

# The use of longitudinal data of childhood and adolescent internalizing problems in genetic studies

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## Introduction

A next step in genome wide association (GWA) studies is to analyze longitudinal data that capture information about the development of symptoms over time. This might decrease the heterogeneity in the phenotype.

## Methods

### Subjects and measures:

Avon Longitudinal Study of Parents and Children (ALSPAC): Depressive and anxiety disorders were assessed at age 7, 10, 13 and 15 with the Development and Wellbeing Assessment (DAWBA)

Netherlands Twin Register (NTR): Anxious and depressive symptoms were rated by the mother at age 7, 10 and 12, and by the twins themselves at age 12, 14, 16 and 18 with the anxious depression scale of the Child Behavior Checklist (CBCL) and Youth Self Report (YSR)

### Statistical analyses:

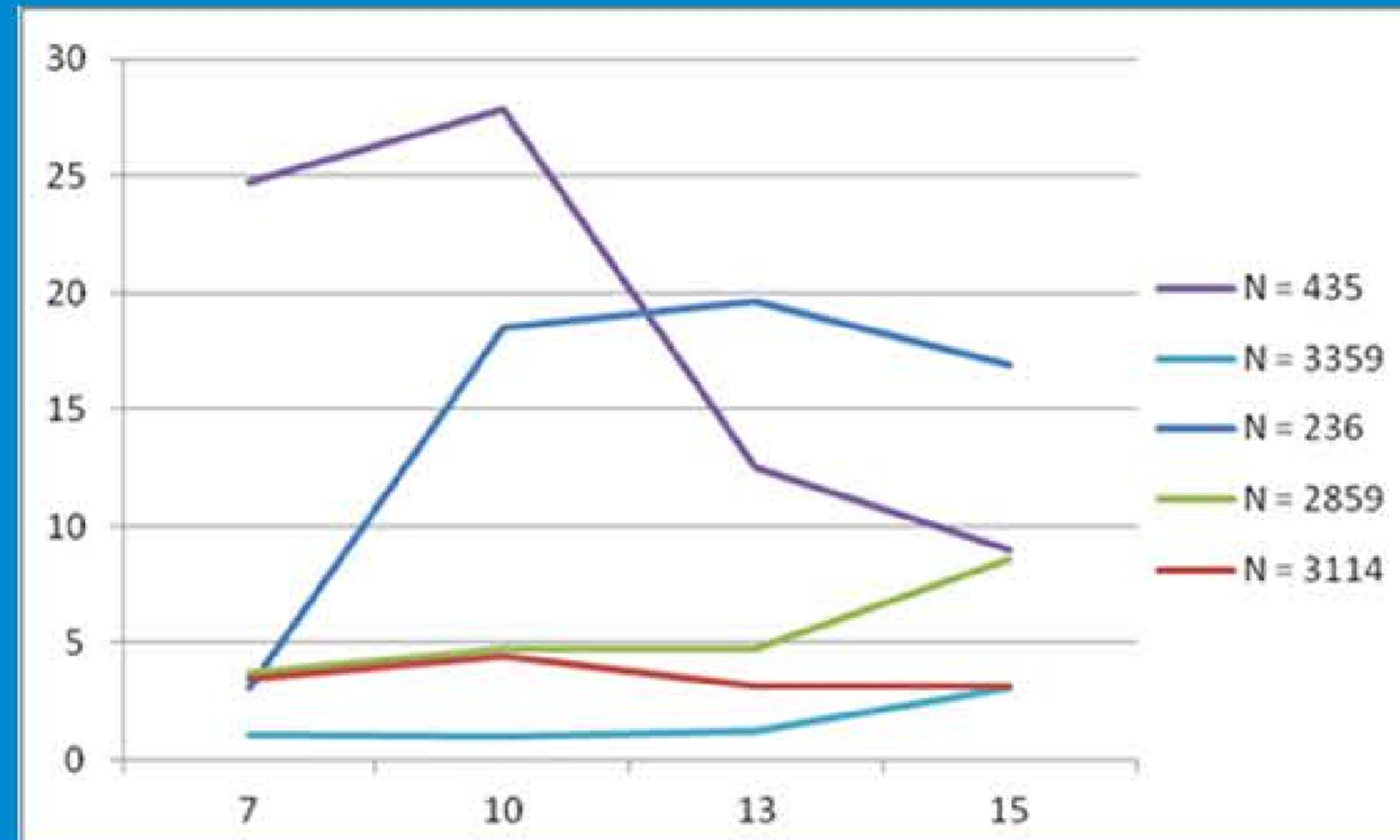
Growth mixture models were fitted to identify distinctive classes of developmental trajectories. In Alspac, sex was included as a covariate.

