Towards Optimal Brain and Psychosocial Development

# Outcomes in high-risk offspring of bipolar parents:

## subtyped by parental response to long-term lithium treatment

Anne Duffy, MD, MSc, FRCPC
IGSLI Santiago Chile, September 2018

Flourish
Mood Disorders Research

Queen's University

Towards Optimal Brain and Psychosocial Development

# Disclosures

- Canadian Institutes of Health Research (CIHR)
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- Campus Alberta Innovates Program
- National Alliance Research Schizophrenia and Affective Disorders (NARSAD)
- Canada Research Chairs Program (CRC)

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## Learning Objectives

1. Highlight background rationale for high-risk studies

2. Present findings from high-risk studies that advance understanding of the trajectory of emerging bipolar disorder

3. Discuss implications & future directions

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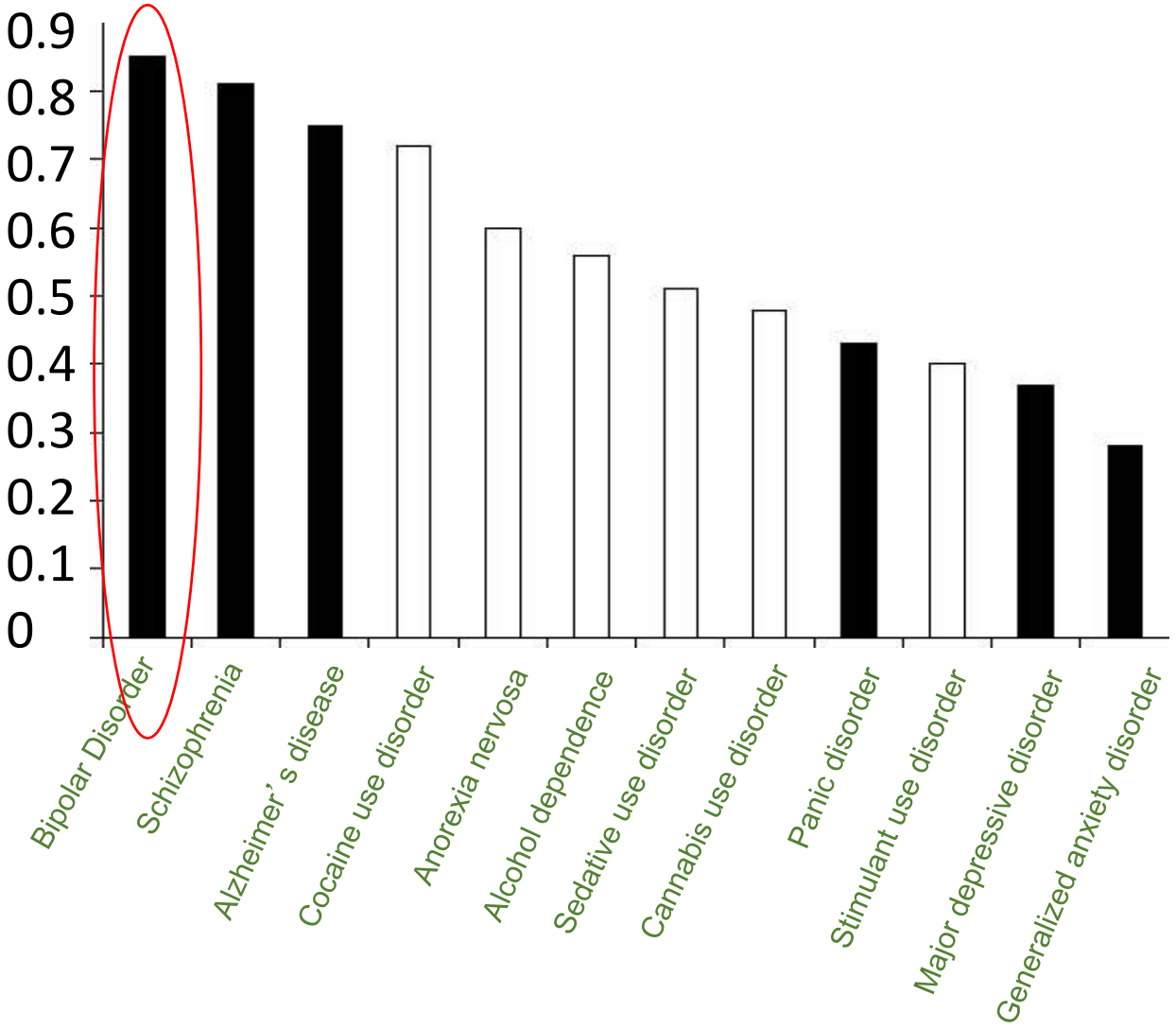
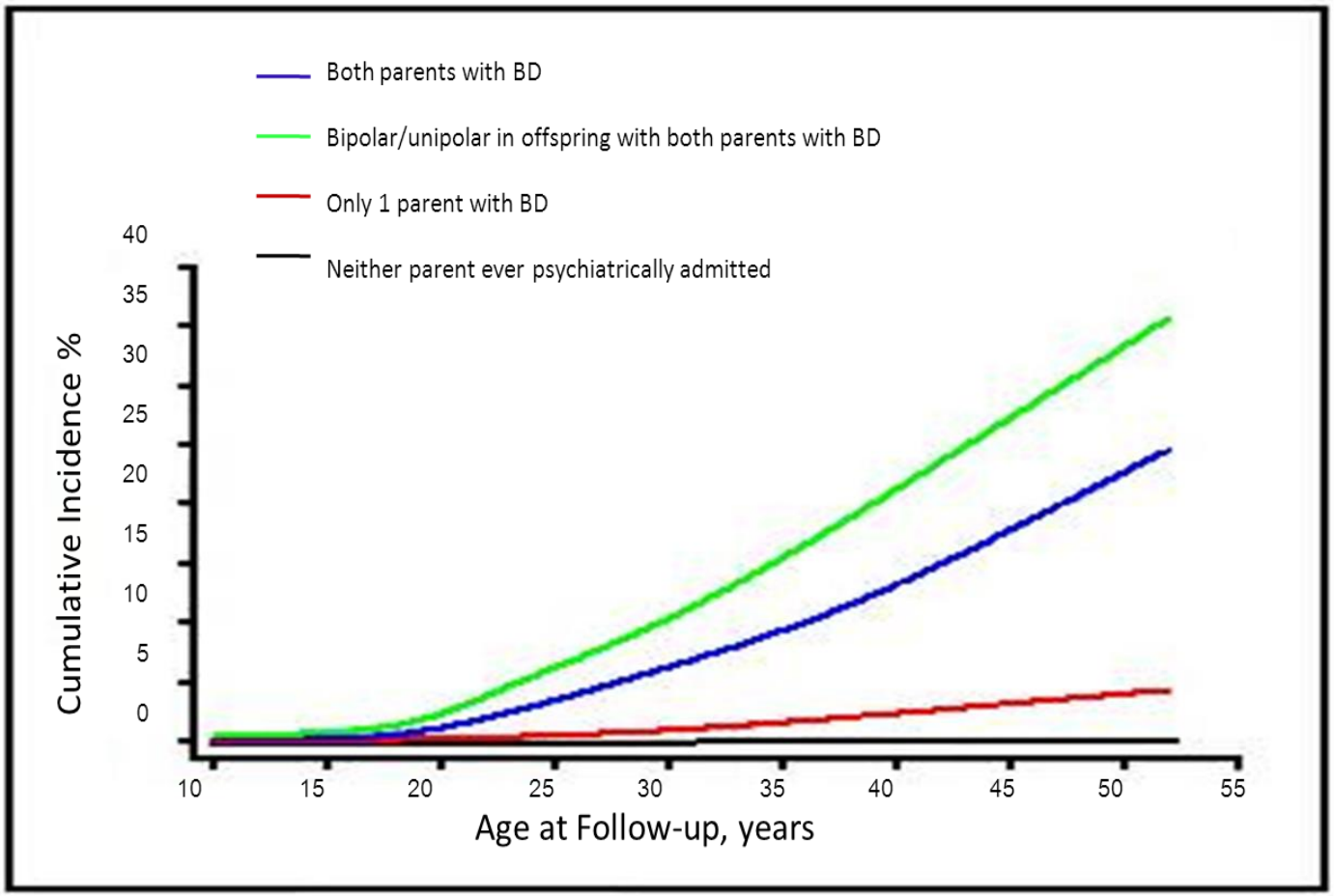
# Heritability Estimation



