Developmental paths and constrained trajectories

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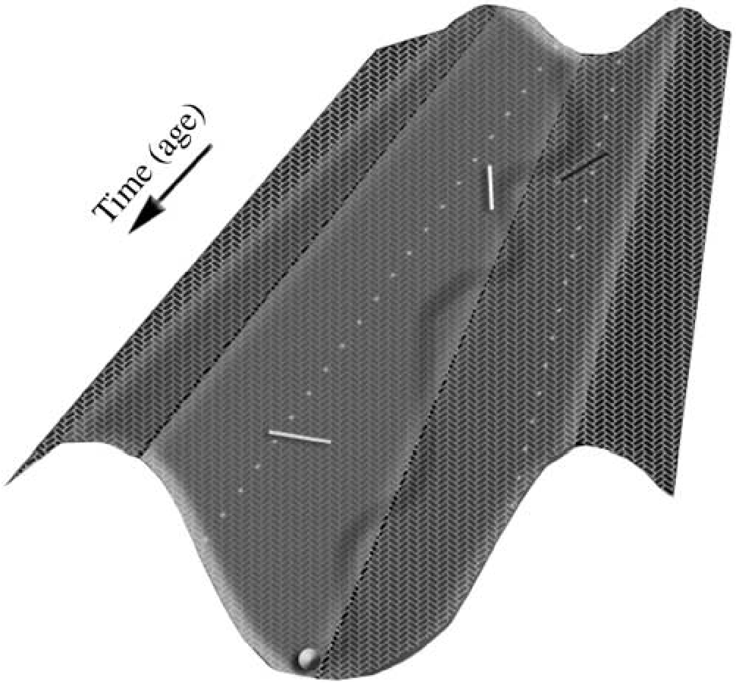
Outline

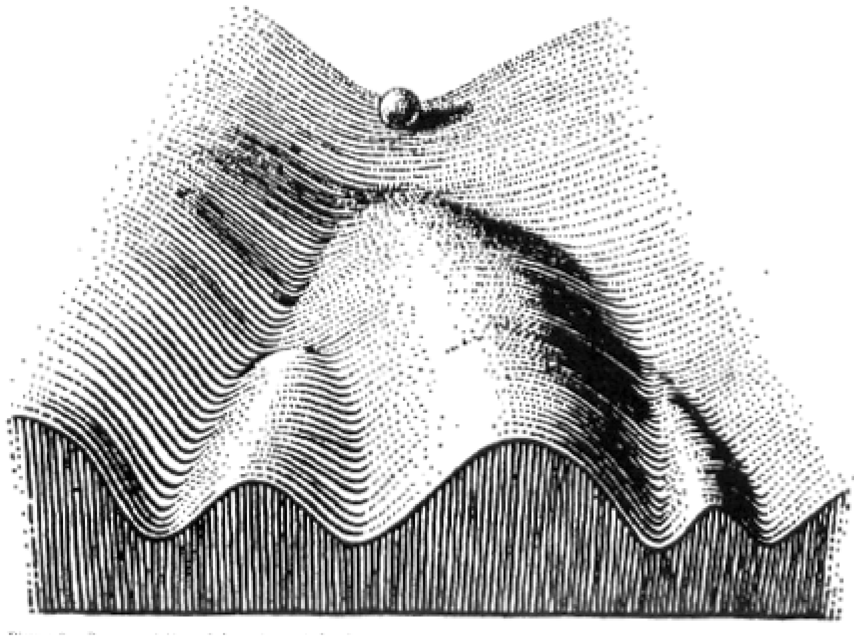
- Examples of multivariate trajectory models
  - LCA with implicit trajectories (wheeze, eczema, cough)
  - Factor based multivariate discrete growth curves (GP and parent wheeze)

- Turning points and time-specific exposures and effects

- Tracking effects in an RCT

Developmental Canalization

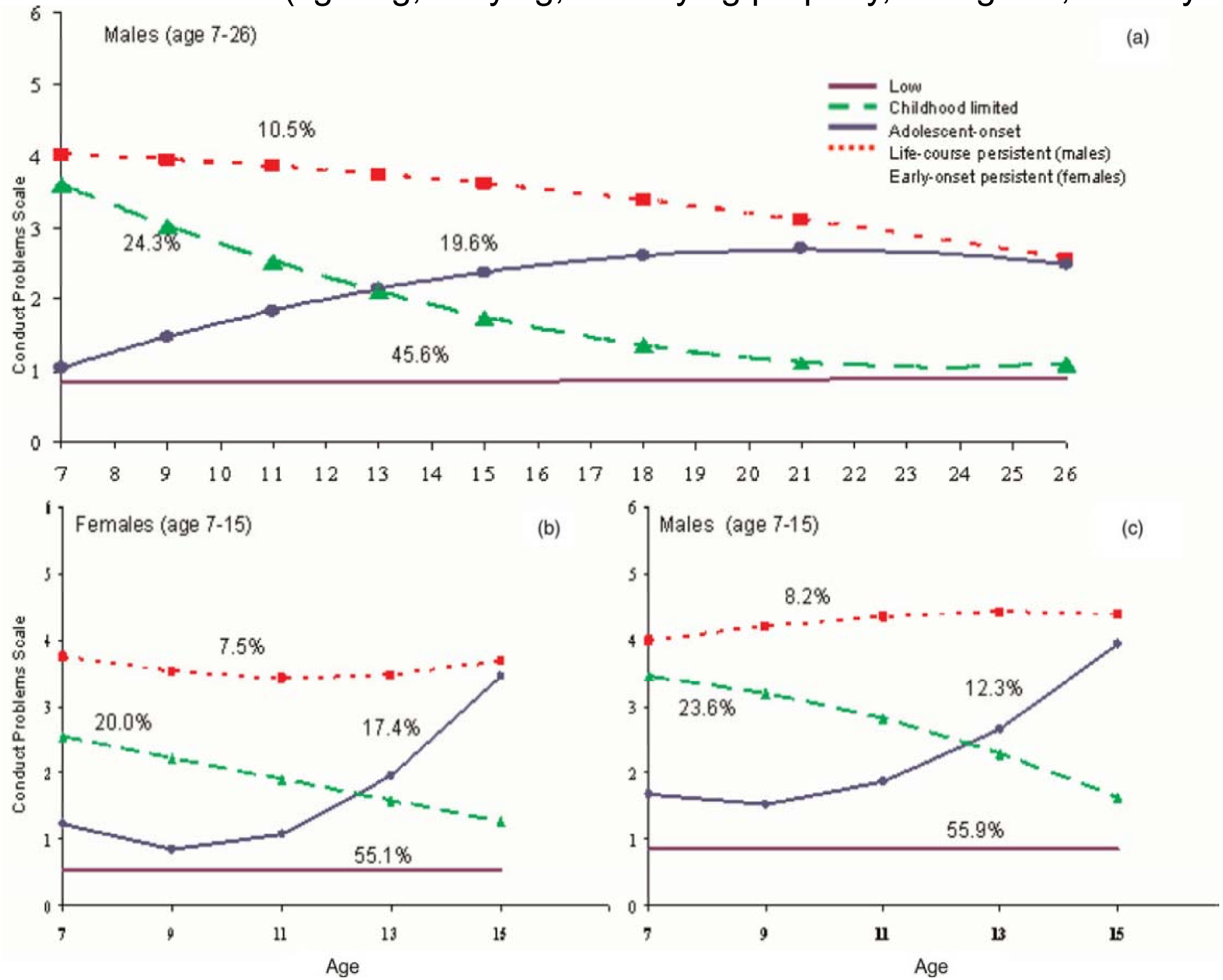




Waddington: Representation of the epigenetic landscape. The ball represents cell fate. The valleys are the different fates the cell might roll into. At the beginning of its journey, development is plastic, and a cell can become many fates. However, as development procedes, certain decisions cannot be reversed. From Waddington.