In the NTR, analyses were performed for males and females.

To investigate the heritability of trajectories we assessed whether MZ and DZ twin pairs belonged to the same latent class more often than expected by chance. The Null distribution was derived by bootstrap draws from the sample using the estimated class proportions. P-values correspond to the probability of the observed number of twin pairs in a class under the Null.

## Results: ALSPAC

Models were fitted with slope variances fixed to zero. A model with intercept variance and 3 classes fitted worse than models without intercept variance.

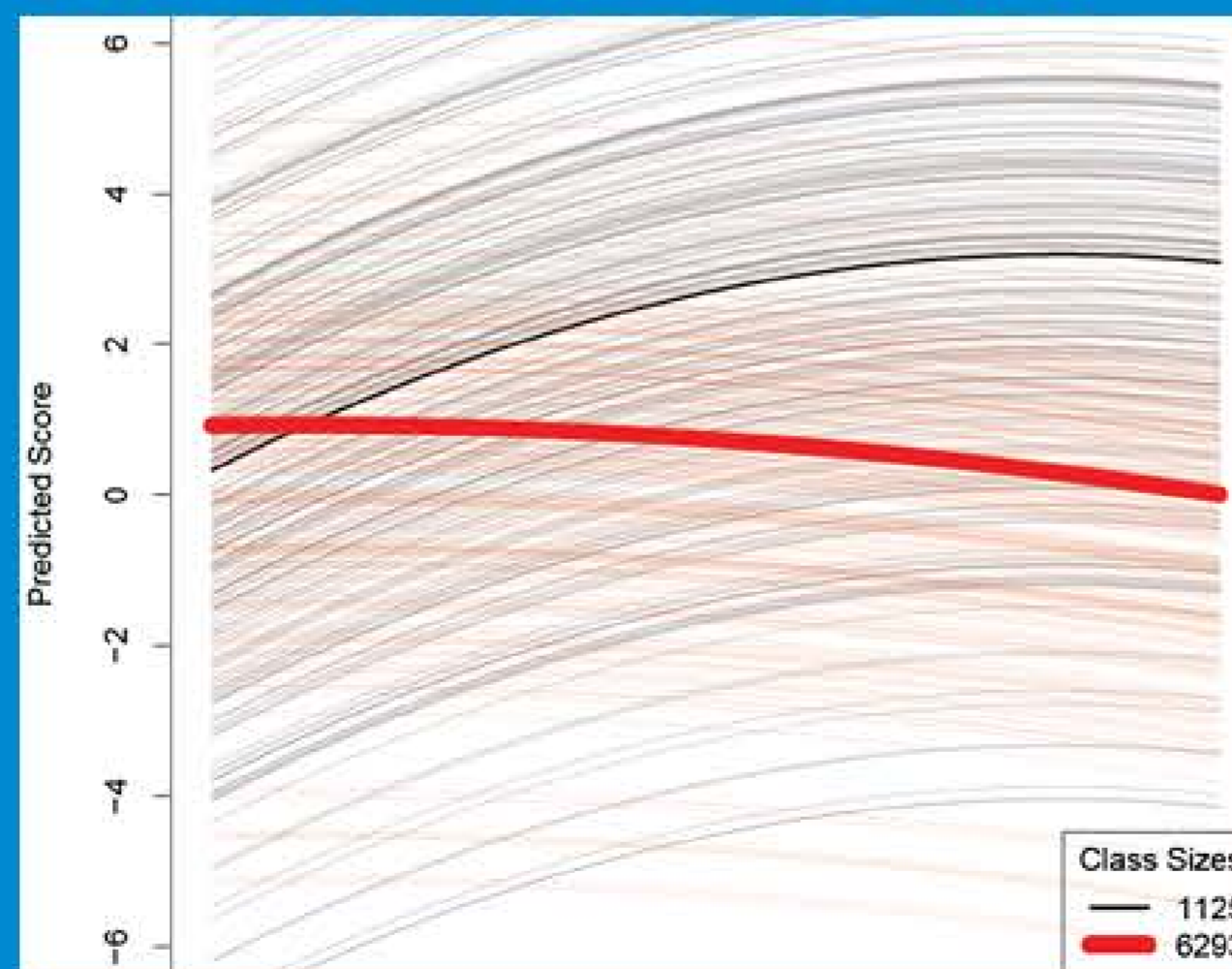


The best fitting model included 5 classes. Girls had a higher probability of being in the high scoring classes.