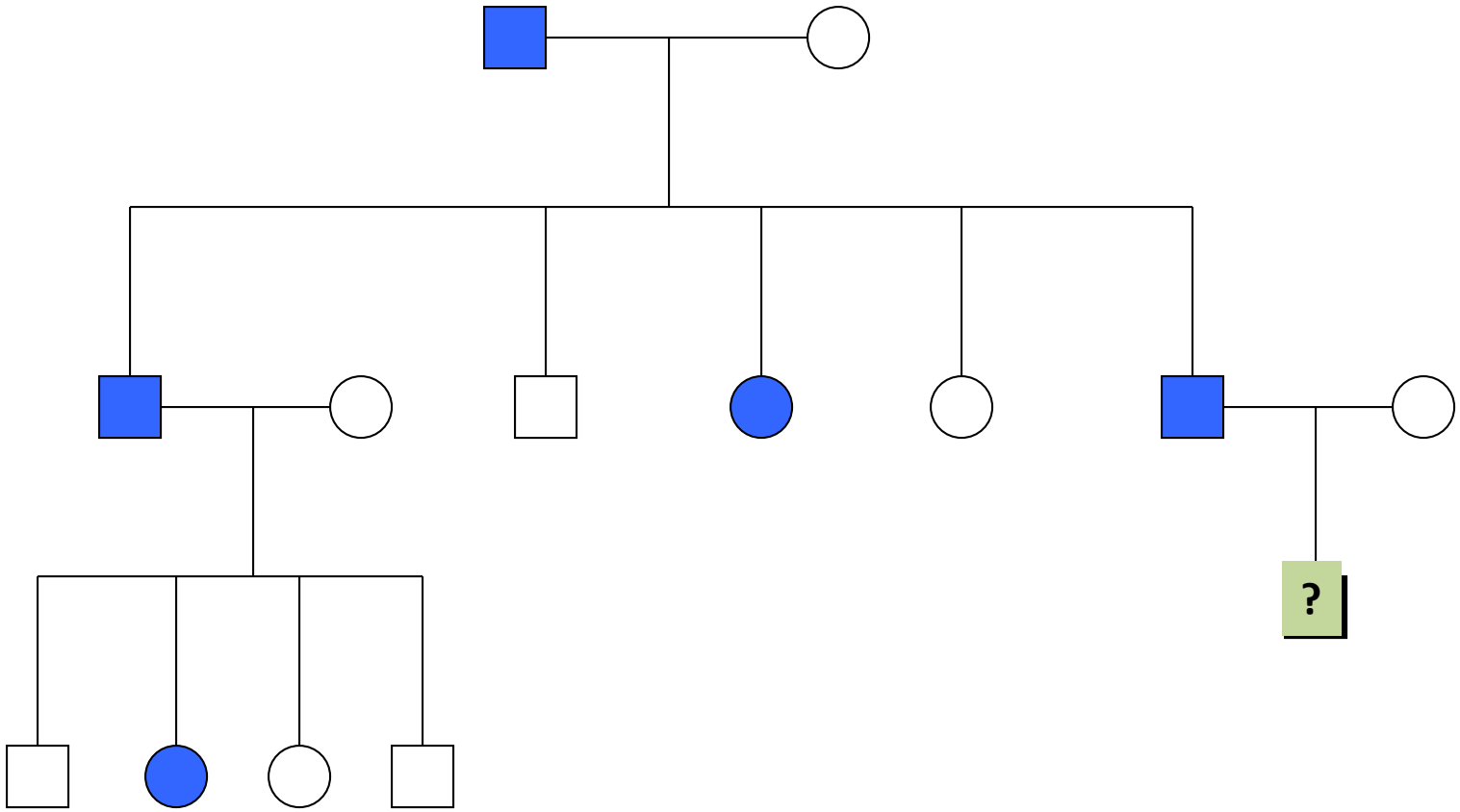

Bienvenu et al., 2010

# Cumulative risk of mood disorder in offspring of BD parents Danish Community Registry Data

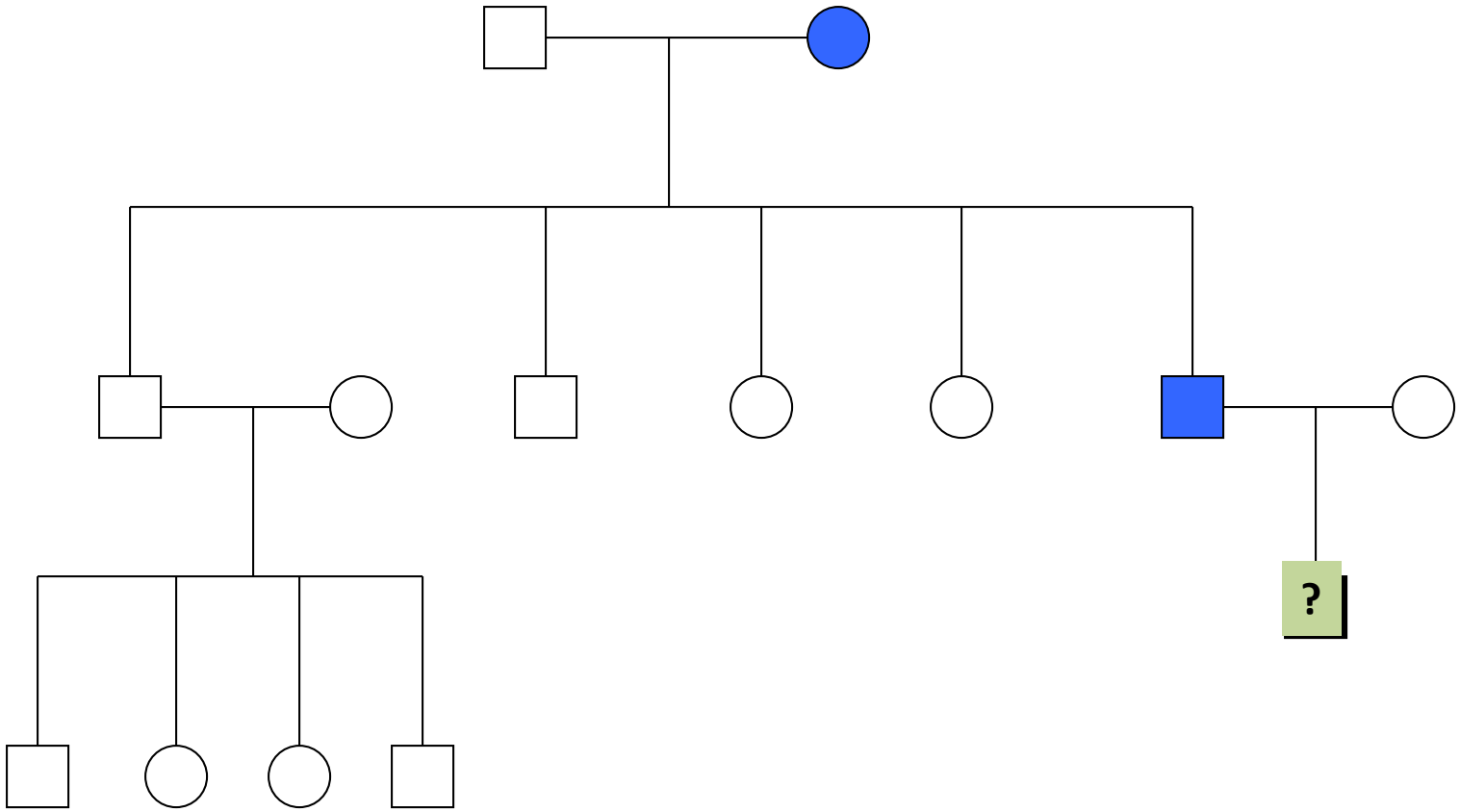



Gottesman et al. 2010

# Pedigree 1



# Pedigree 2



# Risk