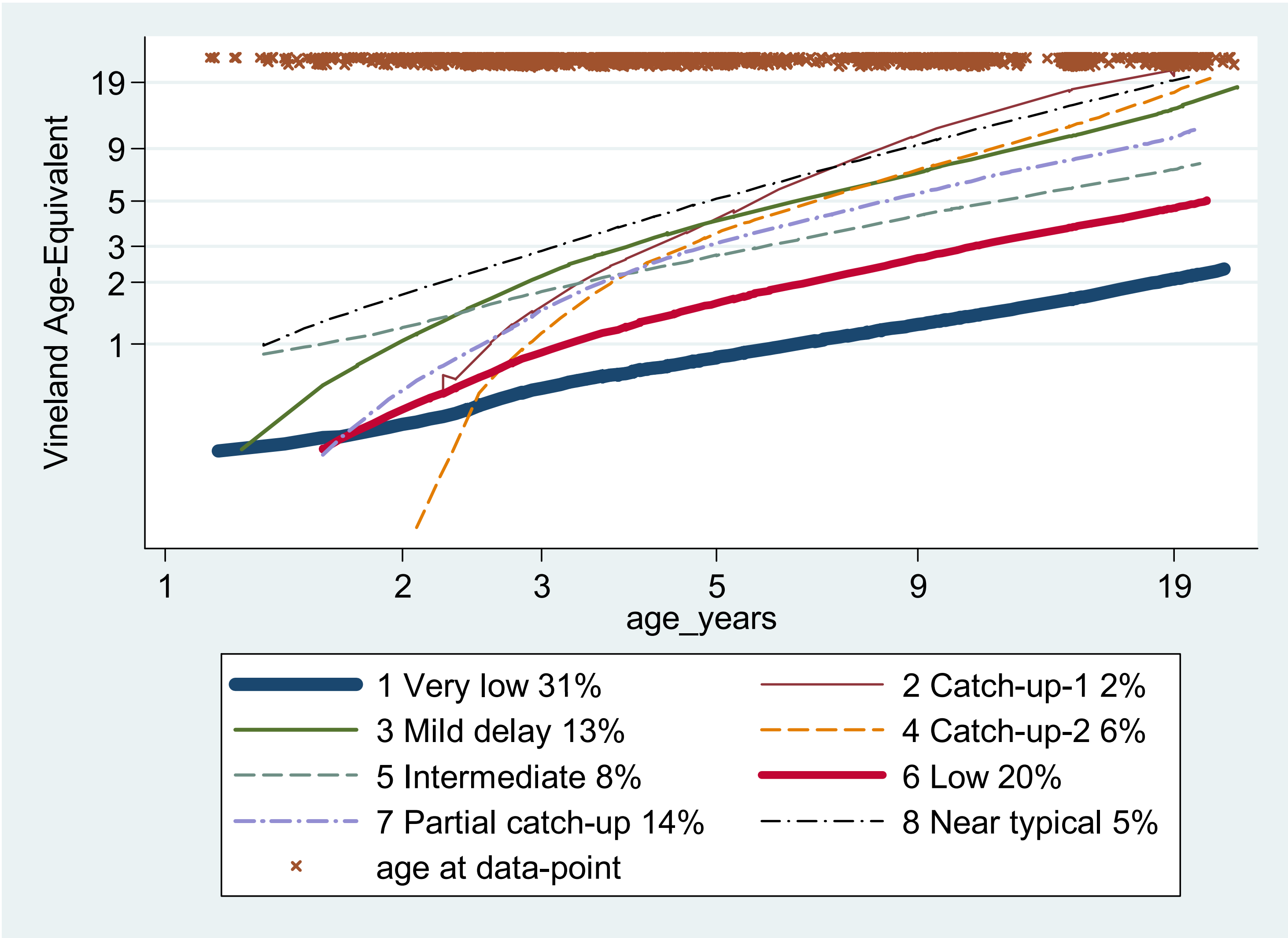
Example: Antisocial Behaviour from 7 to 26 (Dunedin Study)

(fighting, bullying, destroying property, telling lies, truancy & stealing)



Odgers et al. 2008 Female and male antisocial trajectories. Dev't & Psychopath 20, 673-716

Language development in children with ASD symptoms



Latent Class Growth Curve Model (LCGM)

However, the ideas of canalization and distinct pathways may suggest discrete classes rather than multivariate normality of the random effects.

We can replace

$$y_{it} = \alpha_0 + \alpha_1 t + a_{0i} + a_{1i} t + e_{it}, e \sim N(0, \sigma^2)$$
$$a_0, a_1 \sim N(0, \Psi)$$

by

$$E[y_{it}] = \sum_{k=1,K} \pi_k (a_{0k} + a_{1k} t)$$

And can obtain empirical Bayes' estimates of class probabilities for subject i as

$$\hat{\pi}_{ji} = pr(Y_i \mid c = j) / \sum_{k=1,\dots,K} pr(Y_i \mid c = k)$$

or maximum aposteriori class assignment.

Deciding the number of classes

- Assessing fit of models using Information criteria (AIC,BIC etc) and Entropy as a measure of classification performance

- Tests for k-1 versus k classes
  - **Standard LR test** rejects far too often over-estimating the number of classes as LR statistic is not chi-square distributed.
  - **Lo-Mendell-Rubin LR test** derives an approximate distribution as a mixture of LR comparisons. Performs much better.
  - **Parametric Bootstrap LR test** (standard LR test compared to LR-test distribution of k-1 versus k comparison of bootstrap samples simulated under k-1 model). Performs still better than LMR test for both Type-1 error rate and power. Performance declines in sample sizes <200.

Nylund, Asparouhov and Muthén, SEM, 2007.

Conceptualization of latent classes

- Are the groups
  - an approximation or near non-parametric maximum likelihood representation of a continuous random effects distribution

  or

  - a typology of socio-biological discrete pathways that may involve distinct programming/reprogramming

- Choice specific to the context of the data and quality of classification

  (for some risks/outcomes associations may be more via classes while for others associations may be more continuously graded – is light a wave or particulate?)

Question: What problems are posed by these methods that reduce observations made over a period of time to a categorical variable in which time is only implicit?

Including time-fixed covariates in LCGMs -1

In linear predictor with coefficient βs and
in class probabilities with coefficients $\{\lambda\}$

$$E[y_{it}] = \sum_{k=1,K} \pi_k(x_i)(a_{0k} + a_{1k}t + \beta_0 x_i + \beta_{1k} x_i t)$$

$$\pi_{ik}(x) = \exp(\lambda_k x_i) / \sum_{m=1,K} \exp(\lambda_m x_i)$$

With effects in the linear predictor one can postulate individual specific intercepts and slopes under different potential treatment assignments as counterfactuals.

With random assignment can estimate the expected causal effect by the average difference of intercepts and of slopes *by class* *(heterogeneous moderated treatment effect).*

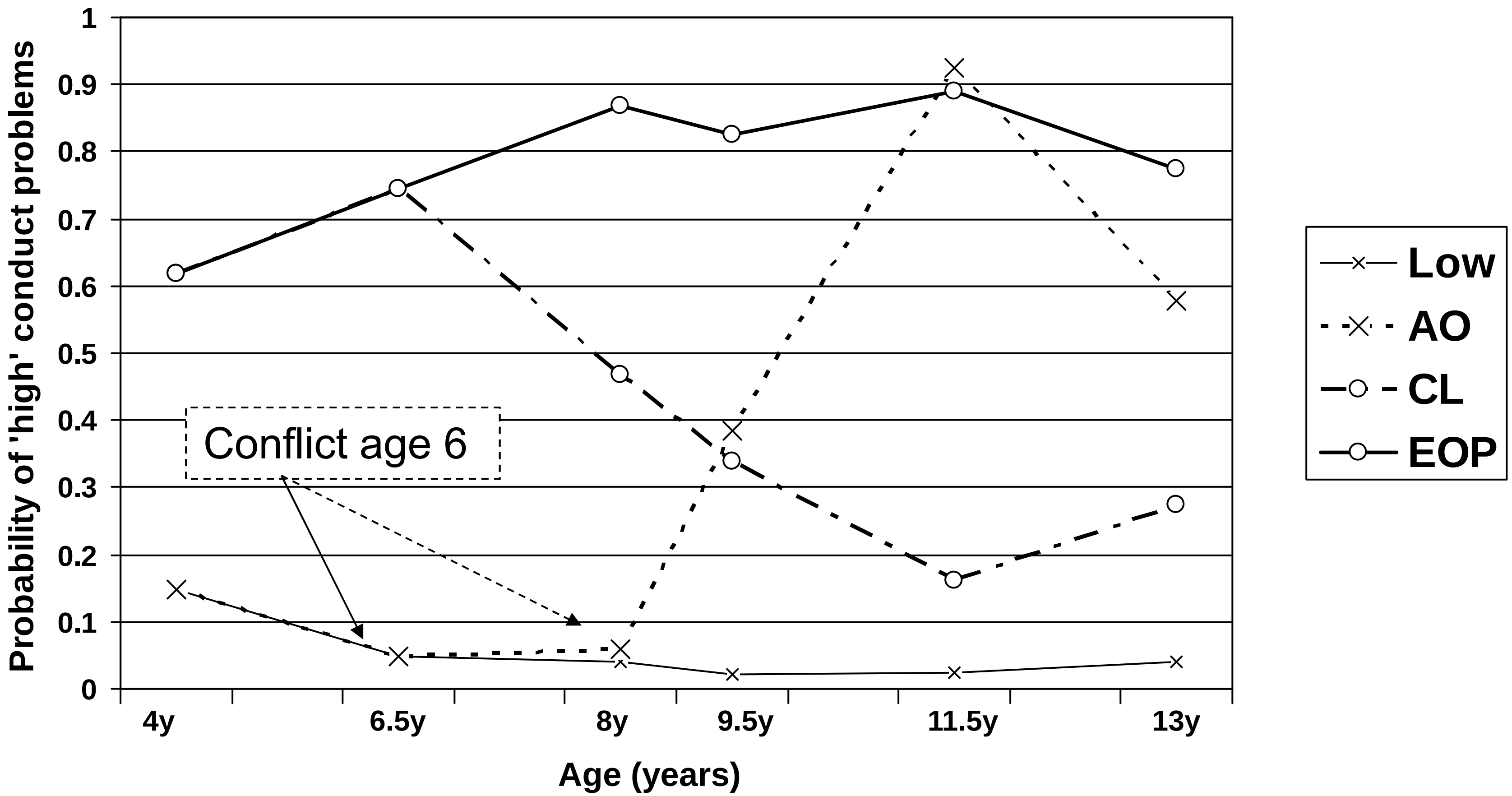
Where assignment not at random can obtain estimates of class probabilities from balanced strata using propensity score