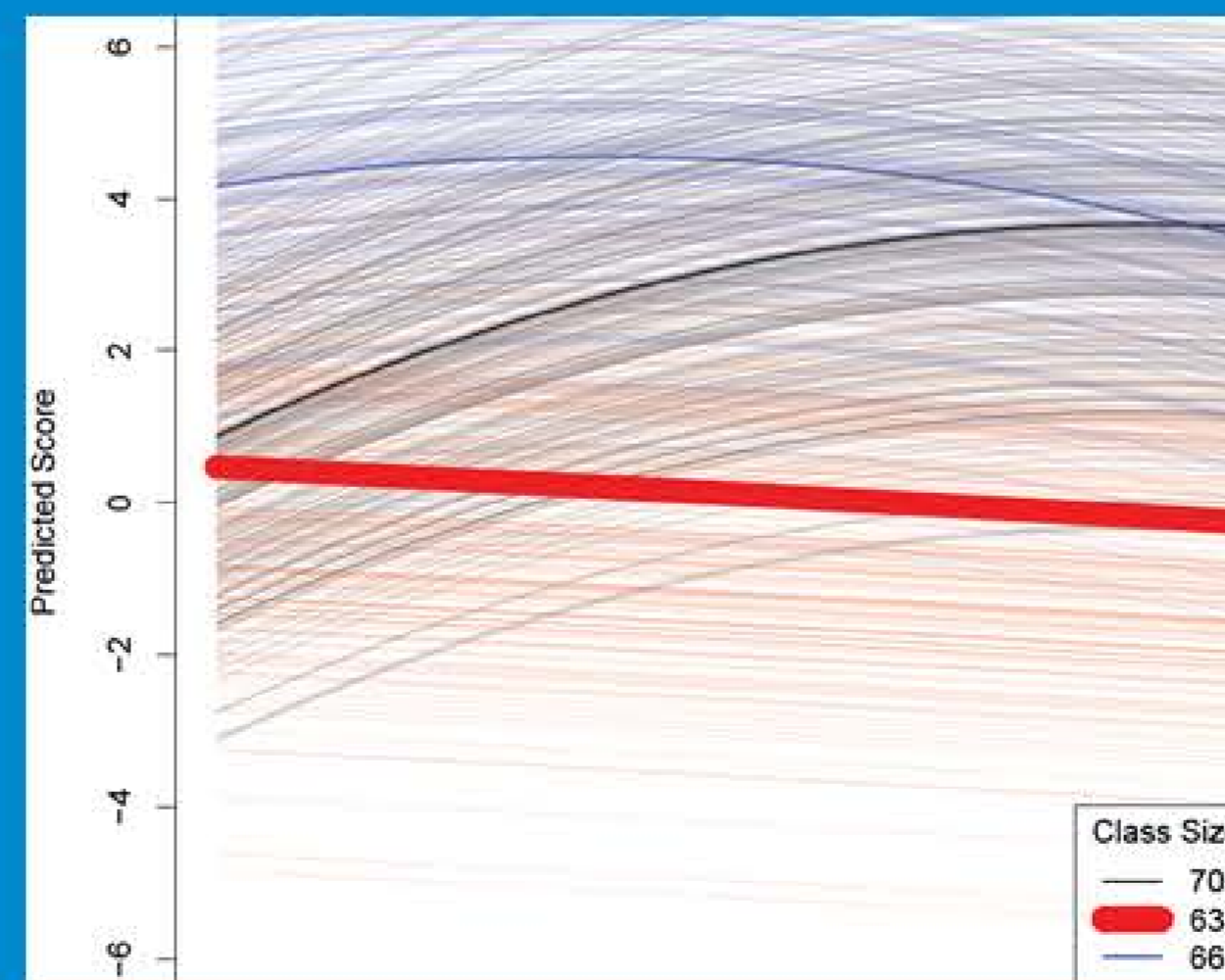
## Results: NTR maternal ratings age 7 to 12

Models estimating intercept variances gave the best fit.

