The Confound Continuum - A 2D confounder assessment for AI in precision medicine

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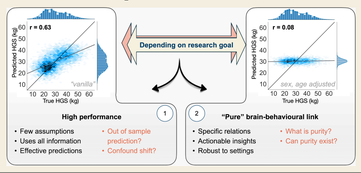
Key take aways

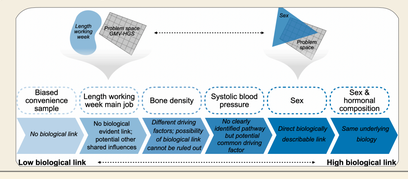
1 **Confounders can have a bigger impact on a model than features & algorithm choice**

Features	Algorithm	Confounders
r = 0.63 ↔ r = 0.36	r = 0.63 ↔ r = 0.59	r = 0.63 ↔ r = 0.08

2 **Distinguish if the predictions target high performance or a pure brain-behavioural link**



3 **Biomedical validity of confound removal needs to be acknowledged independent of statistical considerations**



Think about statistical AND conceptual implications of confound removal → interpret respectively

Introduction

Goal Individual-level behavioural predictions from neuroimaging-derived features

Problem
- ❖ Confounding can influence brain-derived features and phenotypical targets
- ❖ Removing confounders changes the feature-target relationship → affected model interpretation
- ❖ Statistical confounder evaluations cannot account for biomedical validity of confound removal

Objective
- ❖ Develop a use-case dependent conceptual dimension → Confound Continuum
- ❖ Exemplify confounder impact by predicting the robust, reliable and clinically relevant target hand grip strength (HGS)[1]

Methods

Features
- ❖ Gray matter volume (GMV): Cortex[2], Subcortex[3], Cerebellum[4]
- ❖ Functional Connectivity (FC)
- ❖ Cortical Thickness (CT)

Learning Algorithms
- ❖ Linear SVR[5,6] (heuristic C[7], L1 /L2 loss)
- ❖ RBF SVR
- ❖ Ridge regression

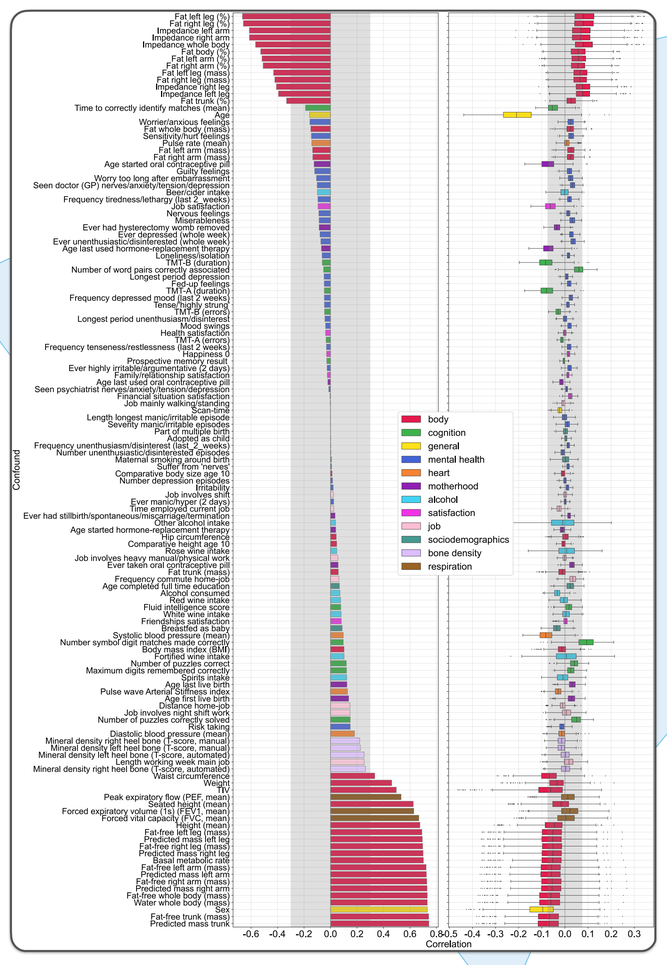
Setups
- ❖ Brain features only
- ❖ Confound features only
- ❖ Brain & confounder features