Building in bifurcation

- Test impact of conflict on divergence of two pairs of latent CP classes that within each pair showed similar rates of CP in early childhood but which then subsequently diverged
  - those with initially ‘high’ CP that subsequently persisted or desisted;
  - those initially ‘low’ in CP that remained low or showed marked increases

- ALSPAC
- ‘Intact’ families (children resident with both biological parents: N=5775; 50.8% boys)
- Inter-parental conflict (verbal/physical arguments, emotional cruelty)
- Estimated models constraining the pairings to be
  - equal at age 4, then deviate
  - equal at ages 4 and 6.5, then deviate
  - equal at ages 4, 6.5 and 8, then deviate
- Since factors associated with CP development may exert their influence differently for boys and girls (Harachi et al., 2006), with family processes potentially more relevant for girls (Kroeneman et al., 2009). analyses separately by gender.

The impact of parental conflict on CP pathways: Conflict at age 6 and increasing conduct problems from age 8.



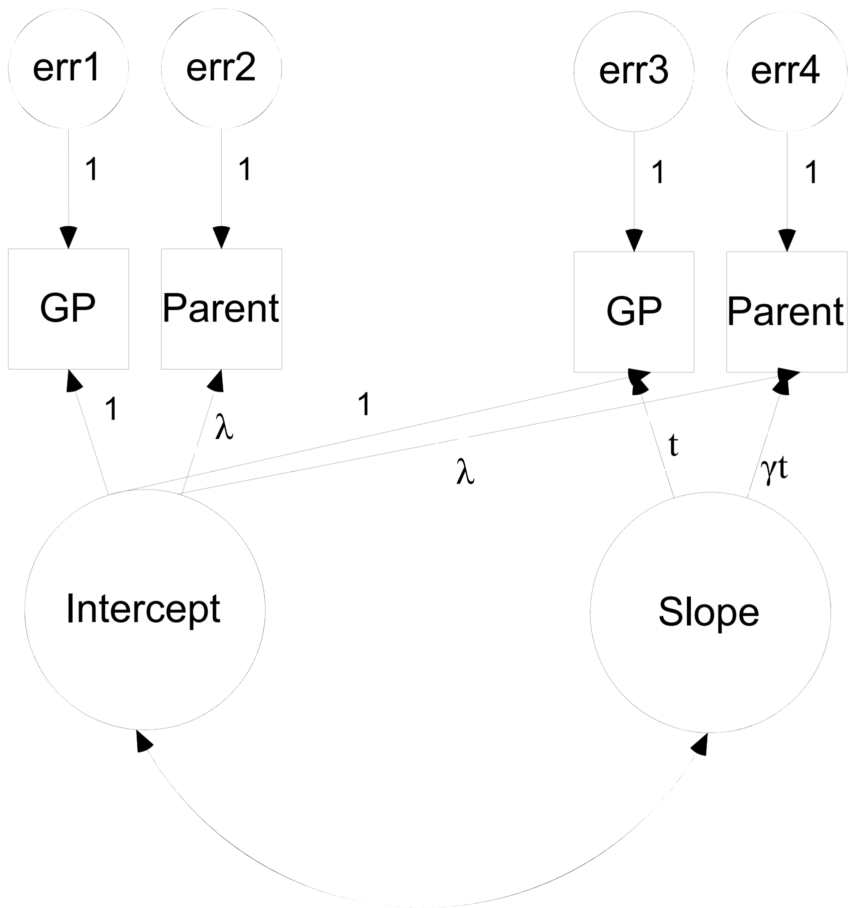
Trajectories in multivariate space

Discrete latent growth model

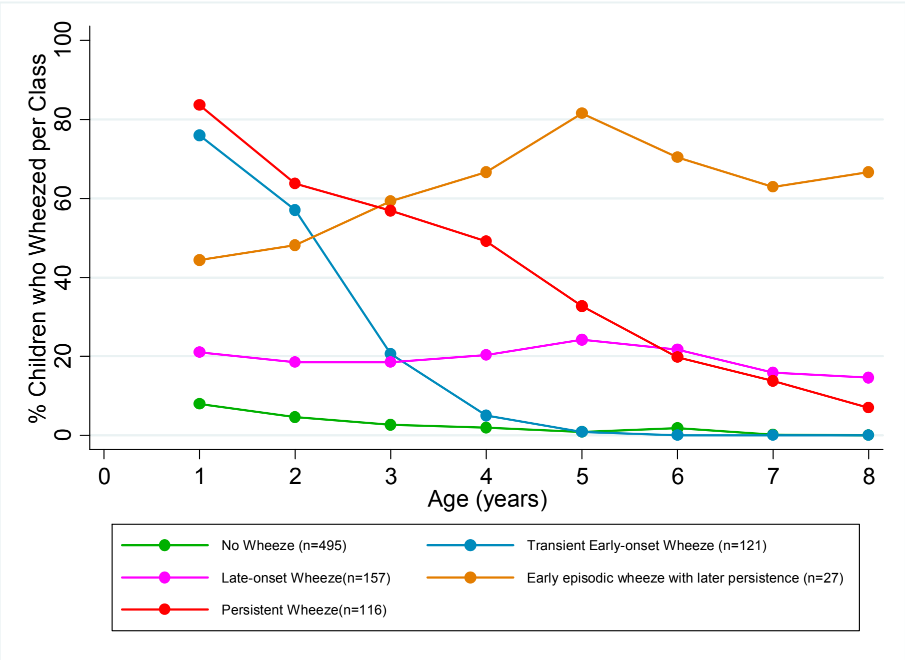
Manchester Allergy and Asthma Study (MAAS)