### Males: 2 class model



### Females: 3 class model



### MZ and DZ twin bootstrapping analyses:

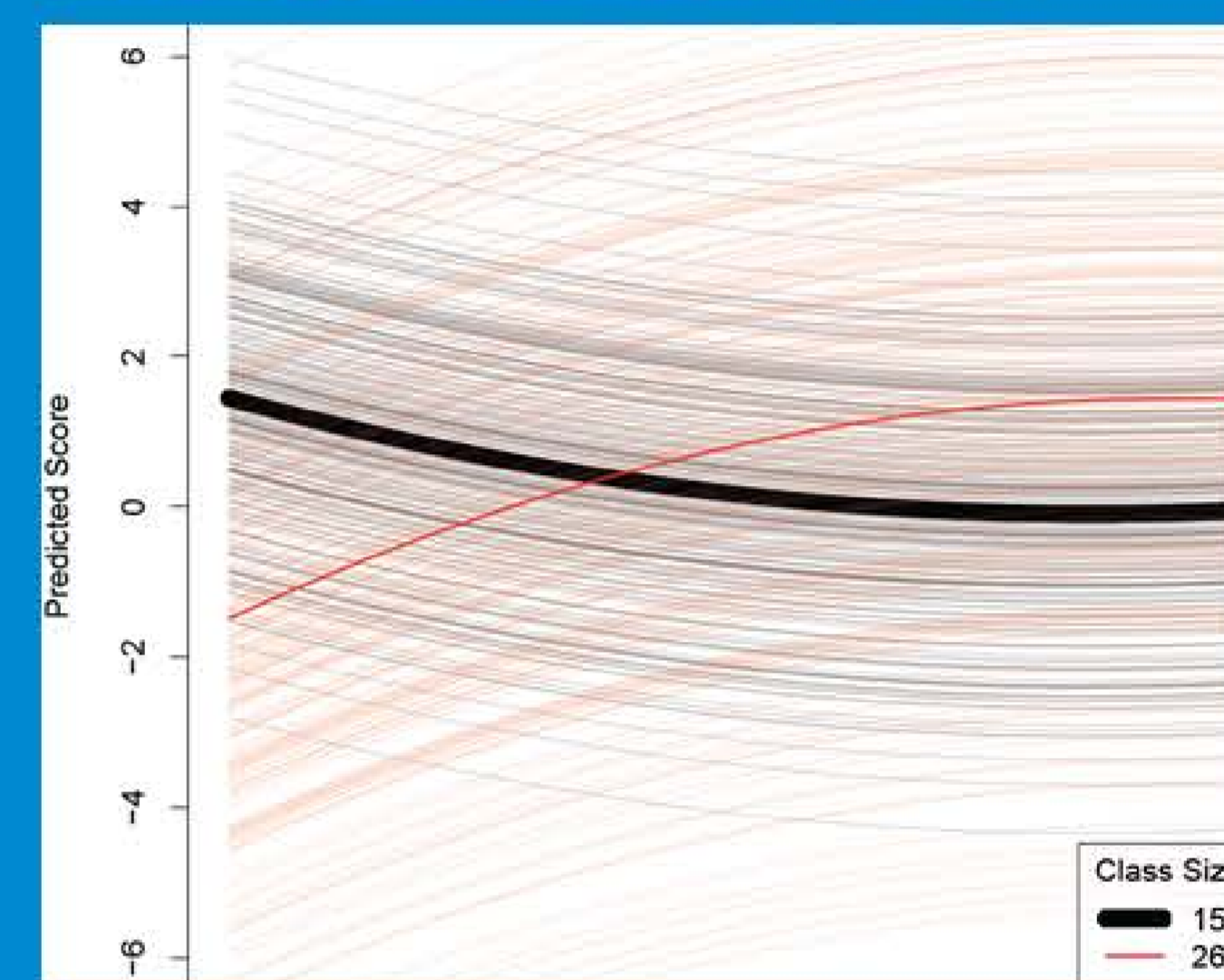
	N Obs pairs	95 <sup>th</sup> perc	p
MZ class 1	97	38	0.000
MZ class 2	1001	948	0.000
DZ class 1	88	36	0.000
DZ class 2	889	893	0.084

	N Obs pairs	95 <sup>th</sup> perc	p
MZ class 1	49	18	0.000
MZ class 2	1094	1023	0.000
MZ class 3	66	16	0.000
DZ class 1	27	15	0.000
DZ class 2	808	807	0.037
DZ class 3	37	14	0.000