to first degree relatives

## of BP Probands

7% risk BP (8 fold)

12.5% risk UP (2-3 fold)

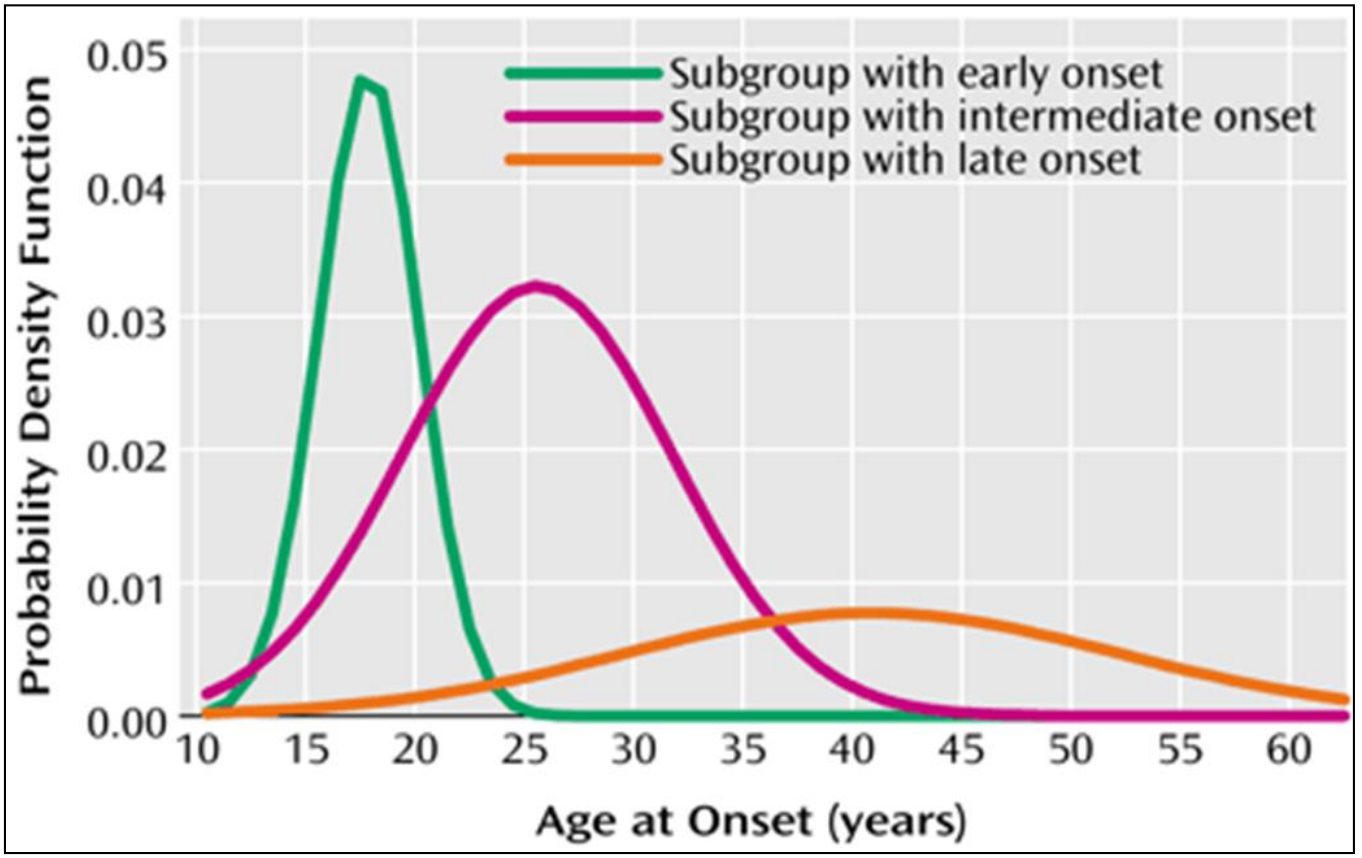
## of UP Probands

1.9% risk BP (1.5 fold)

14.2% risk UP (3-4 fold)

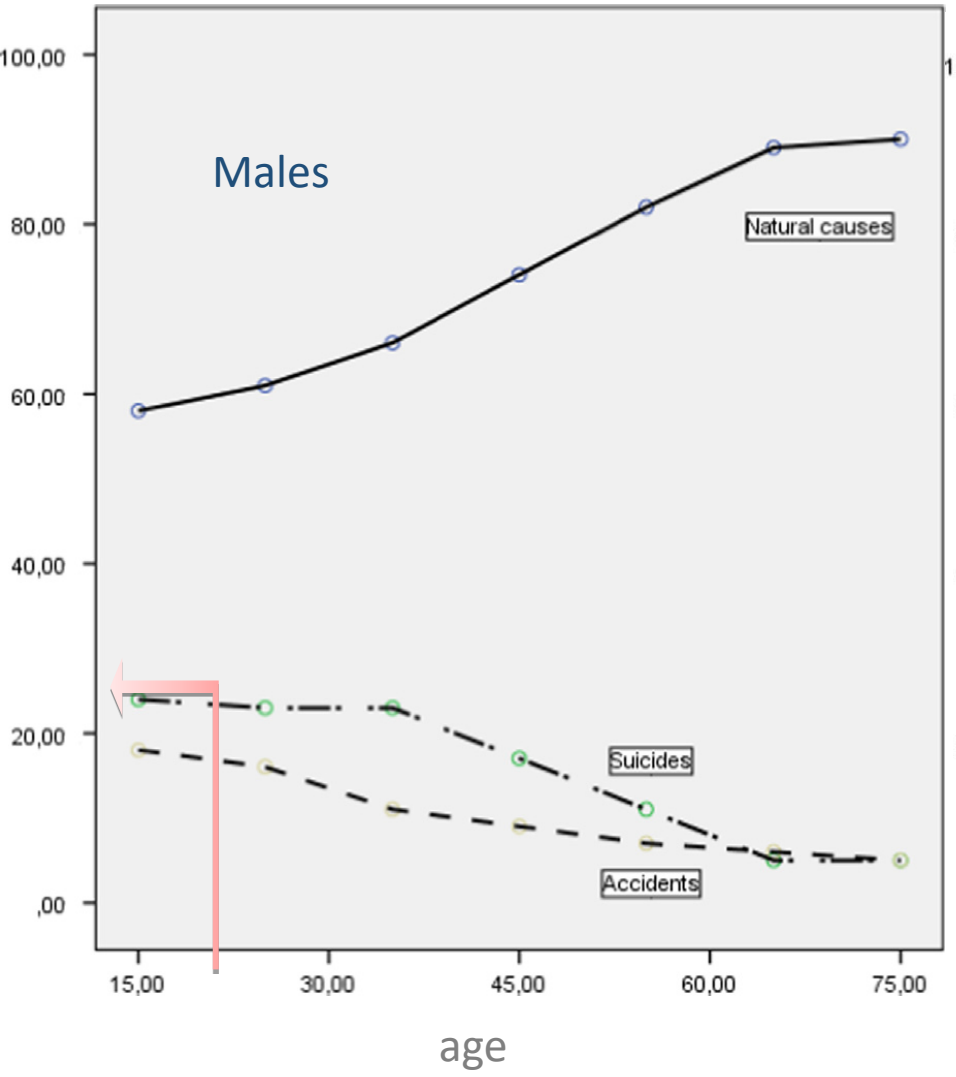
(Duffy et al., 2000)