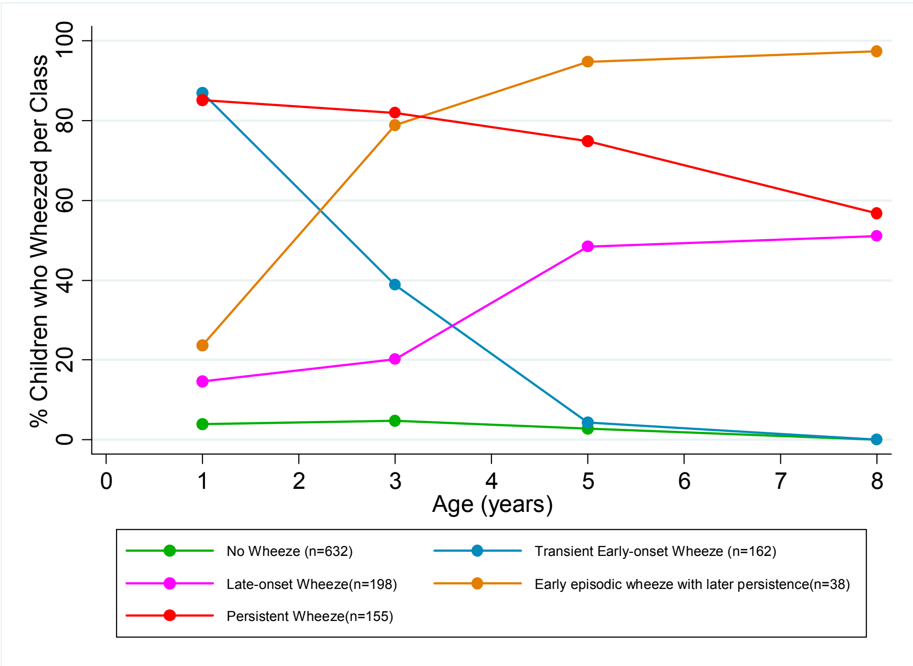
GP records – annual report for wheeze

Parent report of wheeze at 3, 5 and 8



5-class posterior item probabilities: GP and Parent

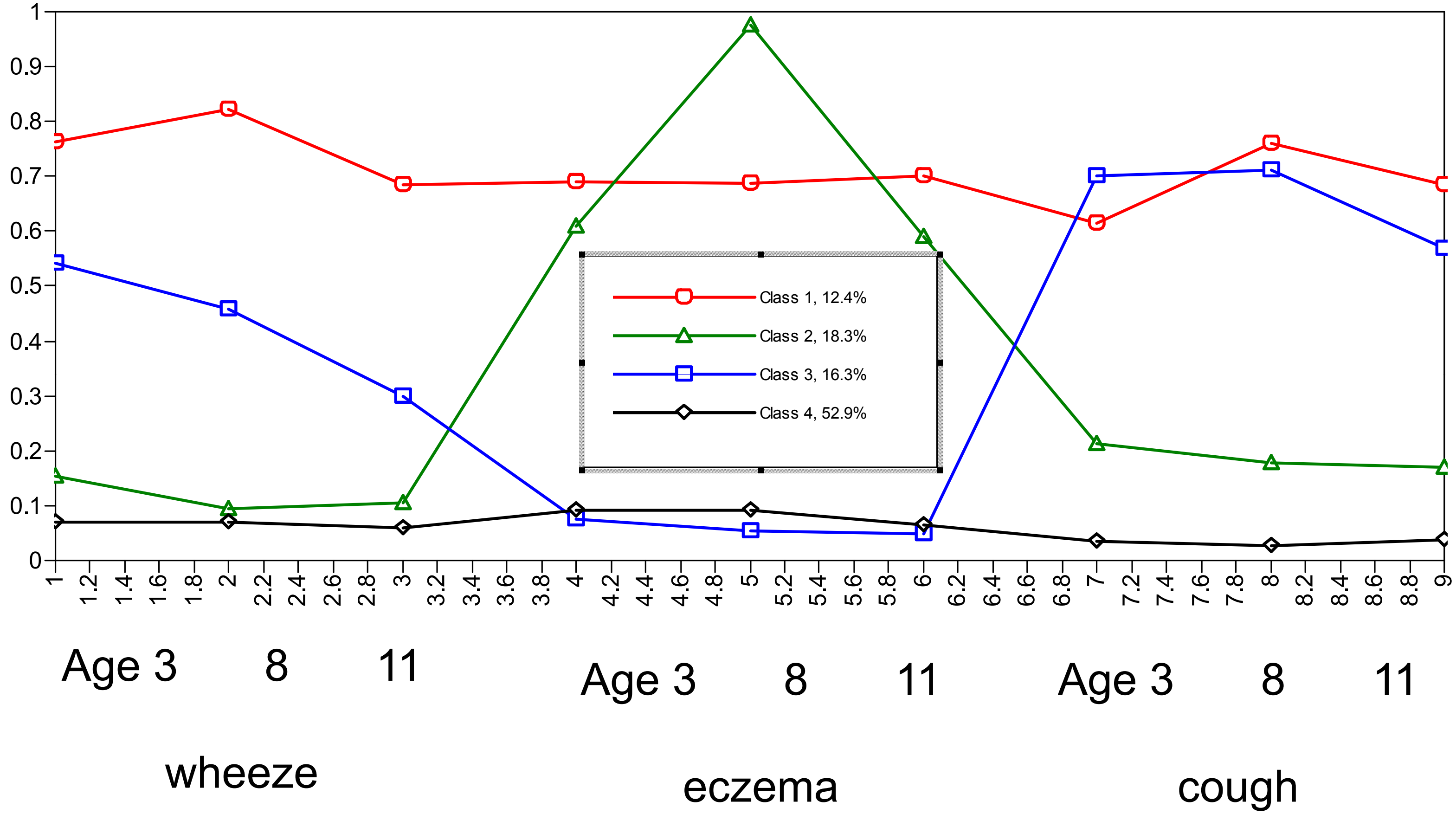




Latent class analysis of wheeze, eczema and cough

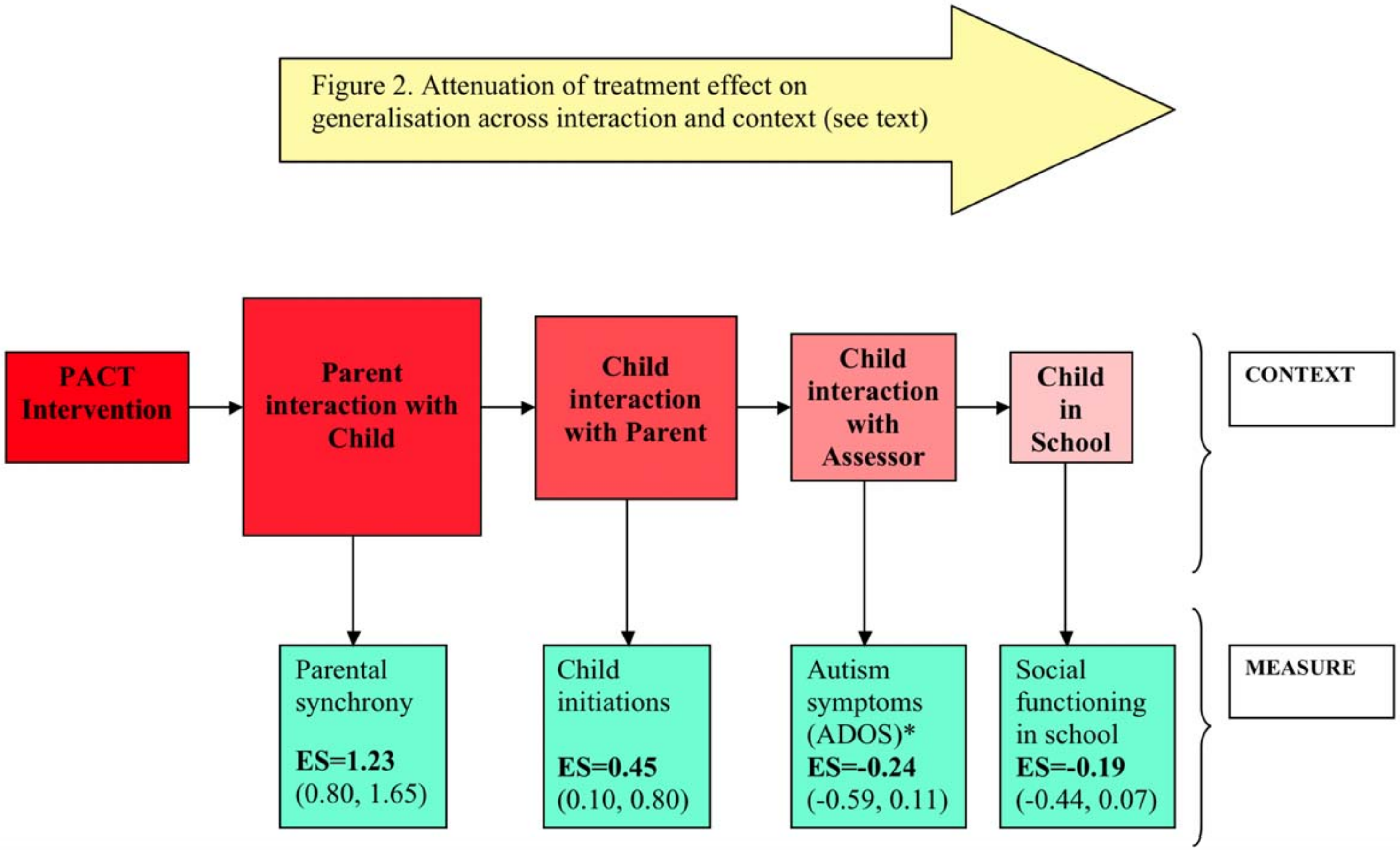
```
 Usevariables are
      cwhz3 cwhz5 cwhz8 cecz3 cecz5 cecz8
      cough3 cough5 cough8 ;
 Classes=c(4);
Analysis:
  Type = mixture; estimator=mlr; starts 500 20;
Model:
   %overall%

Output: Tech1; Tech10;
Plot: Type is plot3;
Series is cwhz3(1) cwhz5(2) cwhz8(3)
          cecz3(4) cecz5(5) cecz8(6)
          cough3(7) cough5(8) cough8(9);
```

Multivariate trajectories: No "Atopy march" class in the Manchester Allergy and Asthma Study (MAAS)

