

Dimensional, Categorical or both? Using Genetics to Explore the Structure of Major Depression.

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Introduction

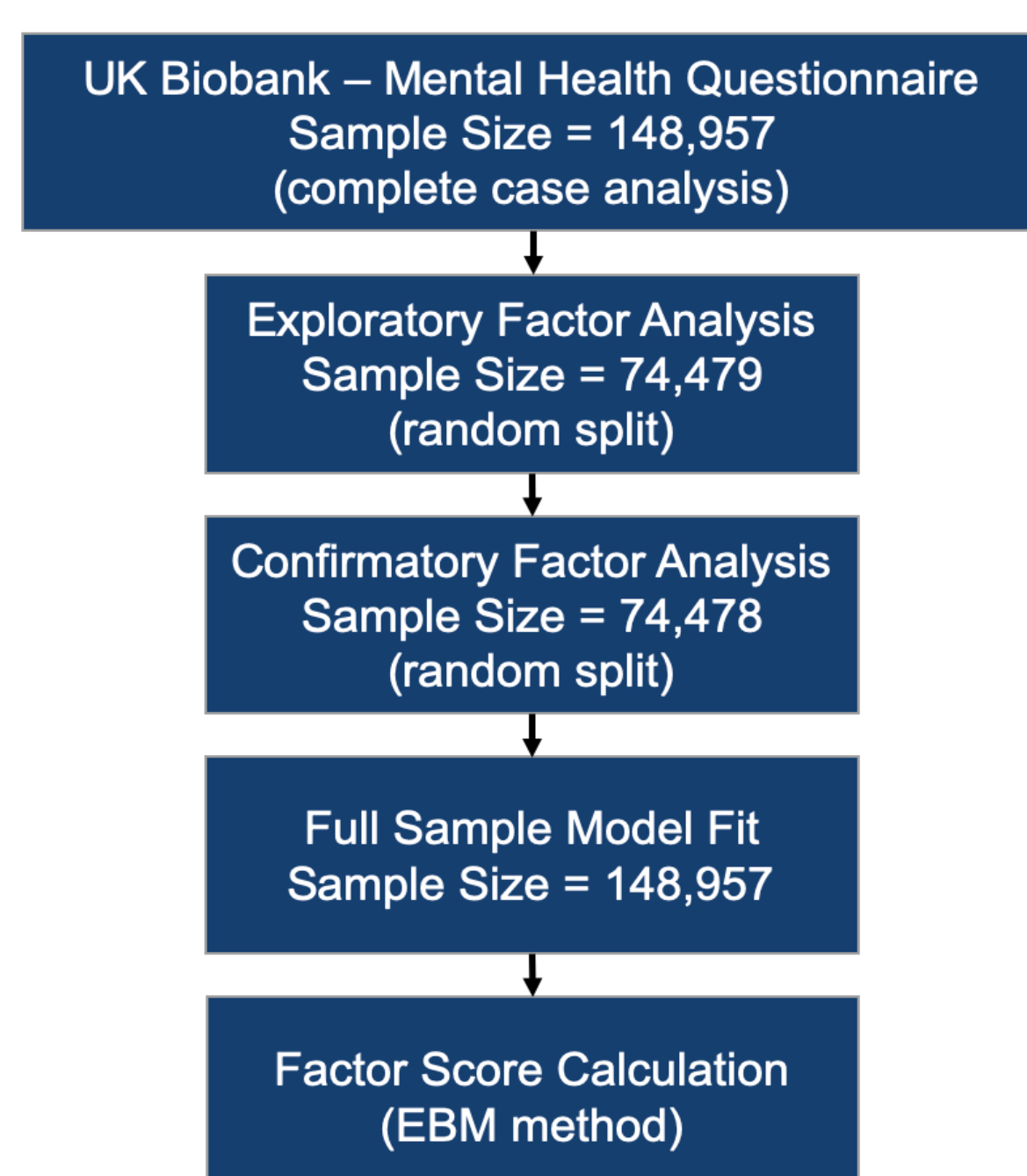
- It is not known whether major depression (MD) exists on a continuum or as its own distinct entity.
- Risk factors and clinical correlates between sub-threshold depression and clinical MD suggest depression is continuous (1,2).
- Polygenic risk as a risk factor has not been considered.

Aims

- To model the latent structure of MD and derive a multi-dimensional phenotype for the disorder.
- To test if polygenic risk scores (PRS), an aggregate measure of an individual's genetic propensity to MD, can predict the continuous MD phenotypes.

Methods

Defining the phenotypes



- **UK Biobank items selected:** Patient Health Questionnaire 9, Generalised Anxiety Disorder 7 and 2 subjective well-being items (belief life is meaningful and general happiness).

Polygenic risk score association testing

- **Base dataset:** Psychiatric Genomics Consortium without 23andMe or UK Biobank samples (3).
- **Covariates:** First 6 principal components, genotype batch and assessment centre.

