

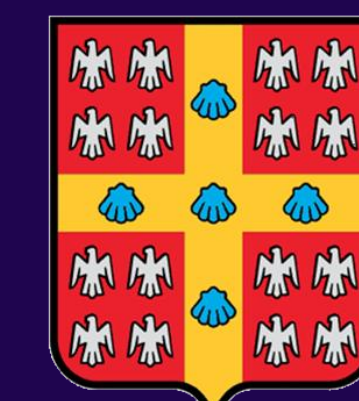
# Long Term Validation Of Neuronal Density With A Mathematical Model Of Brain Health

MEDICS

LABORATORY - LABORATOIRE



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## BACKGROUND

Understanding how biological processes drive neurodegeneration is essential for improving the prediction and monitoring of Alzheimer's disease progression. Our group developed a multiscale mathematical model that simulates the 50-year trajectory of brain health via 19 coupled ordinary differential equations with 75 parameters [1]. The model describes interactions between amyloid- $\beta$  accretion, tau phosphorylation, inflammation processes, and neuronal degeneration. In previous work [2], we performed a local sensitivity analysis by perturbing all 75 parameters and pick up the 30 parameters that have the greatest influence on three selected outcomes (Ab plaques, tau concentration, and neuronal density). This study focuses on real-world validation of the mathematical model by first optimizing these parameters using the ADNI cohort, then applying the optimized model to predict neuronal density (expressed as estimated neuronal mass in grams) in the UK Biobank cohort.