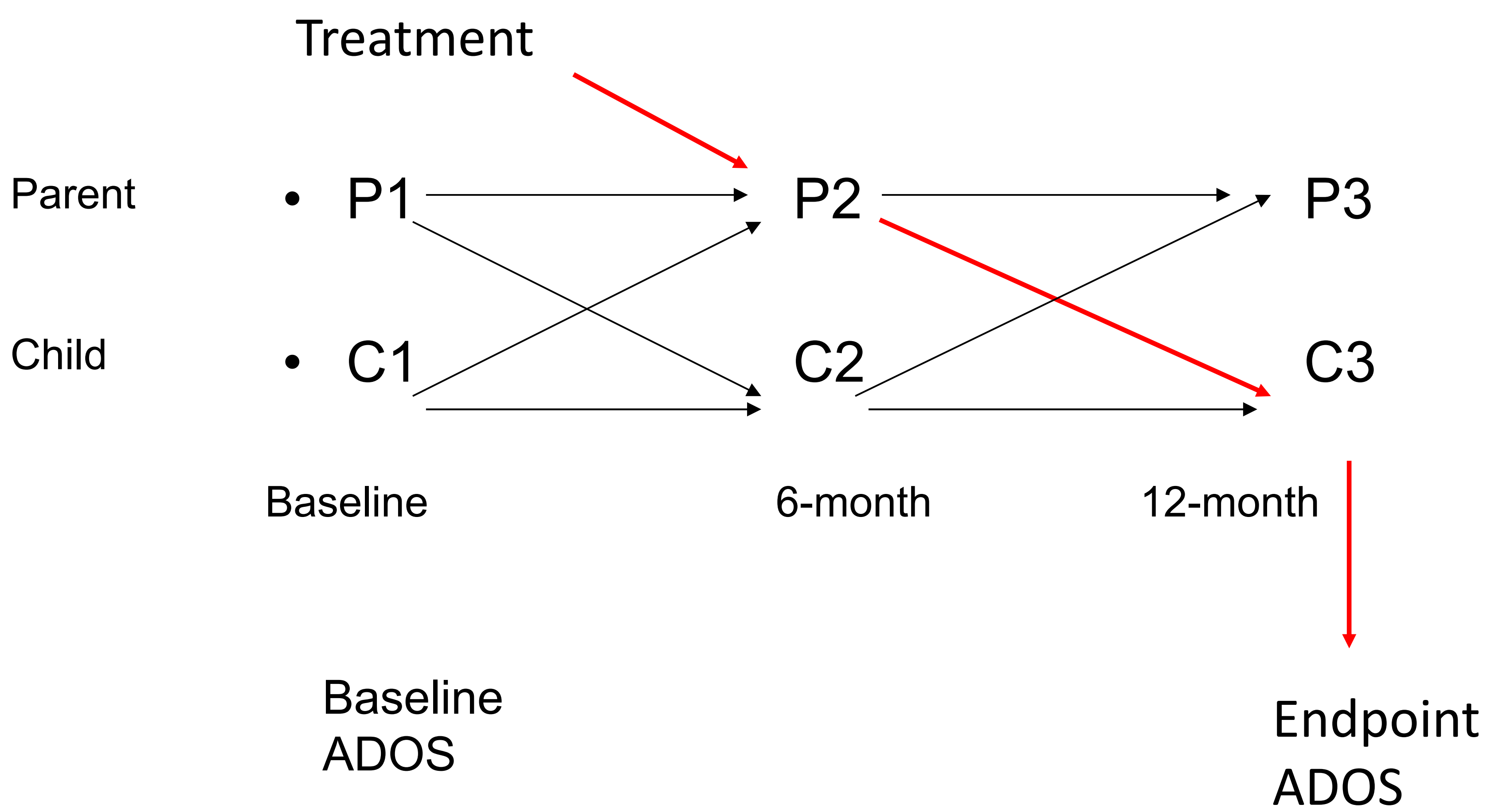


Multivariate constraints:
Trajectories, mediation and "principal stratification"-like analysis

PACT Trial: Attenuation of effects



Treatment Effect Pathway through interaction?

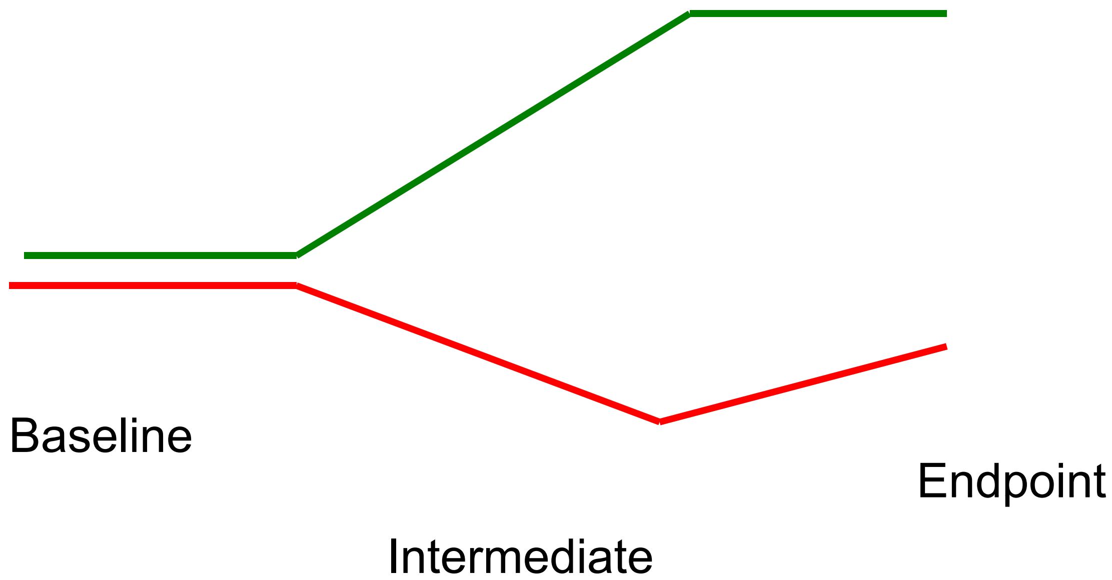


Pathway? Hidden by heterogeneity?

- Are there subgroups in which treatment associated changes in parent synchrony and child initiations are generalized to assessor based interaction (ADOS)

- Fitted latent class model that identified groups on baseline measures and within those groups sub-groups of dyads who had very different behavioral trajectories during the trial

Strata of therapeutic response



Mplus syntax for constrained trajectories-1

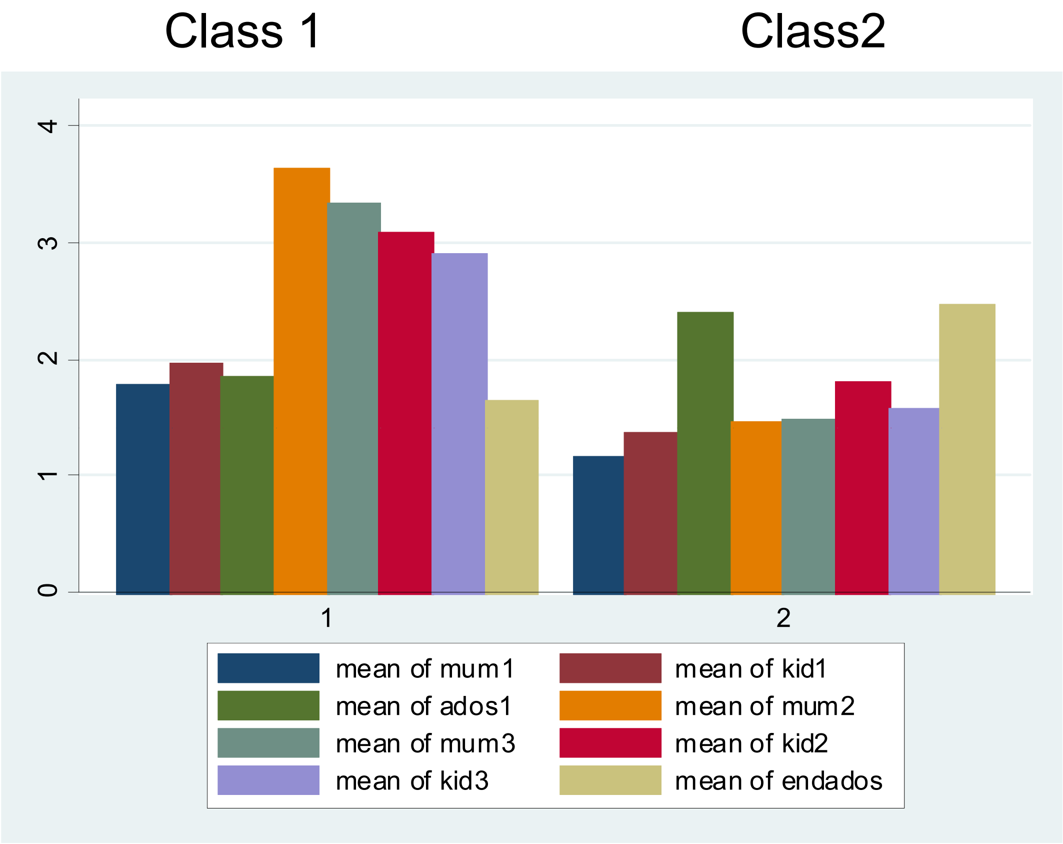
```
 Usevariables are group mum1 mum2 mum3 kid1 kid2 kid3 ados5 endados5;
   Categorical are mum1 mum2 mum3 kid1 kid2 kid3 ados5 endados5;
   Classes=c(2);
Analysis:
   Type = mixture; estimator=mlr; starts 1 1;
Model:
    %overall%
    c#1 on group;

    %c#1%
     [ados5$1] (a11) ; [ados5$2] (a12); [ados5$3] (a13); [ados5$4] (a14);
     [mum1$1] (b11); [mum1$2] (b12); [mum1$3] (b13); [mum1$4] (b14);
     [mum2$1] (c11); [mum2$2] (c12); [mum2$3] (c13); [mum2$4] (c14);
     [mum3$1] (d11); [mum3$2] (d12); [mum3$3] (d13); [mum3$4] (d14);
     [kid1$1] (e11); [kid1$2] (e12); [kid1$3] (e13); [kid1$4] (e14);
     [kid2$1] (f11); [kid2$2] (f12); [kid2$3] (f13); [kid2$4] (f14);
     [kid3$1] (g11); [kid3$2] (g12); [kid3$3] (g13); [kid3$4] (g14);
     [endados5$1] (h11) ; [endados5$2] (h12); [endados5$3] (h13); [endados5$4] (h14);
   %c#2%
     [ados5$1] (a21) ; [ados5$2] (a22); [ados5$3] (a23); [ados5$4] (a24);
     [mum1$1] (b21); [mum1$2] (b22); [mum1$3] (b23); [mum1$4] (b24);
     [mum2$1] (c21); [mum2$2] (c22); [mum2$3] (c23); [mum2$4] (c24);
     [mum3$1] (d21); [mum3$2] (d22); [mum3$3] (d23); [mum3$4] (d24);
     [kid1$1] (e21); [kid1$2] (e22); [kid1$3] (e23); [kid1$4] (e24);
     [kid2$1] (f21); [kid2$2] (f22); [kid2$3] (f23); [kid2$4] (f24);
     [kid3$1] (g21); [kid3$2] (g22); [kid3$3] (g23); [kid3$4] (g24);
     [endados5$1] (h21) ; [endados5$2] (h22); [endados5$3] (h23); [endados5$4] (h24);
```

