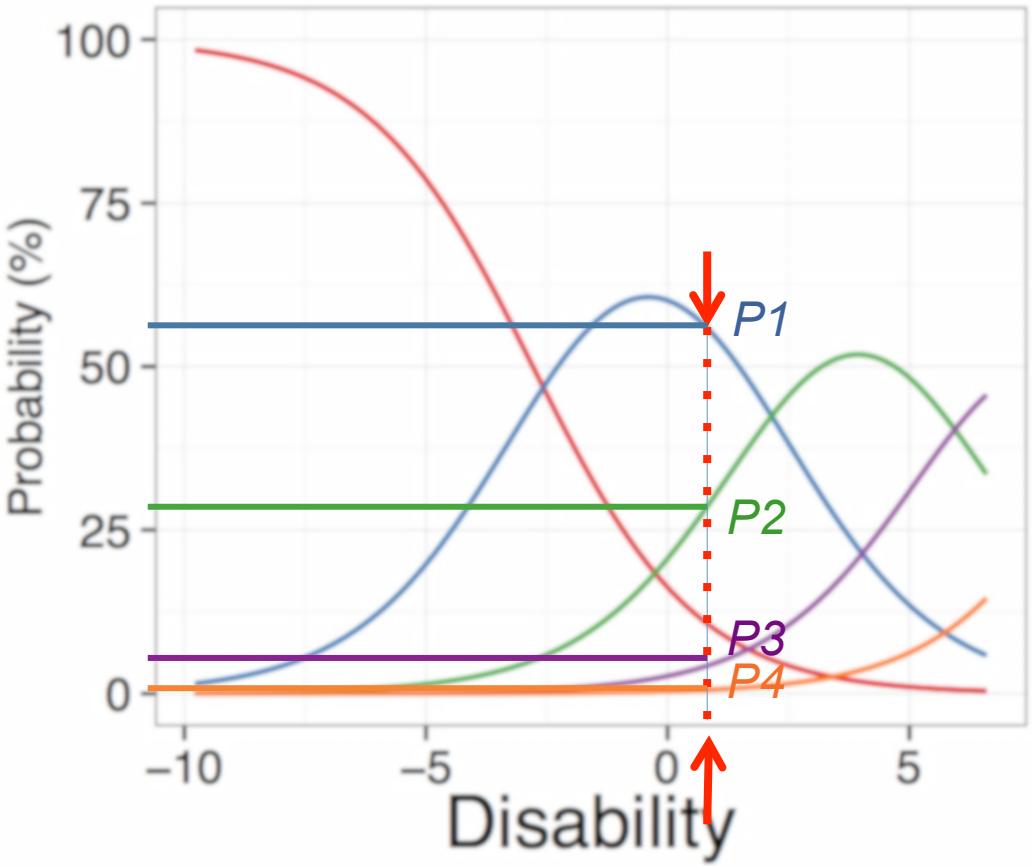
Item Characteristic Curve

Item 23 – Individual probabilities

For i^{th} subject, j^{th} (23^{rd}) item, **DV = 1**

Based on ICC



0
1 ✔
2
3
4

$\mathbf{E_{ij}}$ (weighted prediction)

= P1*1 +
P2*2 +
P3*3 +
P4*4

= (1.289)

RES = DV – $\mathbf{E_{ij}}$

(-0.289)

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Model-based diagnostics of ICC

Correlation among item responses

- Already handled by the IRT model, all item responses are related to the same latent variable - disability

Certain item responses may be more (/less) correlated than what the model predicts

- Investigate multiple latent variables by exploring correlation of residuals among the item responses