Confounders
- ❖ Scan-site ❖ Age ❖ Sex & Age
- ❖ Scan-time ❖ Sex

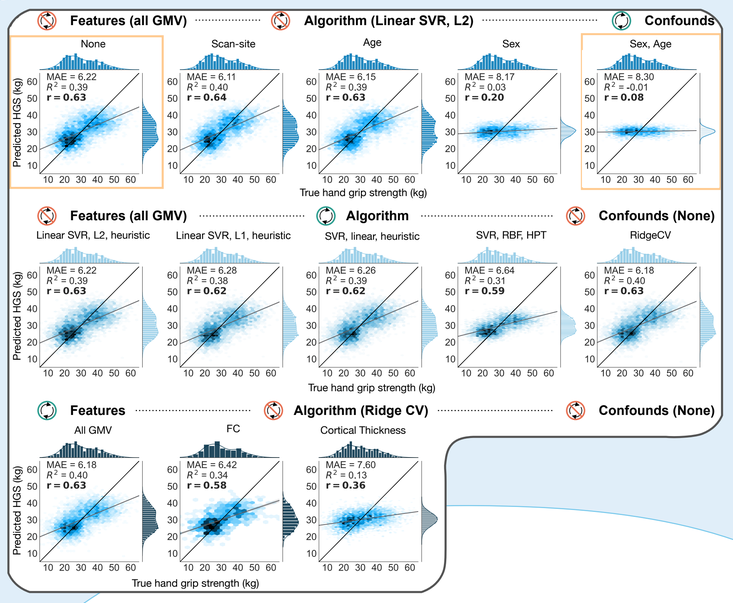
Feature / Algorithm / Confounder setup	N_{train}	N_{test} (hold-out)
GMV / LinearSVR (L2) / Changing confound removal	21,169 to 21,782	5,293 to 5,446
GMV / Changing learning algorithm / No confound removal	21,782	5,446
Changing features / Ridge CV / No confound removal	GMV - 21,782 FC - 3,337 CT - 24,544	GMV - 5,446 FC - 835 CT - 6,137

Results

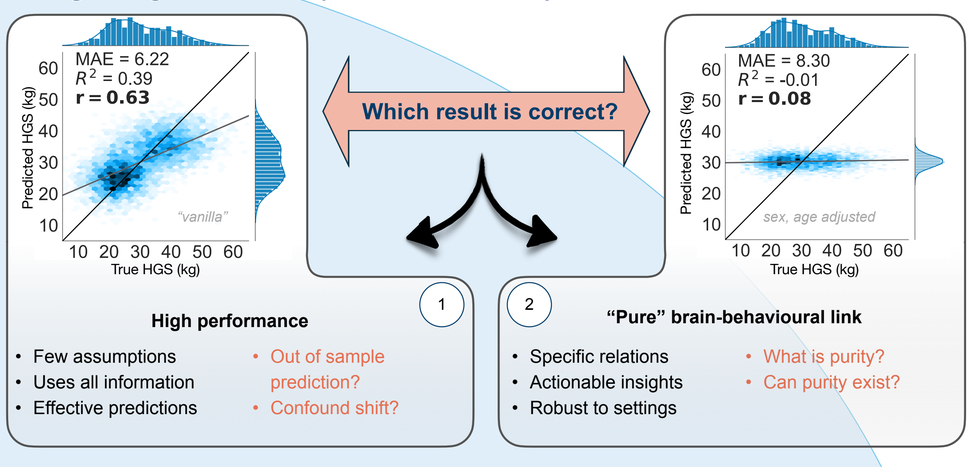
Statistical confounder evaluation



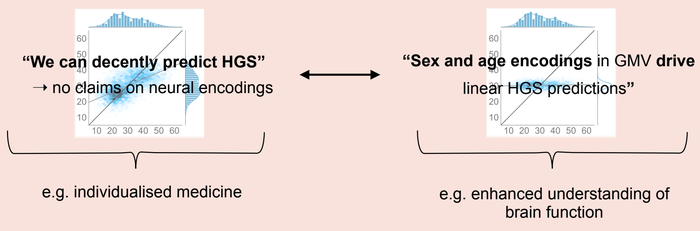
Confound removal impacts predictive performance more than feature or algorithm choice



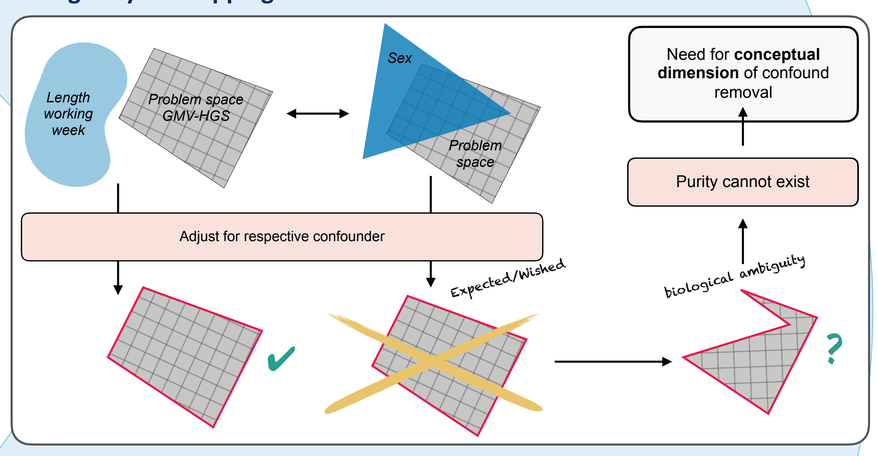
Distinguishing between two possible research objectives