Plus syntax for constrained trajectories-2

```
Model Constraint:
    New (ca1 cb1 cc1 cd1 ce1 cf1 cg1 ch1);

    a11=a21+ca1; a12=a22+ca1; a13=a23+ca1; a14=a24+ca1;
    b11=b21+cb1; b12=b22+cb1; b13=b23+cb1; b14=b24+cb1;
    c11=c21+cc1; c12=c22+cc1; c13=c23+cc1; c14=c24+cc1;
    d11=d21+cd1; d12=d22+cd1; d13=d23+cd1; d14=d24+cd1;
    e11=e21+ce1; e12=e22+ce1; e13=e23+ce1; e14=e24+ce1;
    f11=f21+cf1; f12=f22+cf1; f13=f23+cf1; f14=f24+cf1;
    g11=g21+cg1; g12=g22+cg1; g13=g23+cg1; g14=g24+cg1;
    h11=h21+ch1; h12=h22+ch1; h13=h23+ch1; h14=h24+ch1;

    ca1=0; cb1=0; ce1=0;
```

Mean Scores by MAP Class

Two classes defined to be similar at baseline (blue brown green) but not after (orange grey red lilac sand)



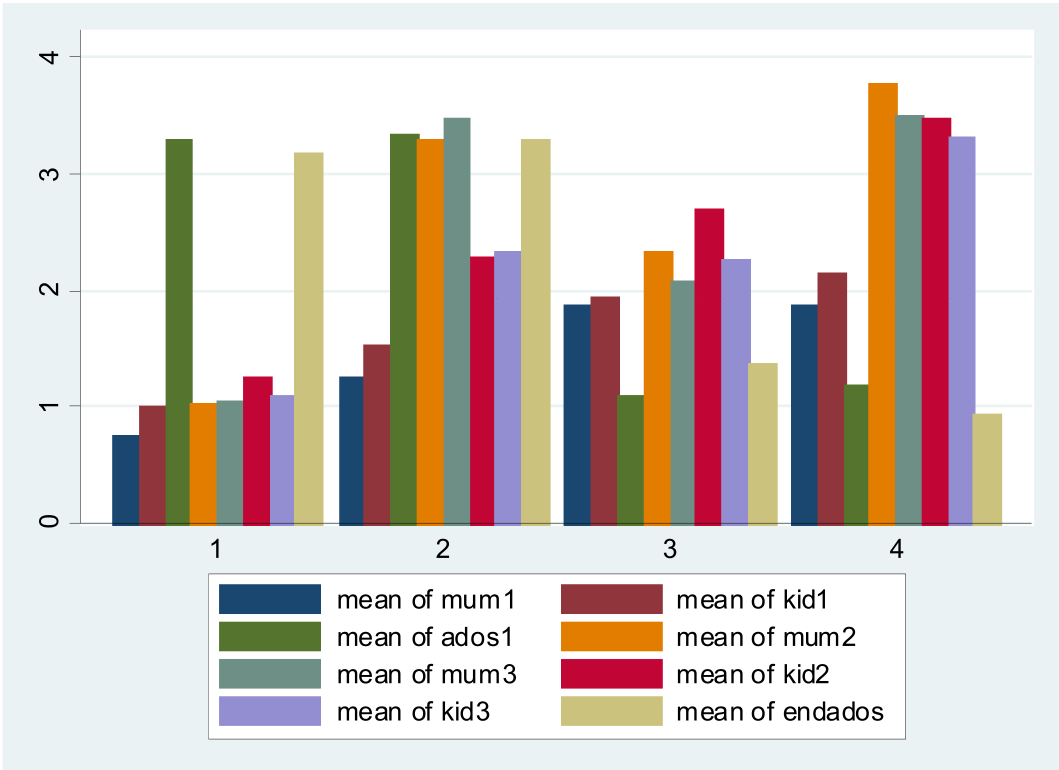
Plus syntax for constrained trajectories: 2 pairs

```
Model Constraint:
    New (ca1 cb1 cc1 cd1 ce1 cf1 cg1 ch1   ca2 cb2 cc2 cd2 ce2 cf2 cg2 ch2
         ca3 cb3 cc3 cd3 ce3 cf3 cg3 ch3);

    a11=a41+ca1; a12=a42+ca1; a13=a43+ca1; a14=a44+ca1;
    a21=a41+ca2; a22=a42+ca2; a23=a43+ca2; a24=a44+ca2;
    a31=a41+ca3; a32=a42+ca3; a33=a43+ca3; a34=a44+ca3;
    b11=b41+cb1; b12=b42+cb1; b13=b43+cb1; b14=b44+cb1;
    b21=b41+cb2; b22=b42+cb2; b23=b43+cb2; b24=b44+cb2;
    b31=b41+cb3; b32=b42+cb3; b33=b43+cb3; b34=b44+cb3;
    c11=c41+cc1; c12=c42+cc1; c13=c43+cc1; c14=c44+cc1;
    c21=c41+cc2; c22=c42+cc2; c23=c43+cc2; c24=c44+cc2;
    c31=c41+cc3; c32=c42+cc3; c33=c43+cc3; c34=c44+cc3;
    d11=d41+cd1; d12=d42+cd1; d13=d43+cd1; d14=d44+cd1;
    d21=d41+cd2; d22=d42+cd2; d23=d43+cd2; d24=d44+cd2;
    d31=d41+cd3; d32=d42+cd3; d33=d43+cd3; d34=d44+cd3;
    e11=e41+ce1; e12=e42+ce1; e13=e43+ce1; e14=e44+ce1;
    e21=e41+ce2; e22=e42+ce2; e23=e43+ce2; e24=e44+ce2;
    e31=e41+ce3; e32=e42+ce3; e33=e43+ce3; e34=e44+ce3;
    f11=f41+cf1; f12=f42+cf1; f13=f43+cf1; f14=f44+cf1;
    f21=f41+cf2; f22=f42+cf2; f23=f43+cf2; f24=f44+cf2;
    f31=f41+cf3; f32=f42+cf3; f33=f43+cf3; f34=f44+cf3;
    g11=g41+cg1; g12=g42+cg1; g13=g43+cg1; g14=g44+cg1;
    g21=g41+cg2; g22=g42+cg2; g23=g43+cg2; g24=g44+cg2;
    g31=g41+cg3; g32=g42+cg3; g33=g43+cg3; g34=g44+cg3;
    h11=h41+ch1; h12=h42+ch1; h13=h43+ch1; h14=h44+ch1;
    h21=h41+ch2; h22=h42+ch2; h23=h43+ch2; h24=h44+ch2;
    h31=h41+ch3; h32=h42+ch3; h33=h43+ch3; h34=h44+ch3;

     ca1=ca2; cb1=cb2; ce1=ce2;
     ca3=0; cb3=0; ce3=0;
```

Mean Scores by MAP Class

Two pairs of classes (1,2) and (3,4) defined to be similar at baseline but not at thereafter