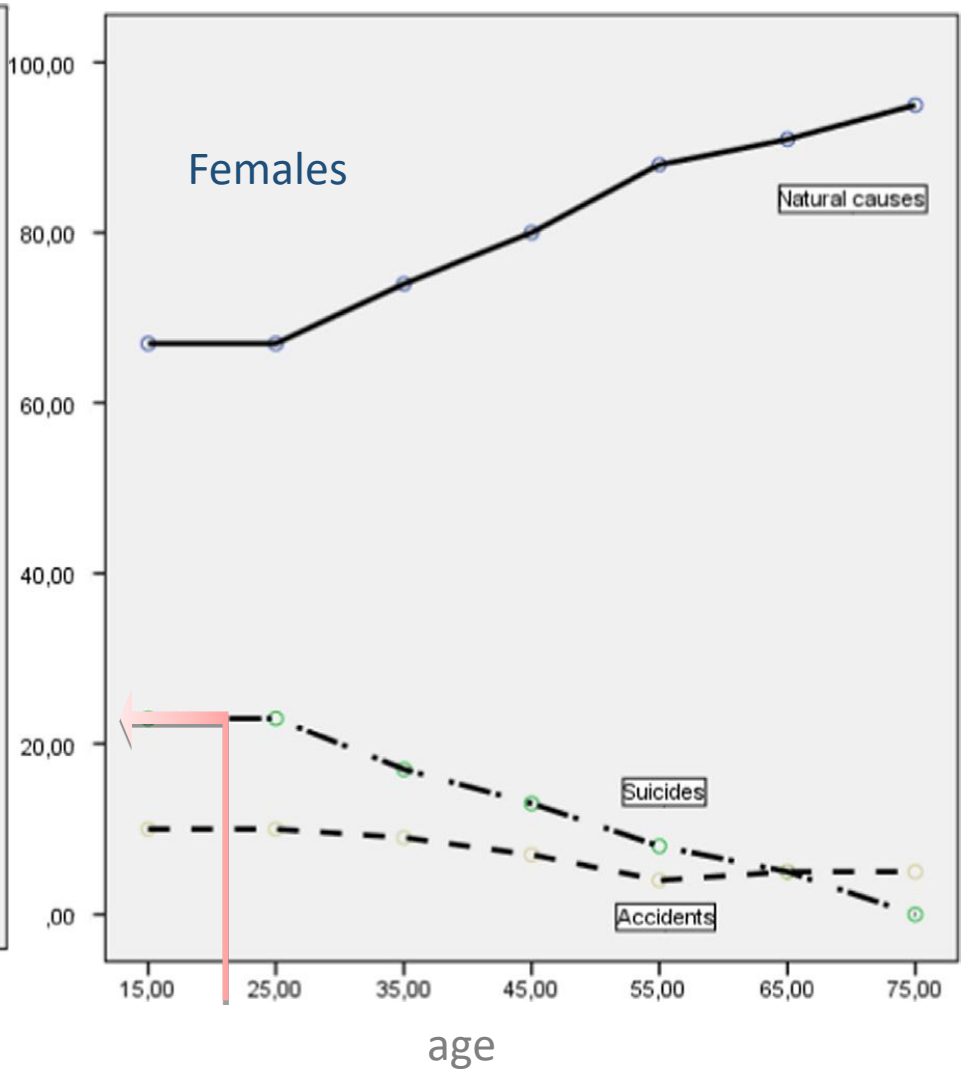
# Distributions of ages at onset




Bellivier et al., 2003; Leboyer et al., 2005

# Percentage of lost life years due to natural causes, suicides and accidents in bipolar patients from Danish National Study