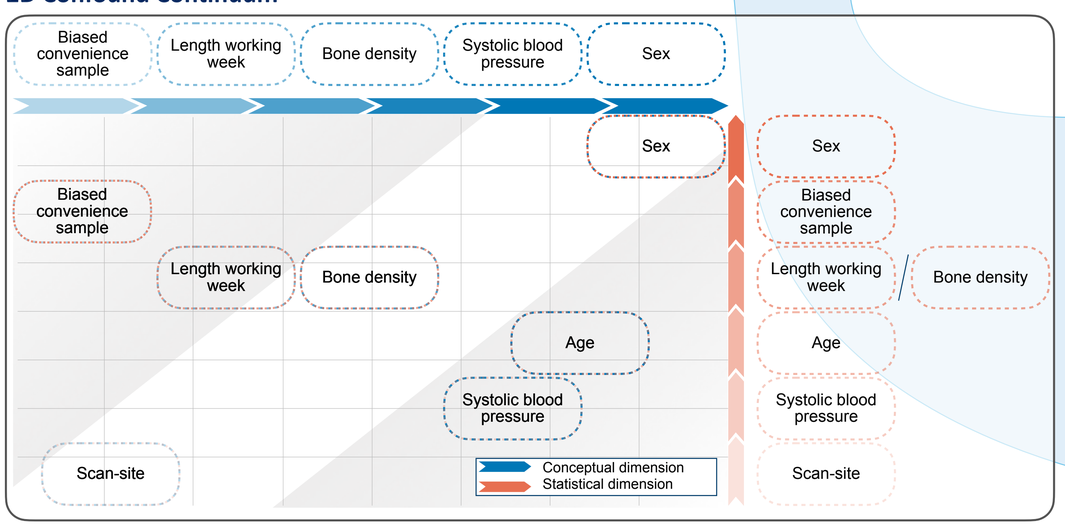
Interpretation matters



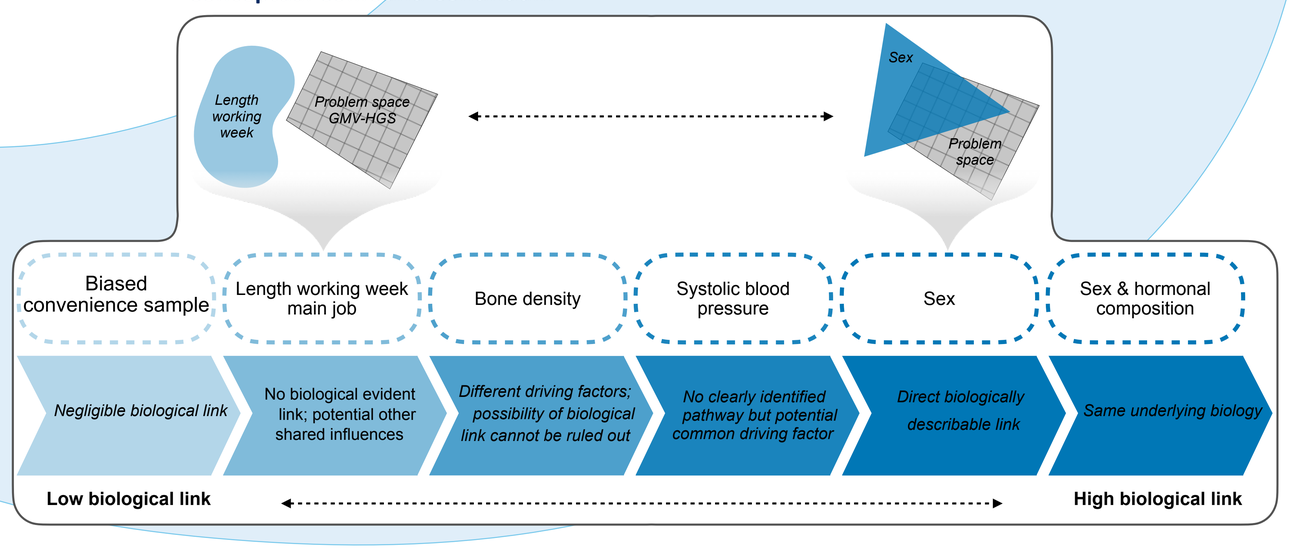
Biologically overlapping confounders



2D Confound Continuum



Conceptual Confound Continuum



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