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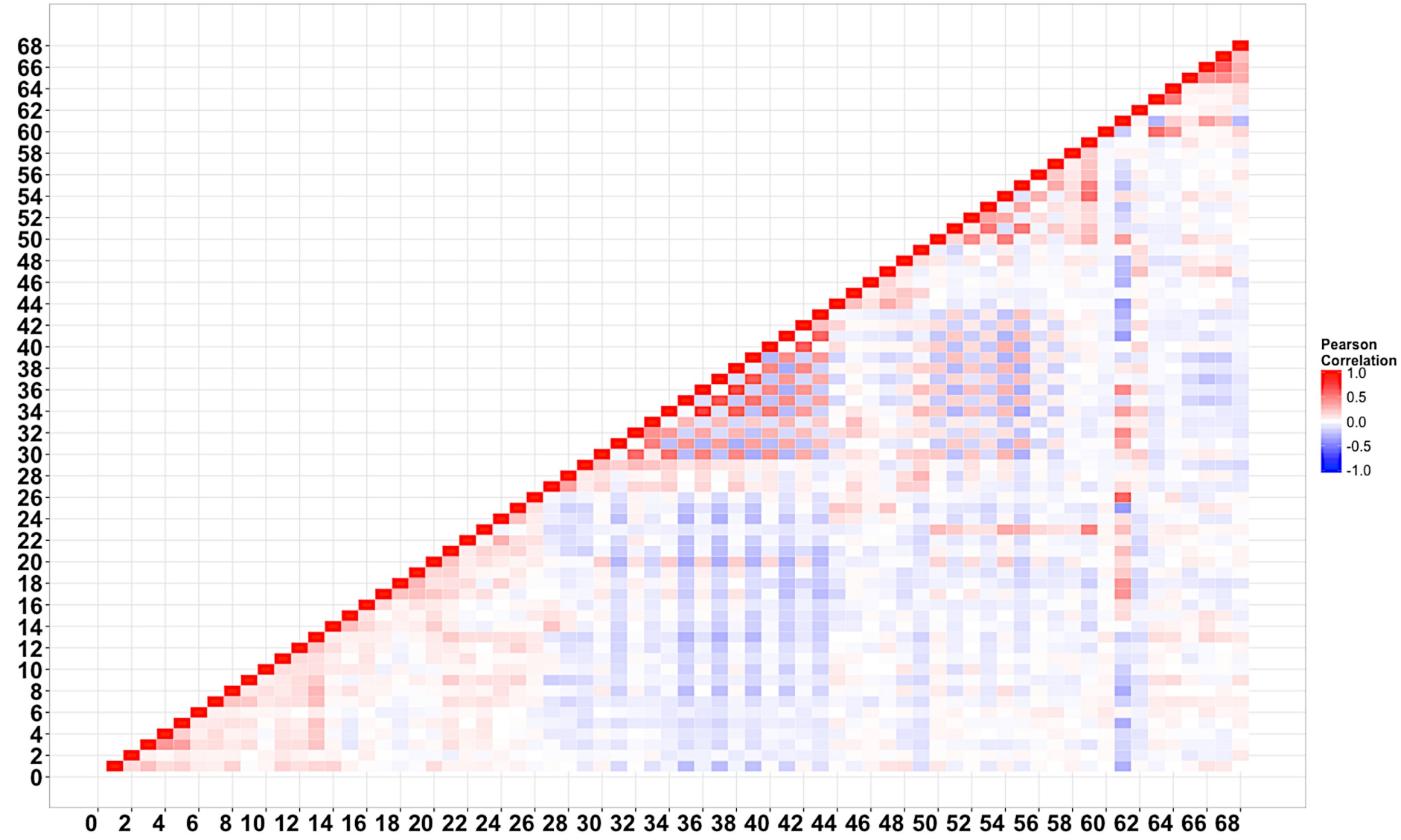
Correlation of residuals