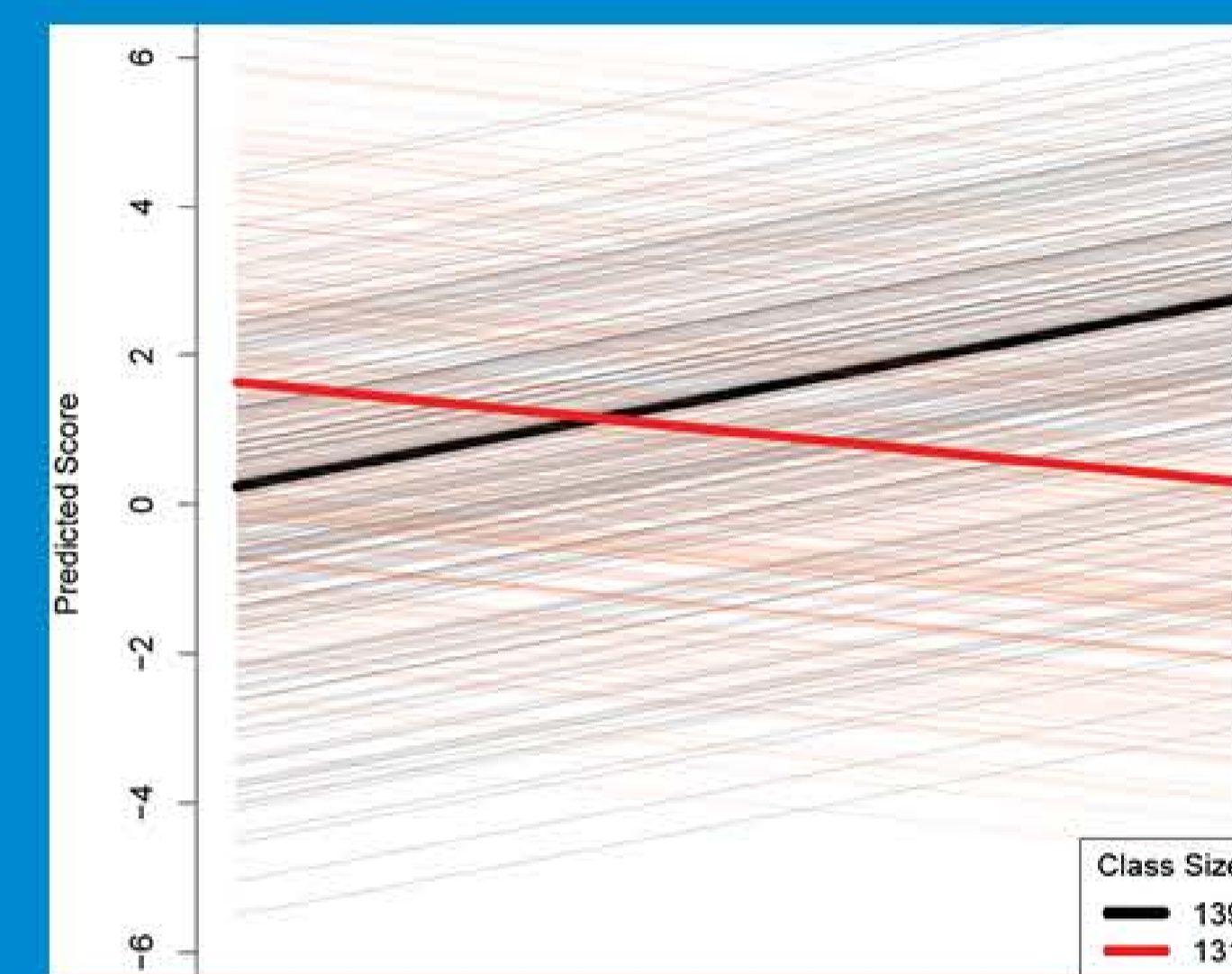
## Results: NTR self ratings age 12 to 18

Models estimating intercept variances gave the best fit.

### Males: 2 class model



### Females: 2 class model



### MZ and DZ twin bootstrapping analyses:

	N Obs pairs	95 <sup>th</sup> perc	p
MZ class 1	244	241	0.017
MZ class 2	24	11	0.000
DZ class 1	196	201	0.193
DZ class 2	12	9	0.002

	N Obs pairs	95 <sup>th</sup> perc	p
MZ class 1	199	164	0.000
MZ class 2	180	147	0.000
DZ class 1	115	110	0.011
DZ class 2	119	100	0.000

## Conclusions

- Developmental trajectories can be identified for anxiety and depression between age 7 and 18.
- Analyses of a DSM-IV based index of internalizing disorders showed 5 distinct classes.
- Analyses of questionnaire data yielded more continuous patterns from low scoring to high scoring subjects and fewer classes.
- The twin analyses show that class membership probabilities are influenced by genetic factors.
- The next step is to include the effect of genetic variants, i.e. on latent class membership probabilities or on intercept and slope.