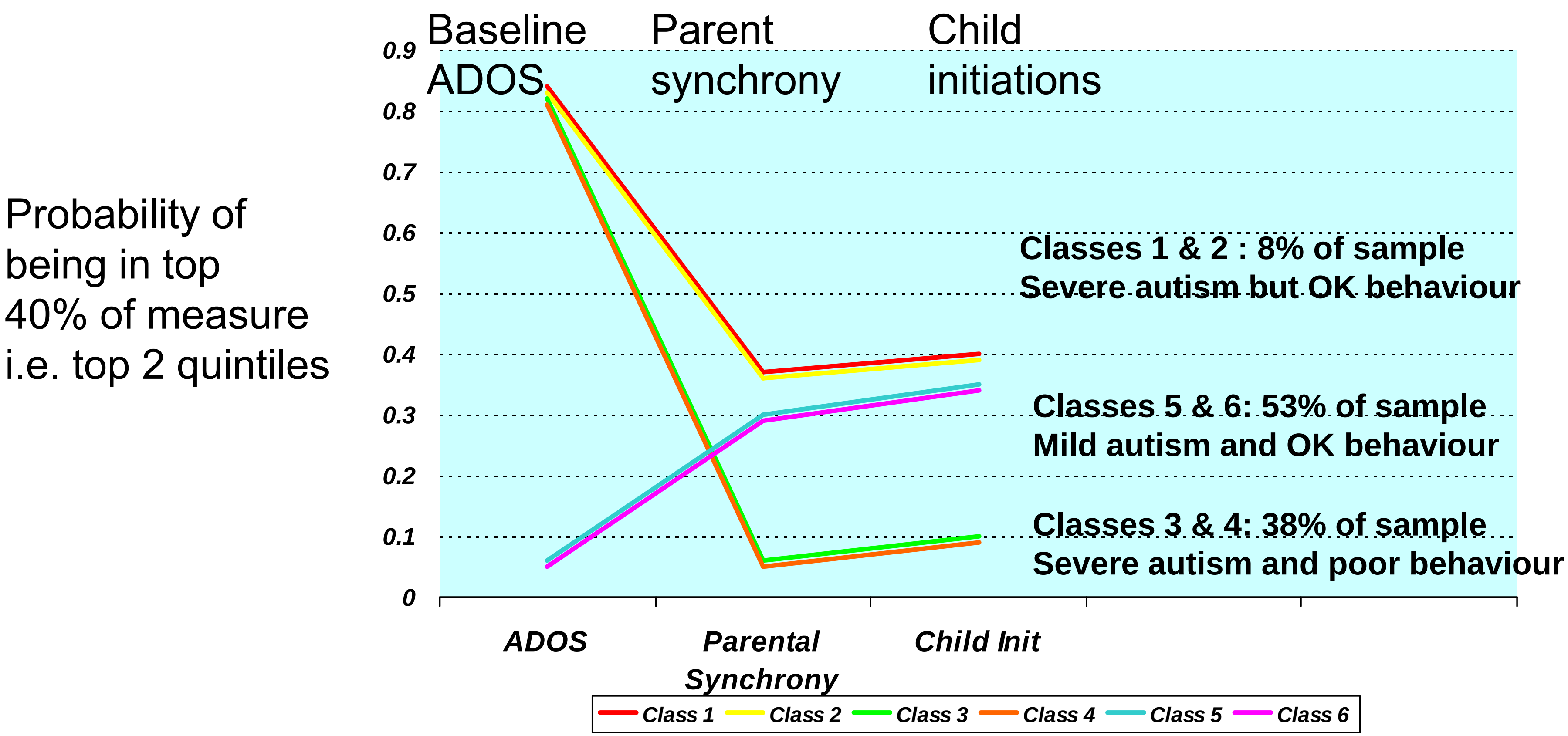
Class1 Class2 Class3 Class4



Three pairs of latent classes

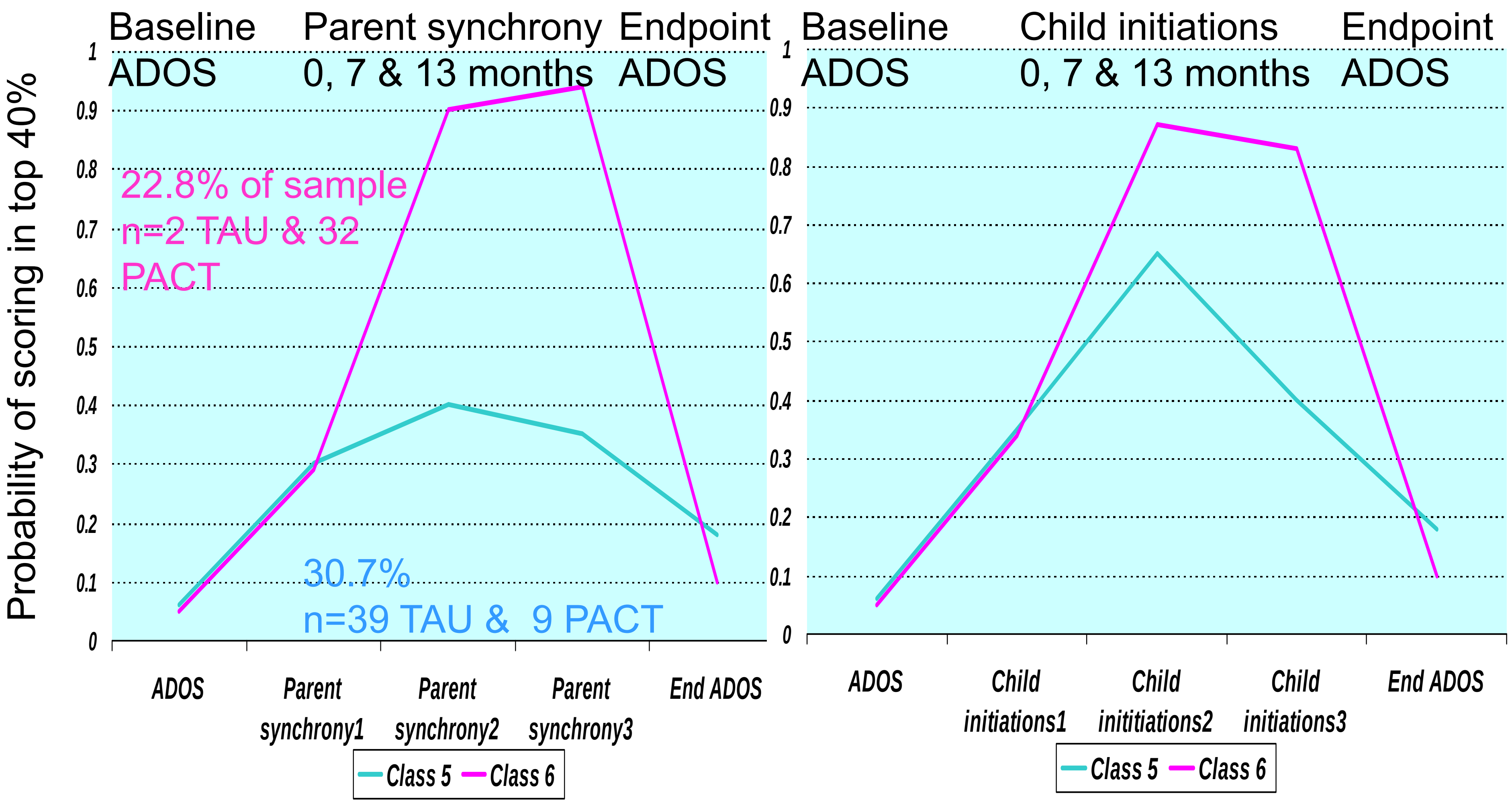
- Pairs defined similar over baseline ADOS & dyadic behaviour (parental synchrony and child initiations)
- Pairs can subsequently differ in 7 & 13 month dyadic behaviour and endpoint ADOS