Kessing et al., 2014

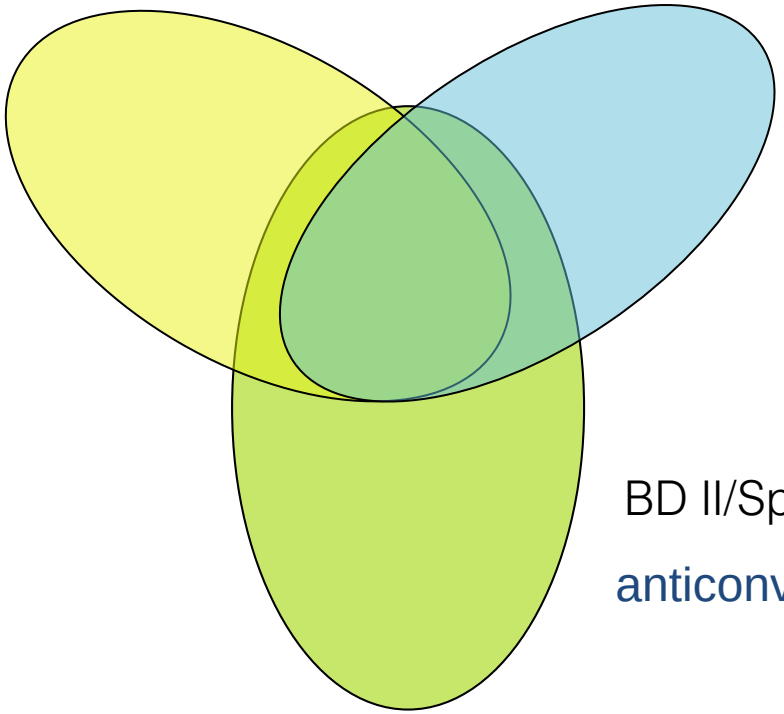
# Heterogeneity of BD

Psychotic Spectrum BDI

antipsychotic responders

Episodic/Classical MDI

lithium responders

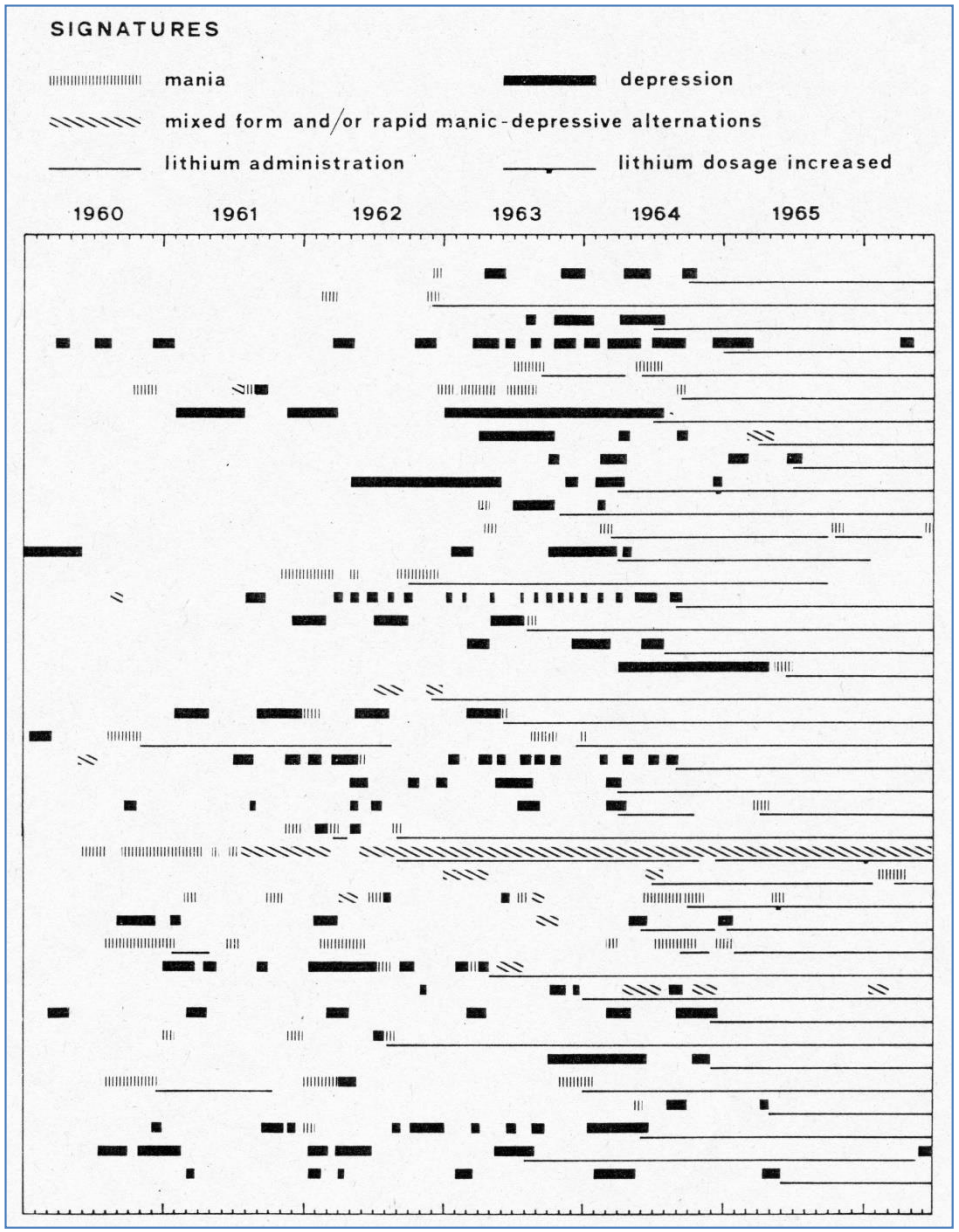


BD II/Spectrum

anticonvulsant responders

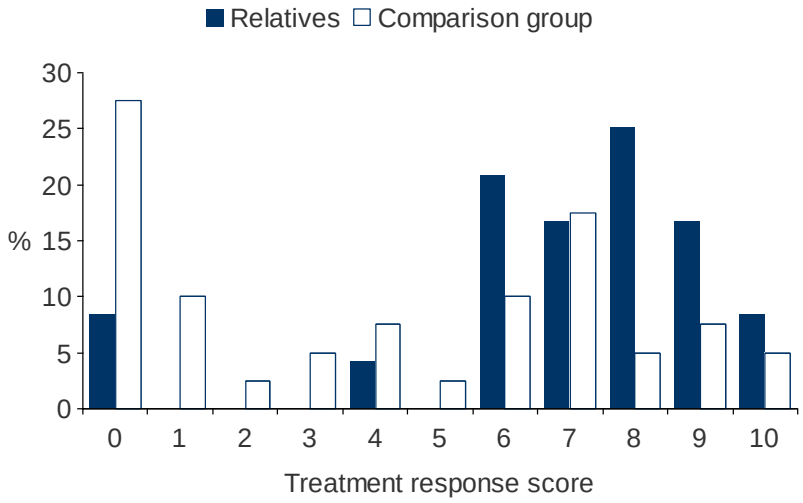
Grof et al., 1994, 2009, Alda 2004

# Lithium Prophylaxis Classical MDI – Danish study

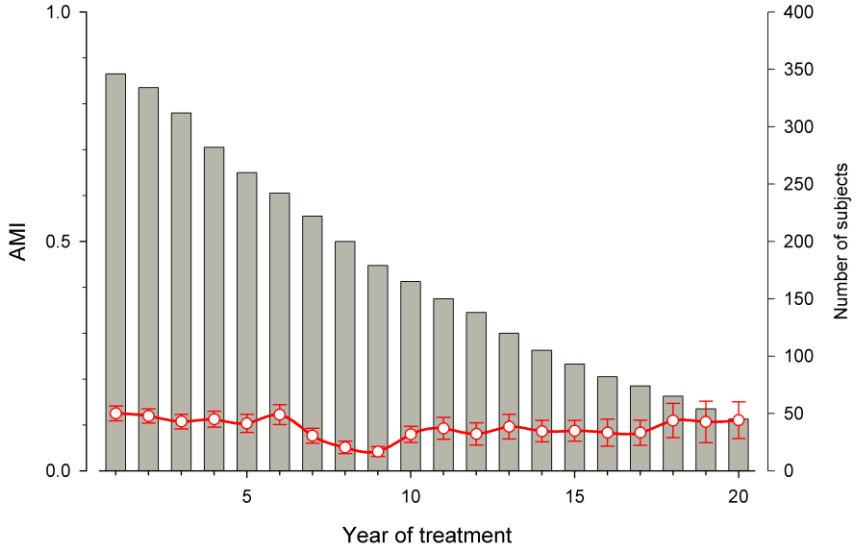



Baastrup & Schou, 1967

# Lithium response clusters in families and is stable




Grof et al., 2002




Berghofer et al., 2013

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# Canadian Flourish High Risk Study