## MODEL DESCRIPTION

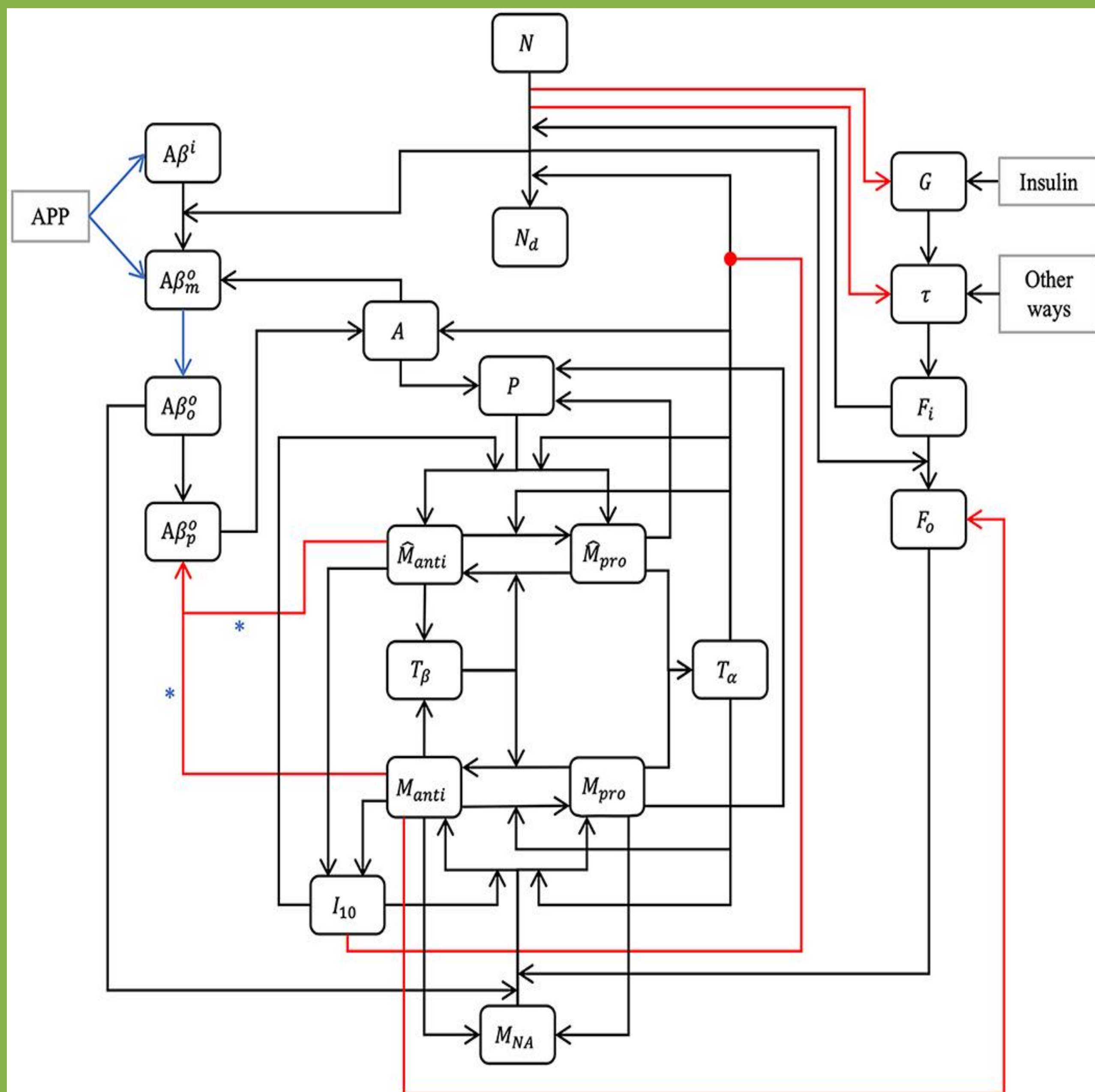


**Figure 1:** Proposed in Chamberland et al. 2024 [1], the model is composed of 19 ordinary differential equations (ODEs) and 75 parameters, covering entities such as the formation of A $\beta$  plaques; tau tangles; neuronal death; and microglia/macrophages interactions in neuroinflammation.