Baseline profiles



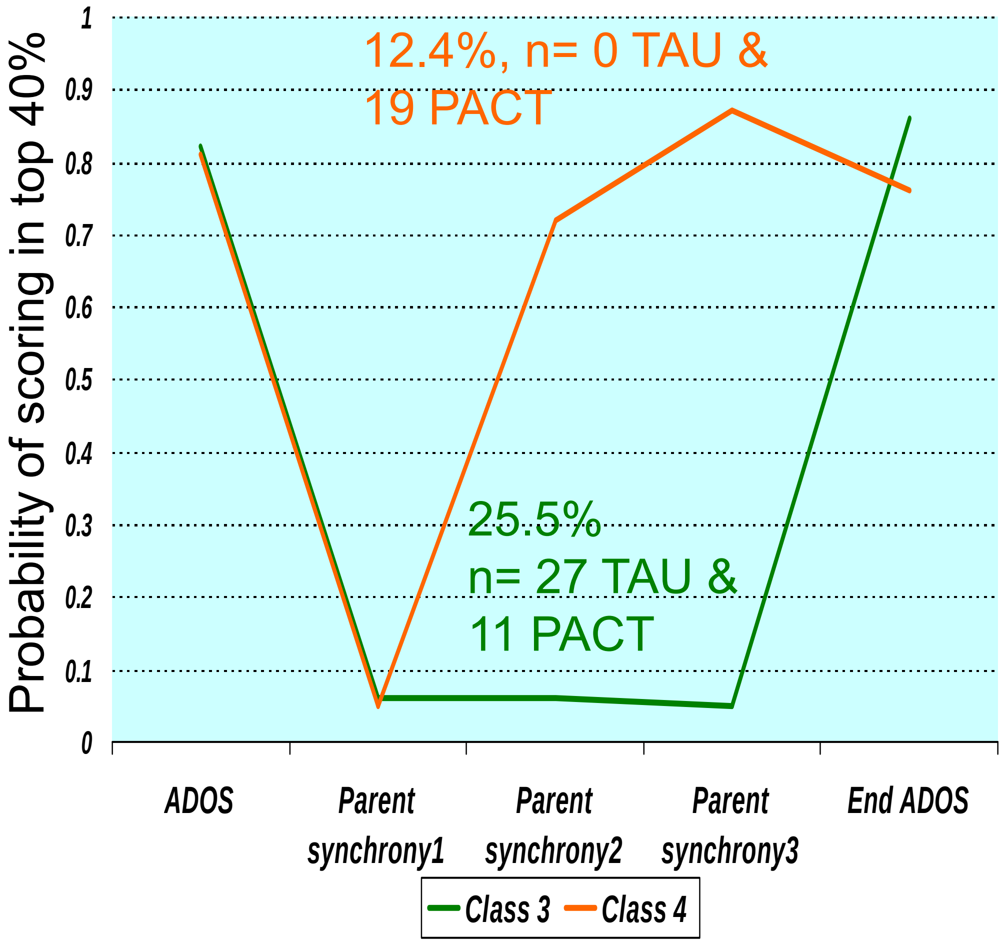
Classes 5 & 6 (53% of sample)

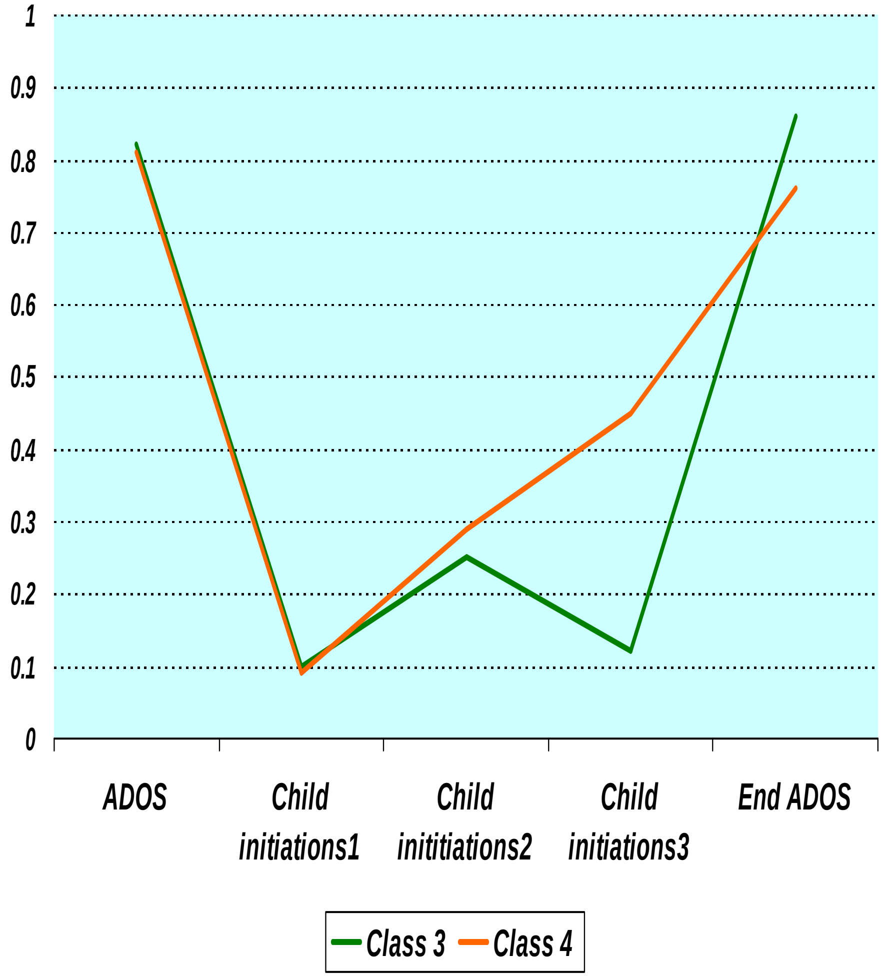
- Similar low baseline ADOS scores and OK dyadic behaviour
- Show very different patterns of change in parent and child behaviour
- At endpoint more behaviourally responsive class has ***slightly*** better ADOS scores



Classes 3 & 4 (38% of sample)

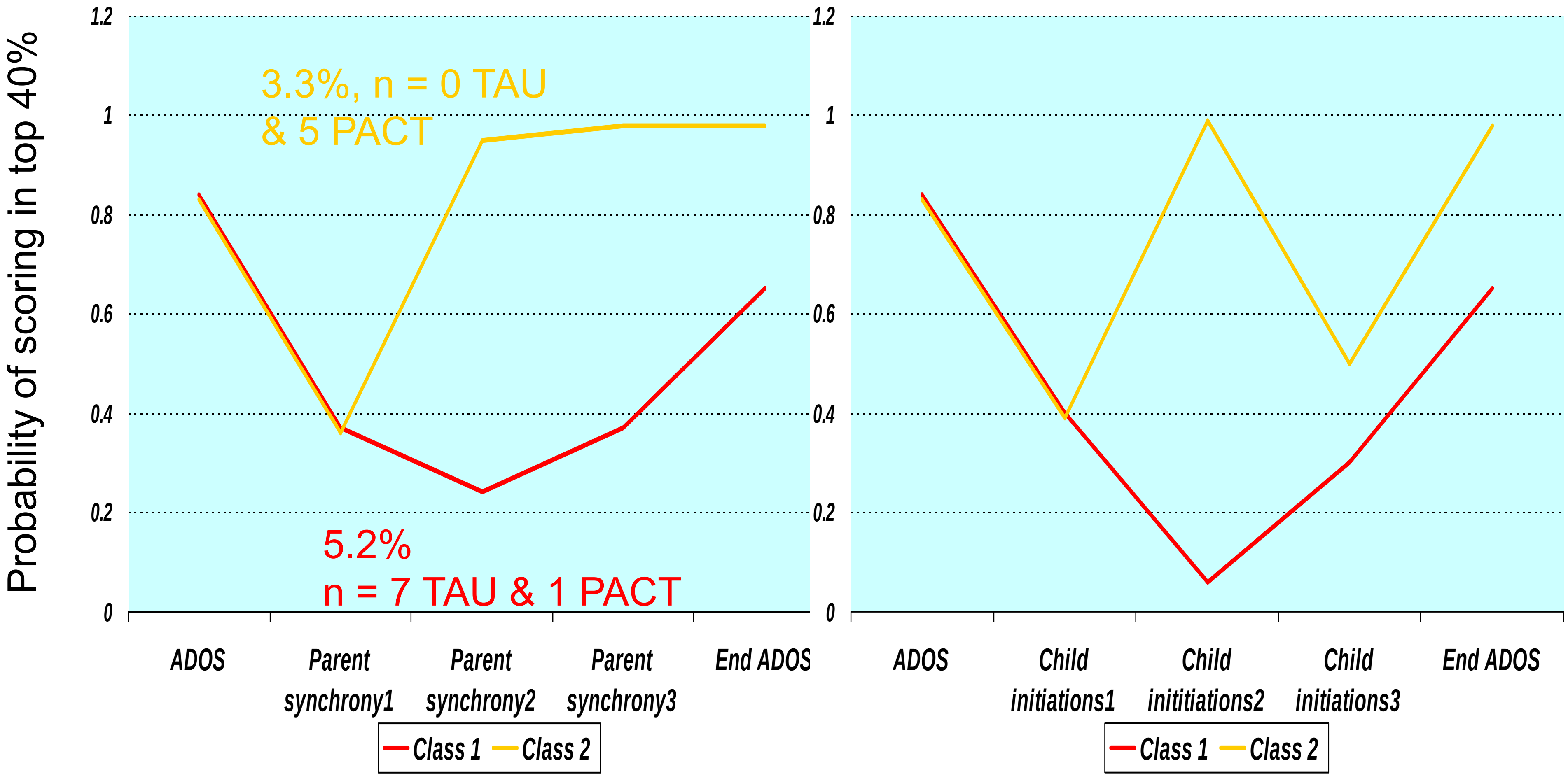
- At baseline have high ADOS scores and very poor dyadic behaviour
- During trial the two classes show ***large*** difference in change in parent and ***some*** difference in child behaviour
- At endpoint more behaviourally responsive class has ***slightly*** better ADOS scores





Classes 1 & 2 (just 8% of sample)

- At baseline have high ADOS scores but OK dyadic behaviour
- During trial show very different patterns of change in parent and child behaviour
- At endpoint more behaviourally responsive class has **worse** ADOS scores



And if you have been,
thank you for listening