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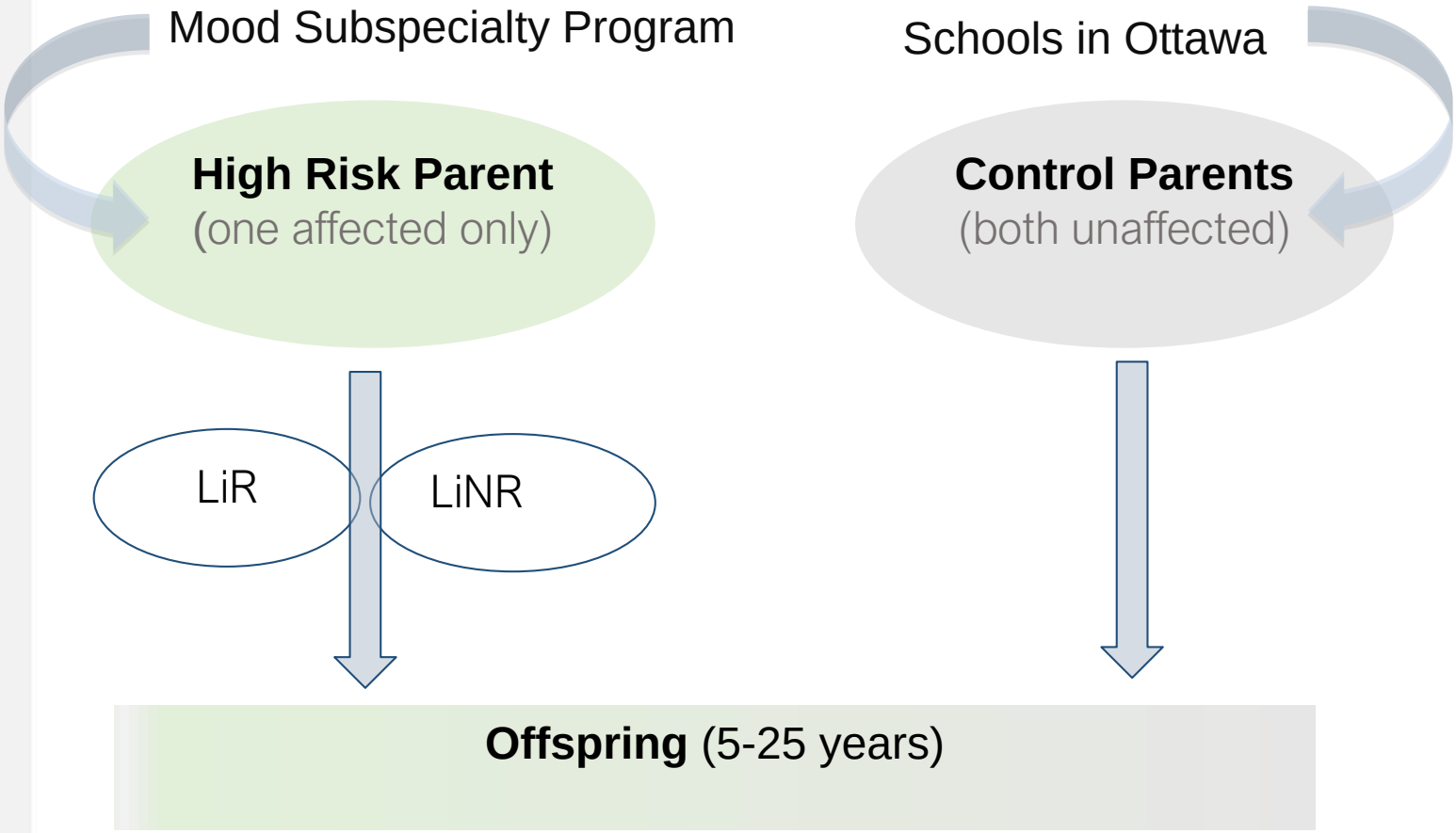


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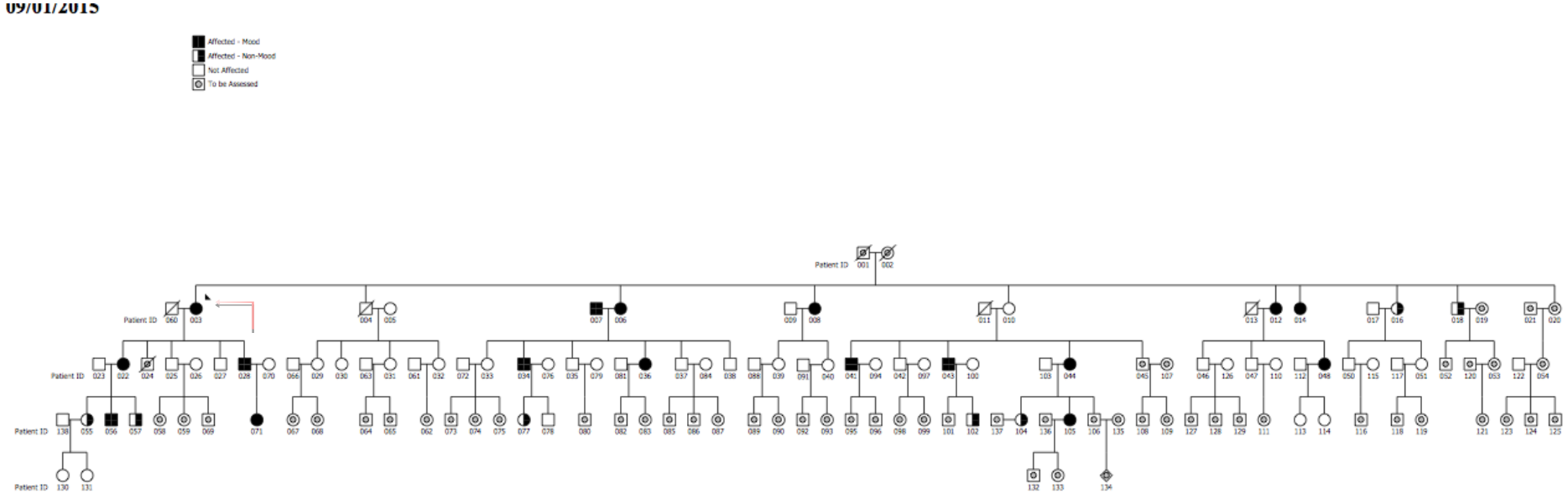
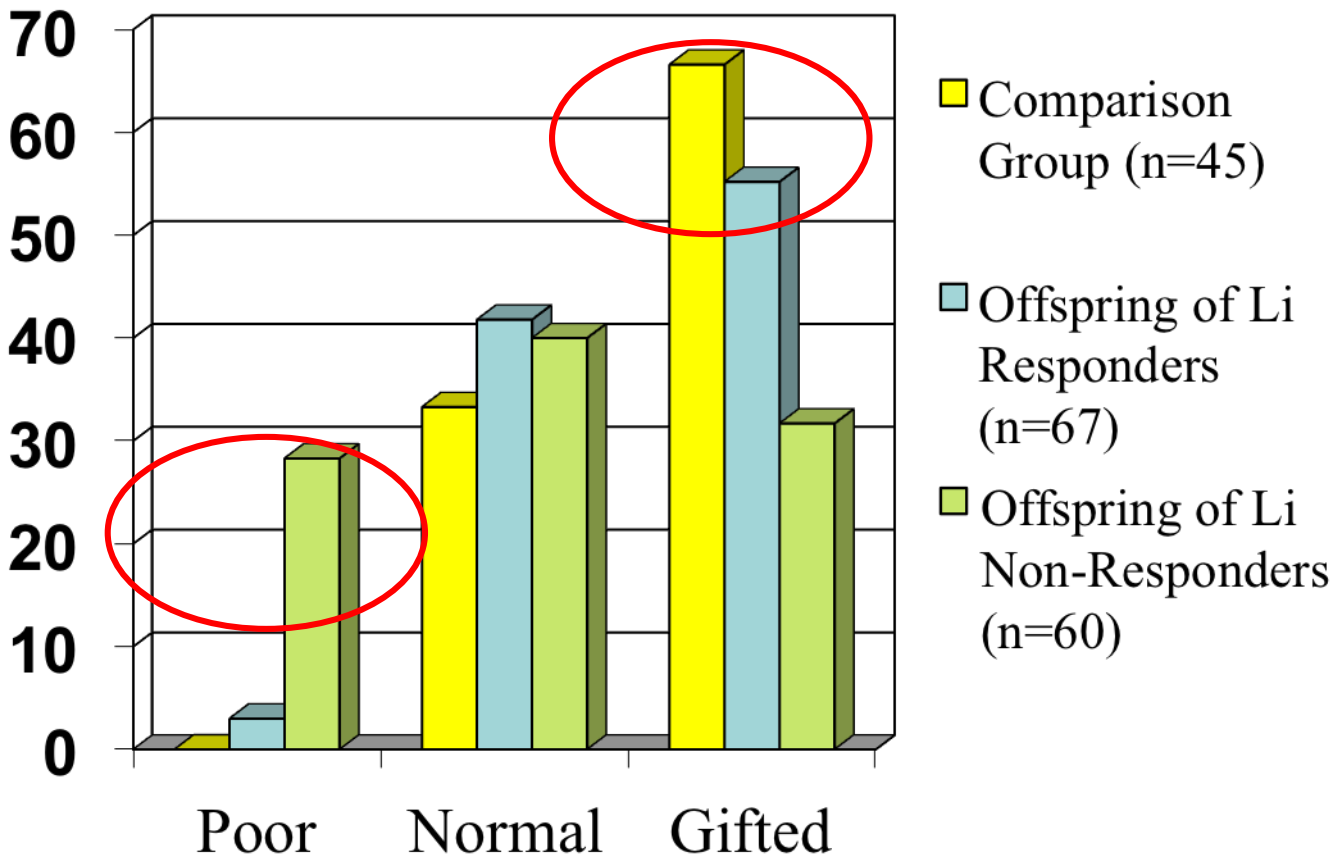
Duffy et al, from 1997