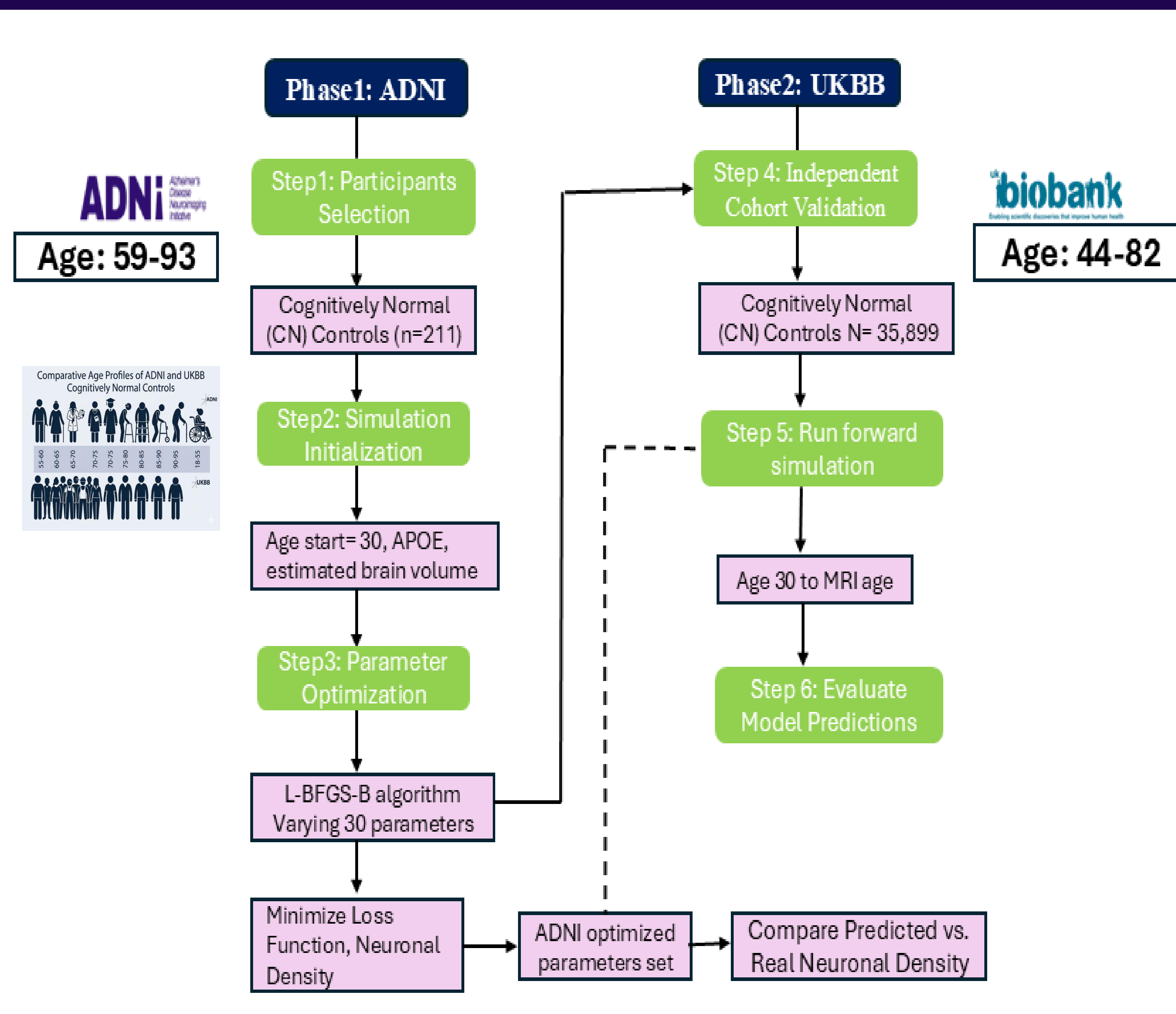
## CONCLUSION

- Our validated **multiscale** mathematical model successfully links mechanistic biological pathways with biological plausibility when compared to real-world population data.
- Calibrated on ADNI and validated on the UK Biobank, the model precisely predicts real-world macroscopic neuronal density over a 50-year lifespan.
- Exceptional predictive performance across 35,899 unseen individuals demonstrates powerful generalizability and population-level reliability without requiring any extra model tuning.