Results

Symptoms of major depression do not represent a single dimension.

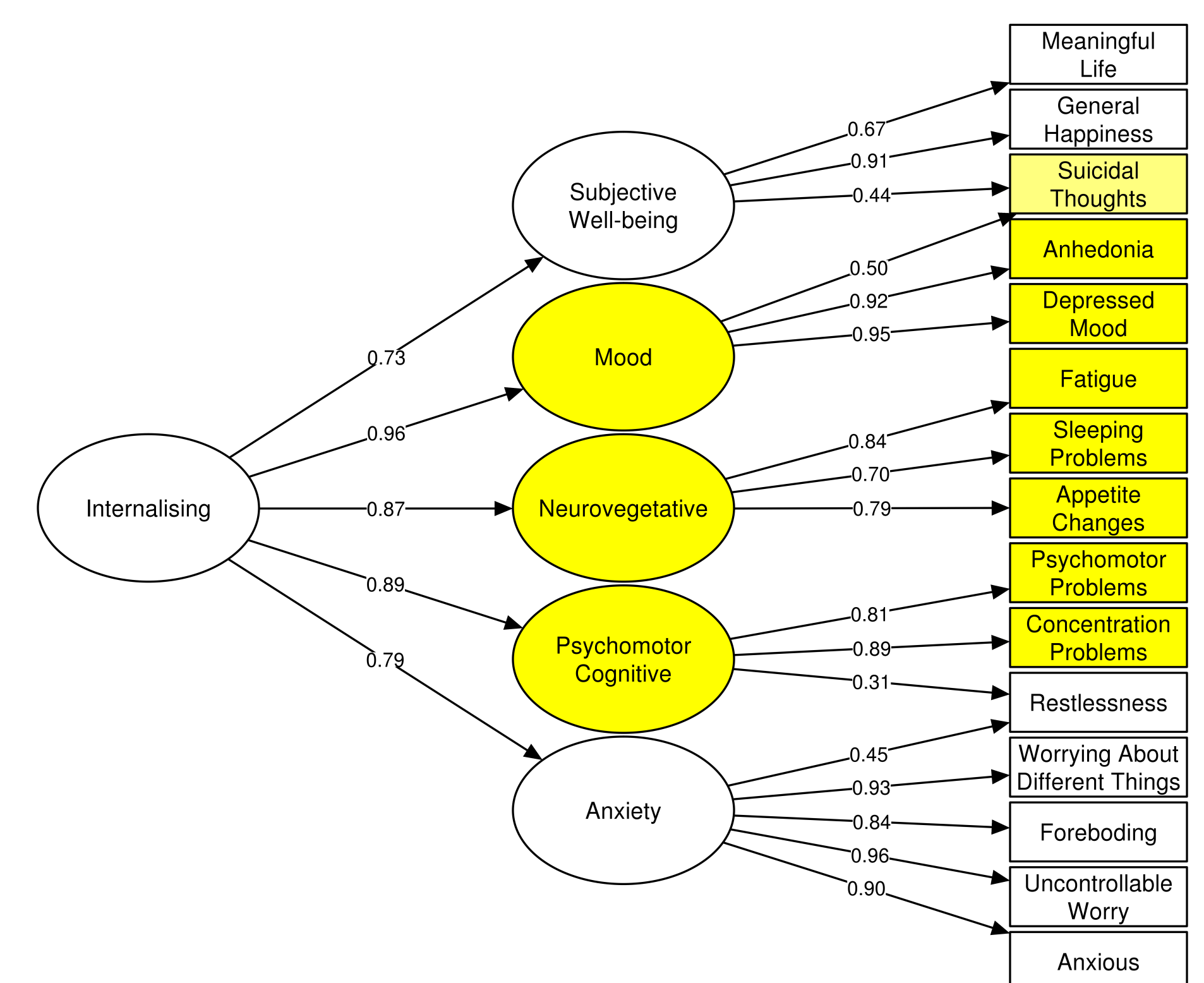


Figure 1. Final model of the latent structure of current major depression.

Polygenic risk scores for major depression predict continuous measures of the disorder.