*All data from De Novo cohort ONLY – **One** latent variable*



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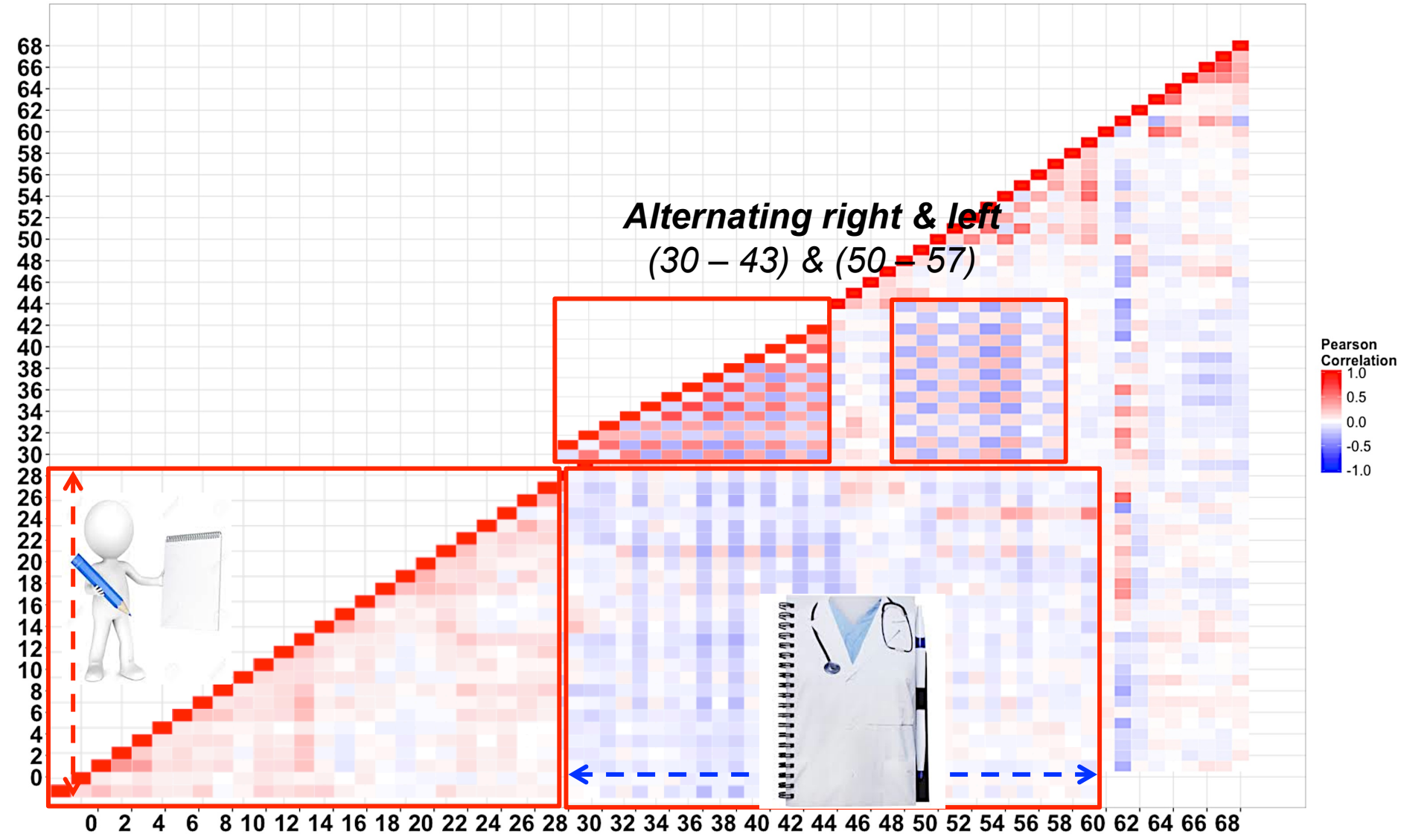
Correlation of residuals