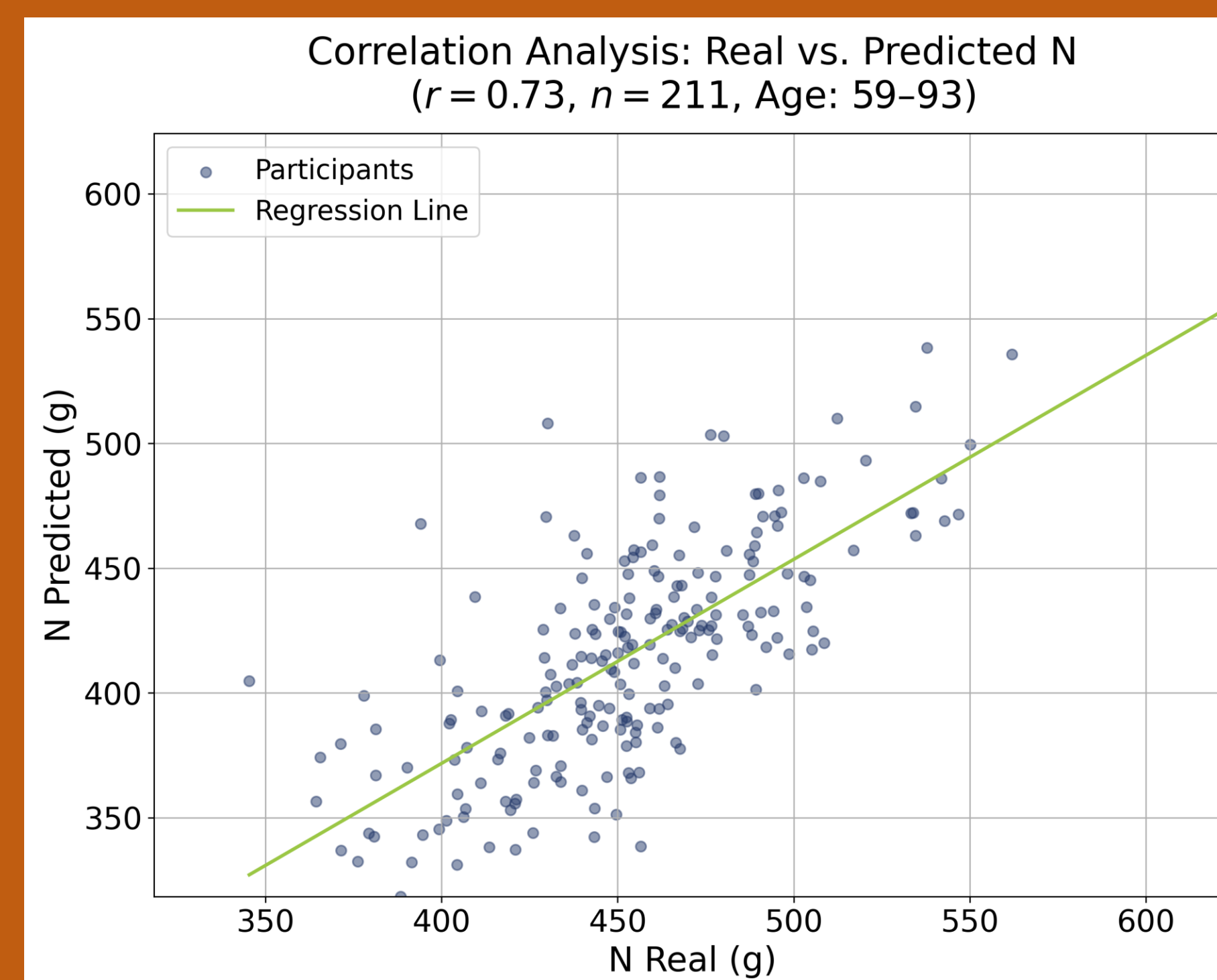
## METHODS

Two different approaches are used for this analysis:

- Global Model Optimization (ADNI)
- External Validation (UK Biobank)