# Pedigree – Lithium responsive proband



# Quality of early childhood functioning






Duffy et al., 2007

# Lifetime Psychopathology HR Subgroups vs Controls

| Diagnosis | Maximum likelihood chi-square | Follow-up pairwise comparisons | | |
|---|---|---|---|---|
| | | LiR vs C | LiNR vs C | LiR vs LiNR |
| **Bipolar disorder** | $\chi^2$ (2)= 22.4 *p*= .000 | ** | ** | |
| **Schizoaffective-bipolar disorder** | $\chi^2$ (2)= 2.3 *p*= .317 | | | |
| **Depressive disorder** | $\chi^2$ (2)= 20.7 *p*= .000 | ** | ** | |
| **Anxiety & sleep disorder** | $\chi^2$ (2)= 15.9 *p*= .000 | ** | ** | |
| **Eating disorder** | $\chi^2$ (2)= 1.8 *p*= .412 | | | |
| **Adjustment disorder** | $\chi^2$ (2)= 2.4 *p*= .307 | | | |
| **Substance use disorder** | $\chi^2$ (2)= 19.8 *p*= .000 | ** | ** | |

* $p < .05$, ** $p < .01$ LiR n=67; LiNR n=60; C n=61)

Duffy et al., 2007

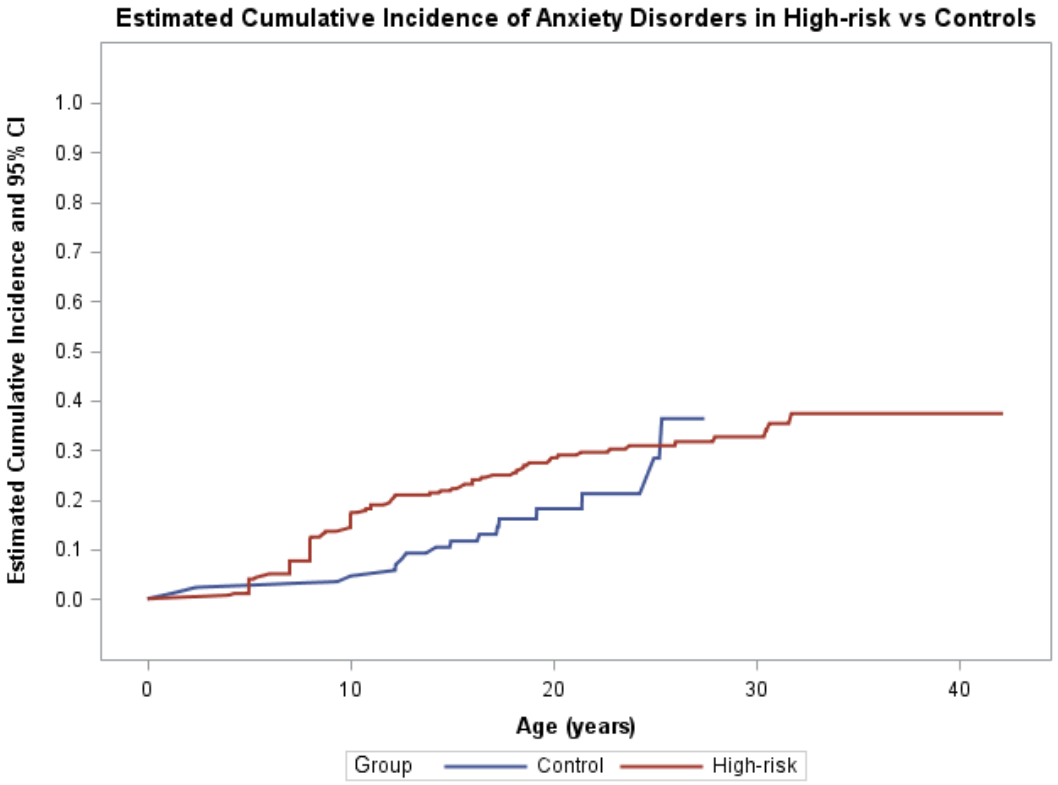
# Lifetime Psychopathology HR subgroups vs Controls

| Diagnosis | Maximum likelihood chi-square | Follow-up pairwise comparisons | | |
|---|---|---|---|---|
| | | LiR vs C | LiNR vs C | LiR vs LiNR |
| **Conduct disorder** | $\chi^2$ (2)= 2.3<br>*p*= .317 | | | |
| **Somatoform disorder** | $\chi^2$ (2)= 2.3<br>*p*= .317 | | | |
| **Cluster A traits** | $\chi^2$ (2)= 10.4<br>*p*= .006 | | ** | * |
| **Psychosis NOS** | $\chi^2$ (2)= 2.3<br>*p*= .317 | | | |
| **ADHD and/or LD** | $\chi^2$ (2)= 10.9<br>*p*= .004 | | ** | * |
| **Unaffected** | $\chi^2$ (2)= 50.1<br>*p*= .000 | ** | ** | |