*All data from De Novo cohort ONLY – **One** latent variable*



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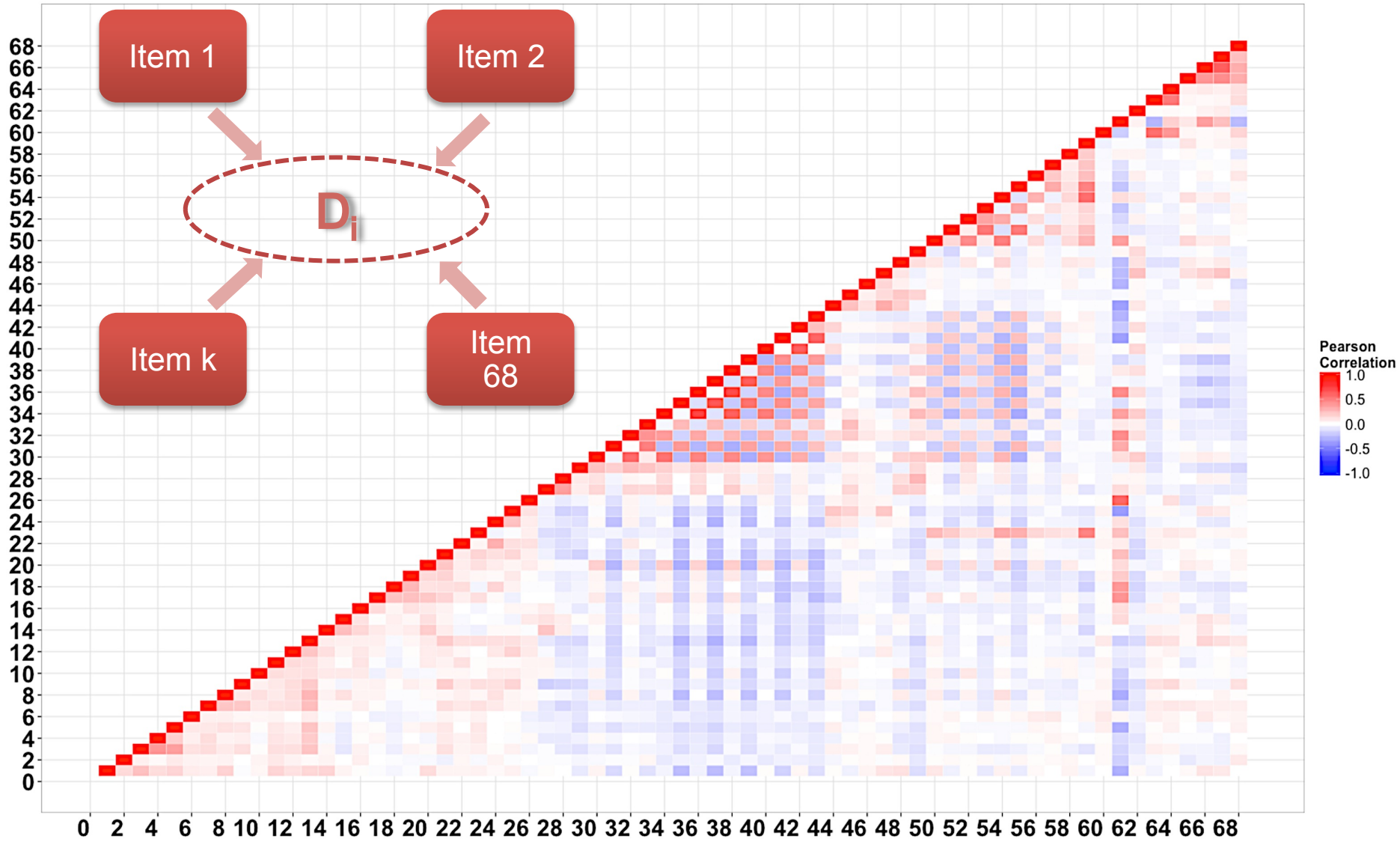
Diagnostics – Residuals