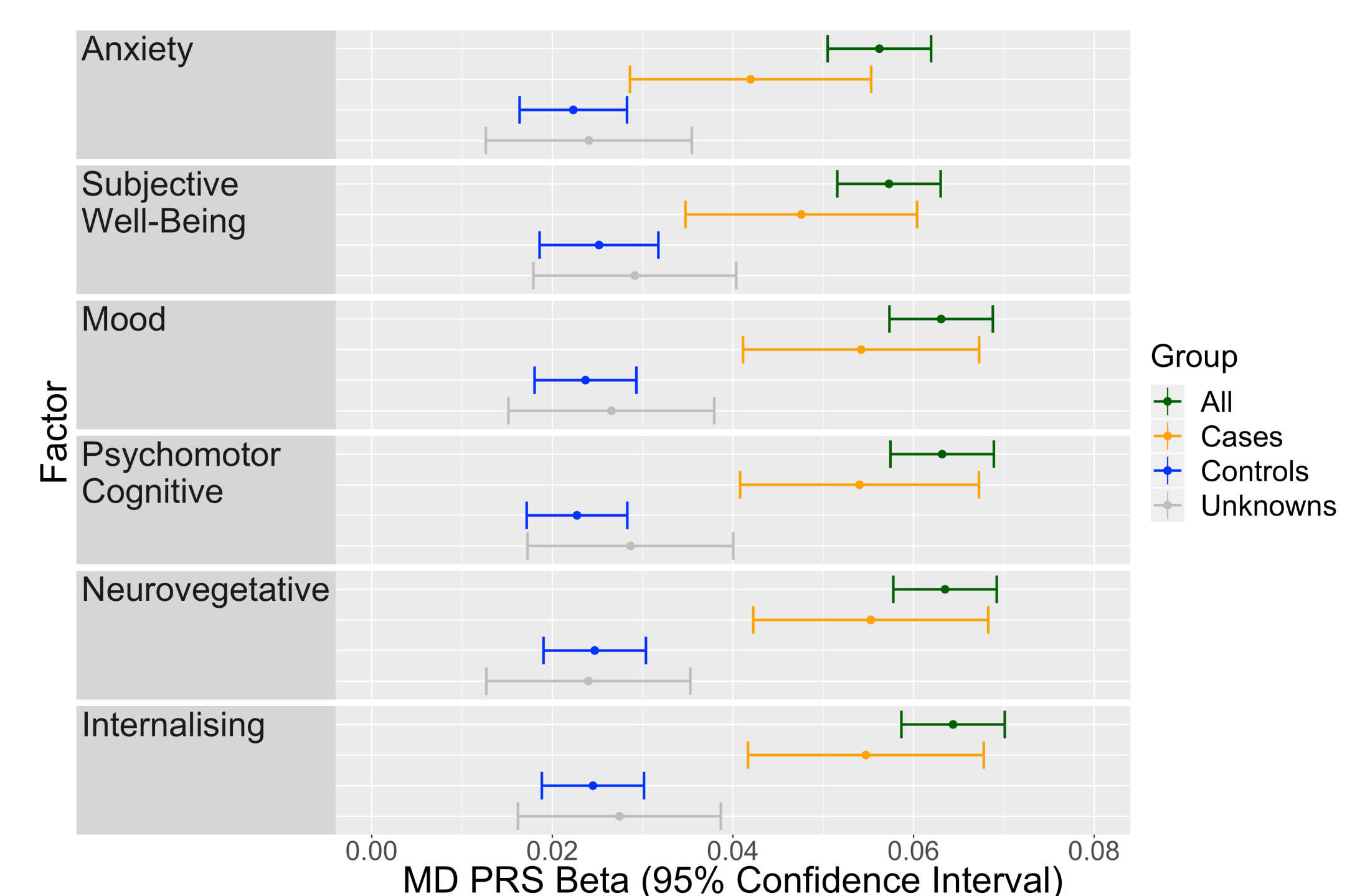


Figure 2. Association of MD PRS on each factor in full and stratified instances

Recurrent cases of major depression are genetically distinct to controls for continuous phenotypes.

Factor	All cases (N=27,692)		Single Episode Cases Only (N=10,590)		Recurrent Cases Only (N=10,726)	
	Effect Size (β)	P-value	Effect Size (β)	P-value	Effect Size (β)	P-value
Anxiety	0.020	2.28*10 ⁻³	-0.009	0.288	0.008	0.364
Psychomotor Cognitive	0.031	4.56*10 ⁻⁷	-0.005	0.540	0.021	0.013
Neurovegetative	0.031	8.32*10 ⁻⁷	-0.008	0.354	0.023	0.006
Mood	0.031	8.48*10 ⁻⁷	-0.006	0.476	0.020	0.016
Subjective Well-Being	0.022	7.66*10 ⁻⁴	-0.008	0.378	0.005	0.572
Internalising	0.030	1.11*10 ⁻⁶	-0.007	0.420	0.019	0.021

Table 1. Interaction effects of MD PRS and MD diagnostic status on factor score. In each test controls are the reference.

Implications

- Sufficient signal is contained within a PRS for MD to distinguish severity across the continuum.
- A stronger association of PRS in recurrent cases relative to controls indicates MD may be best conceptualised as continuous within a categorical underpinning.
- Future studies should seek to understand the optimal demarcation suggested by this genetic boundary

References

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- 3) Wray NR, Ripke S, Mattheisen M et al. DOI: 10.1038/s41588-018-0090-3

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