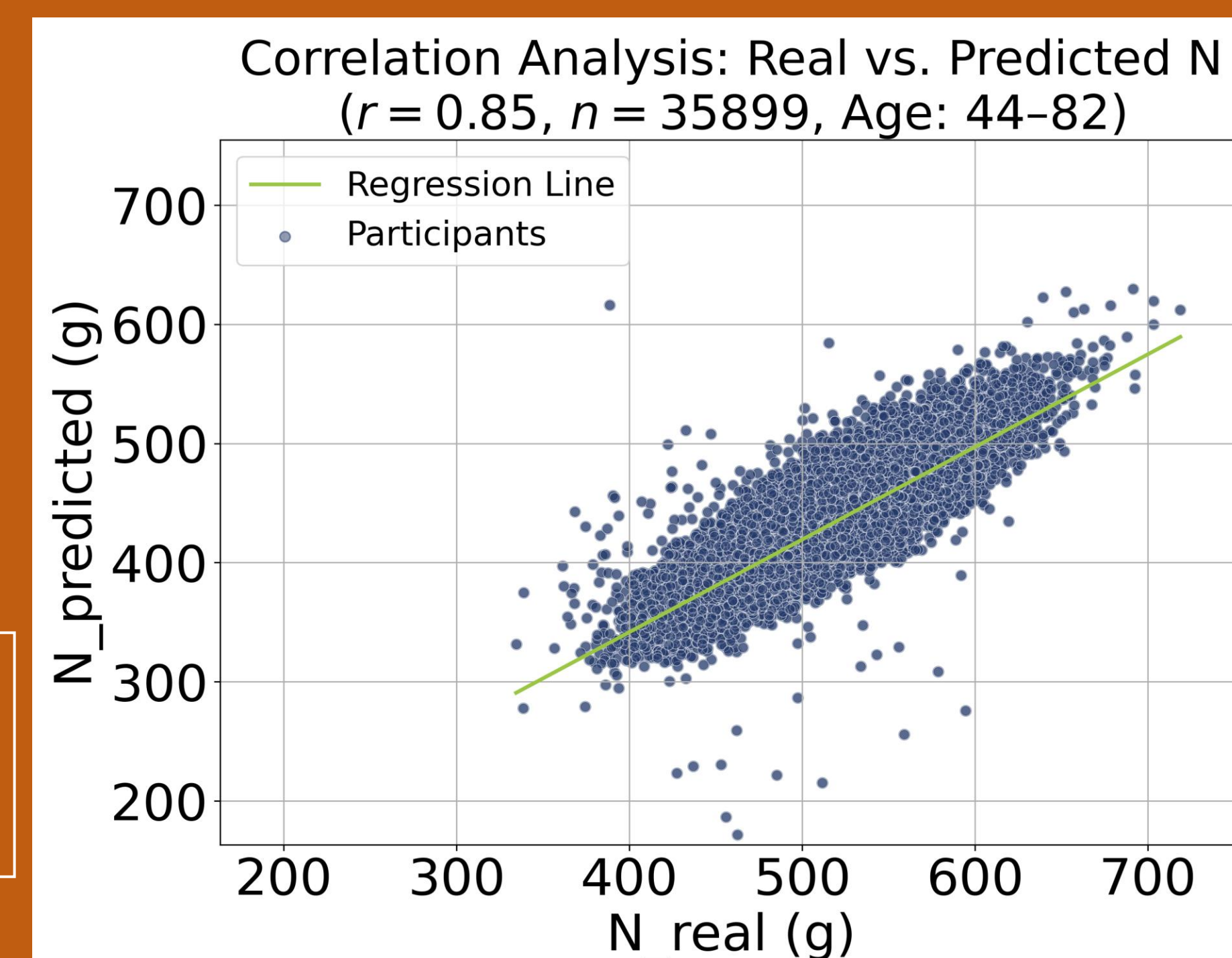


## RESULTS



Training & Optimization (ADNI)

Independent External Validation (UKBB)



- Parameter optimization on ADNI yielded a strong baseline correlation of  $r = 0.73$  ( $n = 211$ ), which generalized beautifully to the independent UK Biobank cohort ( $n = 35,899$ ) with an exceptional out-of-the-box correlation of  $r = 0.85$ .
- The model higher accuracy in the UK Biobank is attributed to a shorter average simulation timeline (34 years vs. 44 years in ADNI), which naturally minimized long-term ordinary differential equation (ODE) simulation drift.

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## Estimated Brain Volume Calculation

- Model initialized at Age 30 with participants' biological Sex and initial brain volume, estimated using the Total Intracranial Volume (eTIV) from MRI as follows:

$$V_{\text{brain}, 30} = -150,000 + 0.75 \times \text{eTIV} + 45,000 \times \text{Sex}$$

Adopted from [3]

Real Neuronal Density

Brain Segmentation of the MRI

## GUIDING QUESTIONS

- How well do our simulated trajectories predict real-world neuronal density?
- Can a mechanistic model accurately capture age-related brain atrophy?

## REFERENCES

- [1] Chamberland, E. et al. (2024). Frontiers in Neuroinformatics, 18, 1348113.
- [2] Moravveji S., Sadia H., et al. (2025) Frontiers in Neuroinformatics, 19, 2025.
- [3] O'Brien LM., Et al. (2011). Psychiatry Research: Neuroimaging. 2011;193(2):113-22.