*All data from De Novo cohort ONLY – **One** latent variable*



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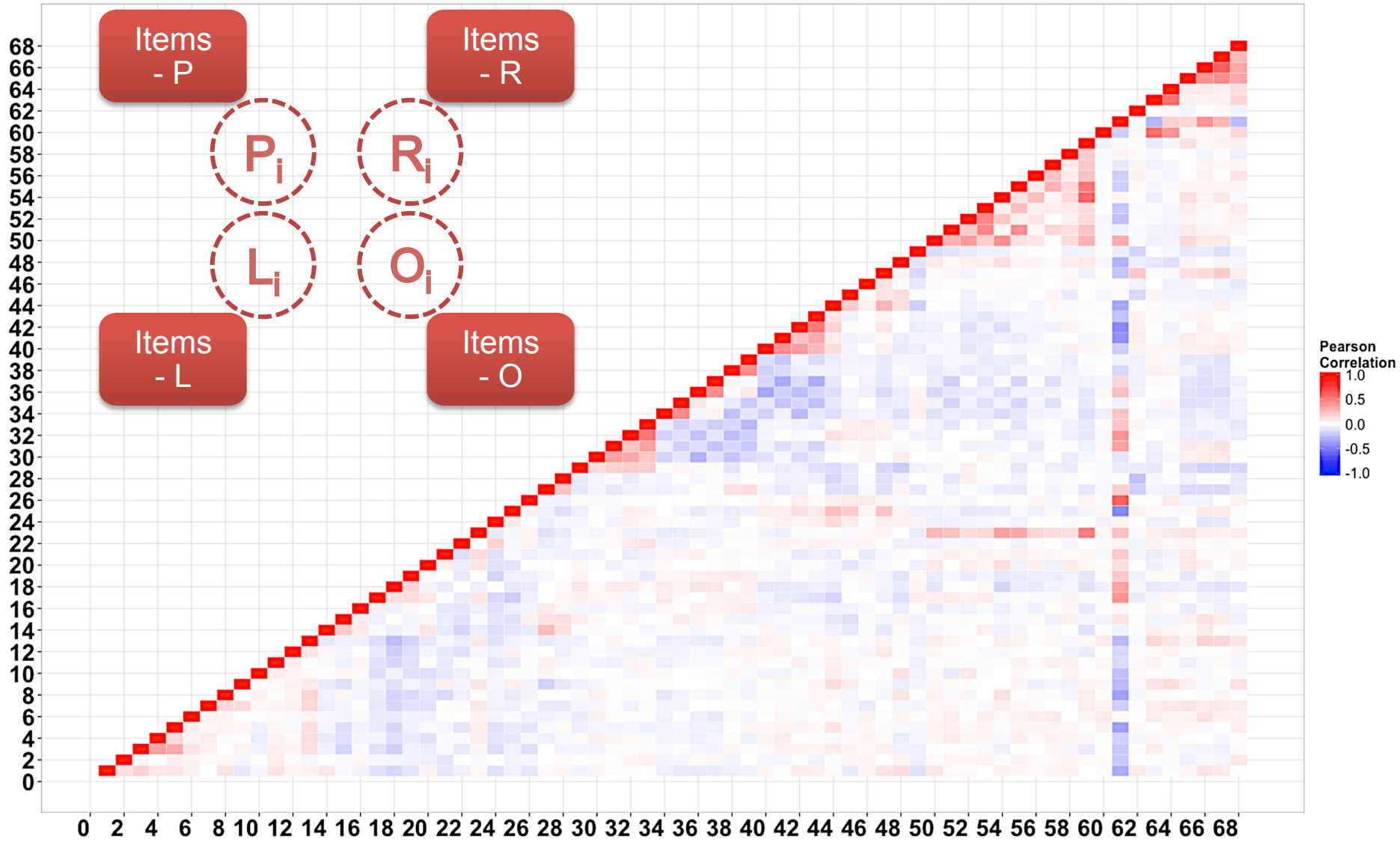
Diagnostics – Residuals

*All data from De Novo cohort ONLY – **Four** latent variables*



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Conclusions

Methodology

- Simultaneous estimation of IRT parameters with the longitudinal changes described the data well.
  - The IRT model simulations for the **total score and at item level** were in good agreement with observations

- Model-based diagnostics based on the residuals can be used as a tool to assess the need for multiple latent variables to improve the IRT models

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Future direction

Disease/patient population

This framework may be then extended:

- To characterize the disease progression in Parkinson's
- As a basis for design and analysis of trials in Parkinson's
- Identifying false positive patients (e.g., misdiagnosed Parkinson's subjects) such as SWEDD

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Acknowledgement

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