* *p*< .05, ** *p*< .01

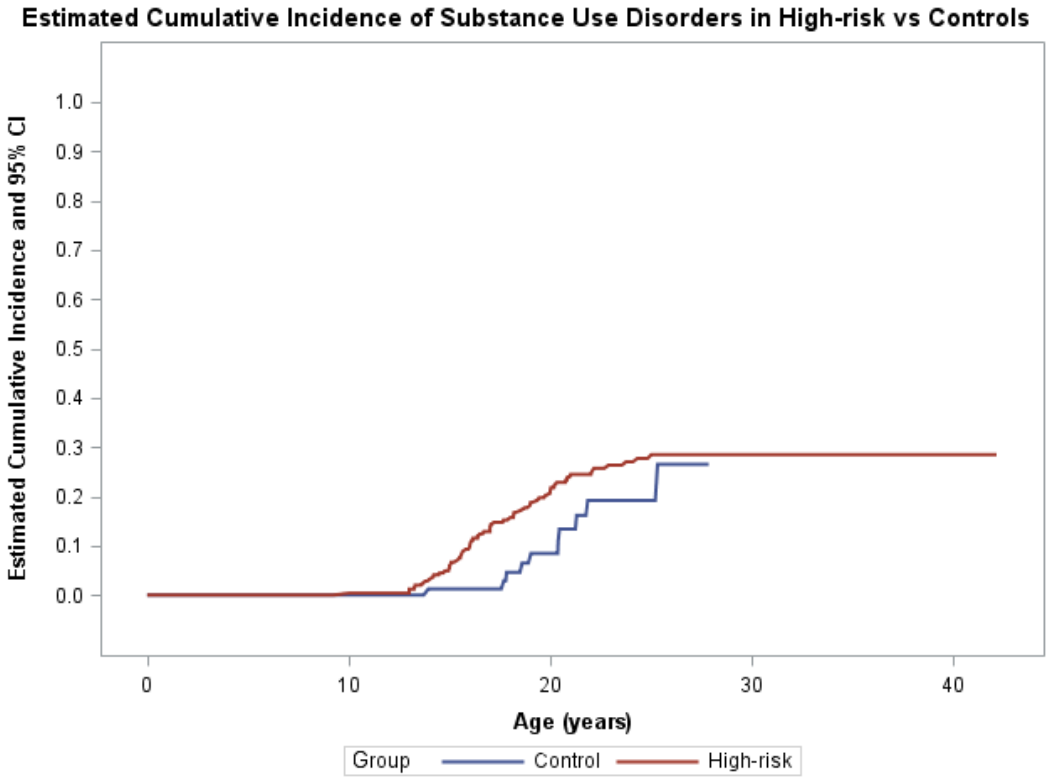
Duffy et al., 2007

# Most recent:
# Risk of anxiety disorders in high-risk offspring compared to controls



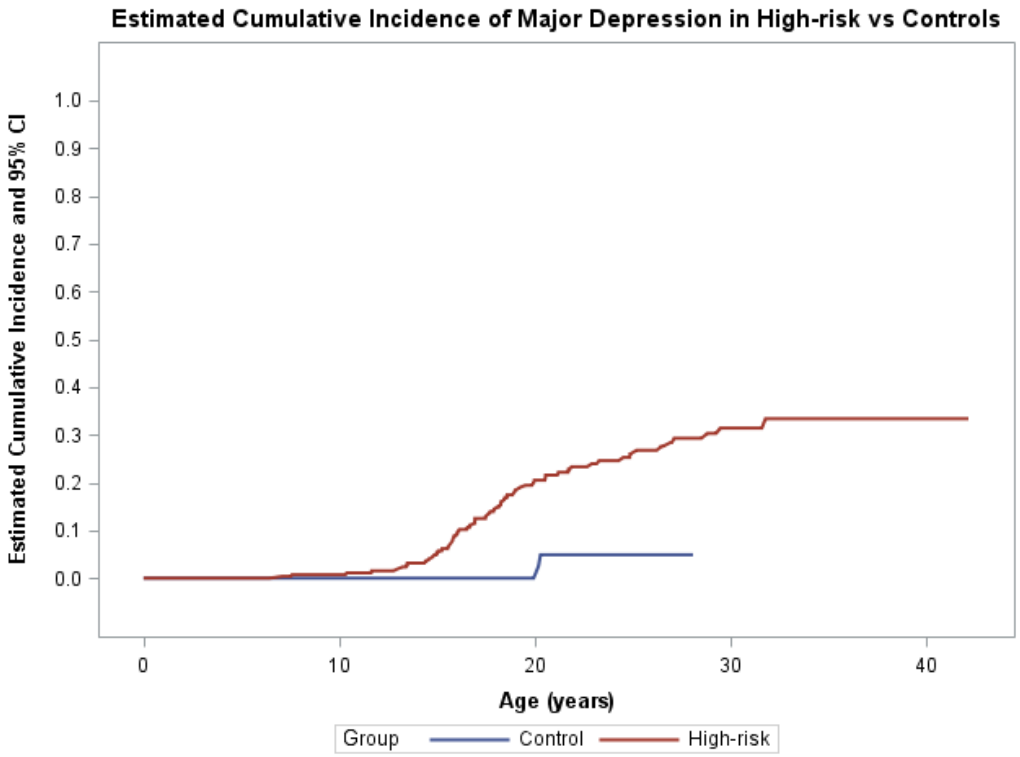

Duffy et al., in press AJP

# Most recent:
# Risk of substance use disorders in high-risk offspring compared to controls



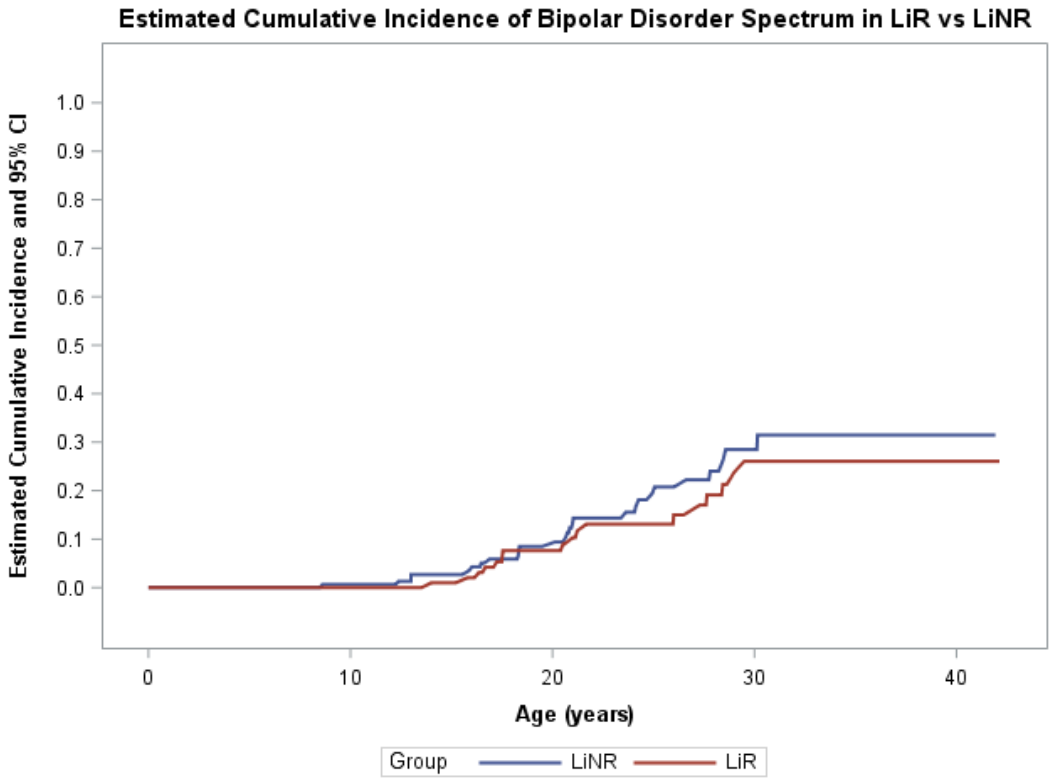

Duffy et al., in press, AJP

# Most recent:
# Major depressive disorder in high-risk offspring compared to controls



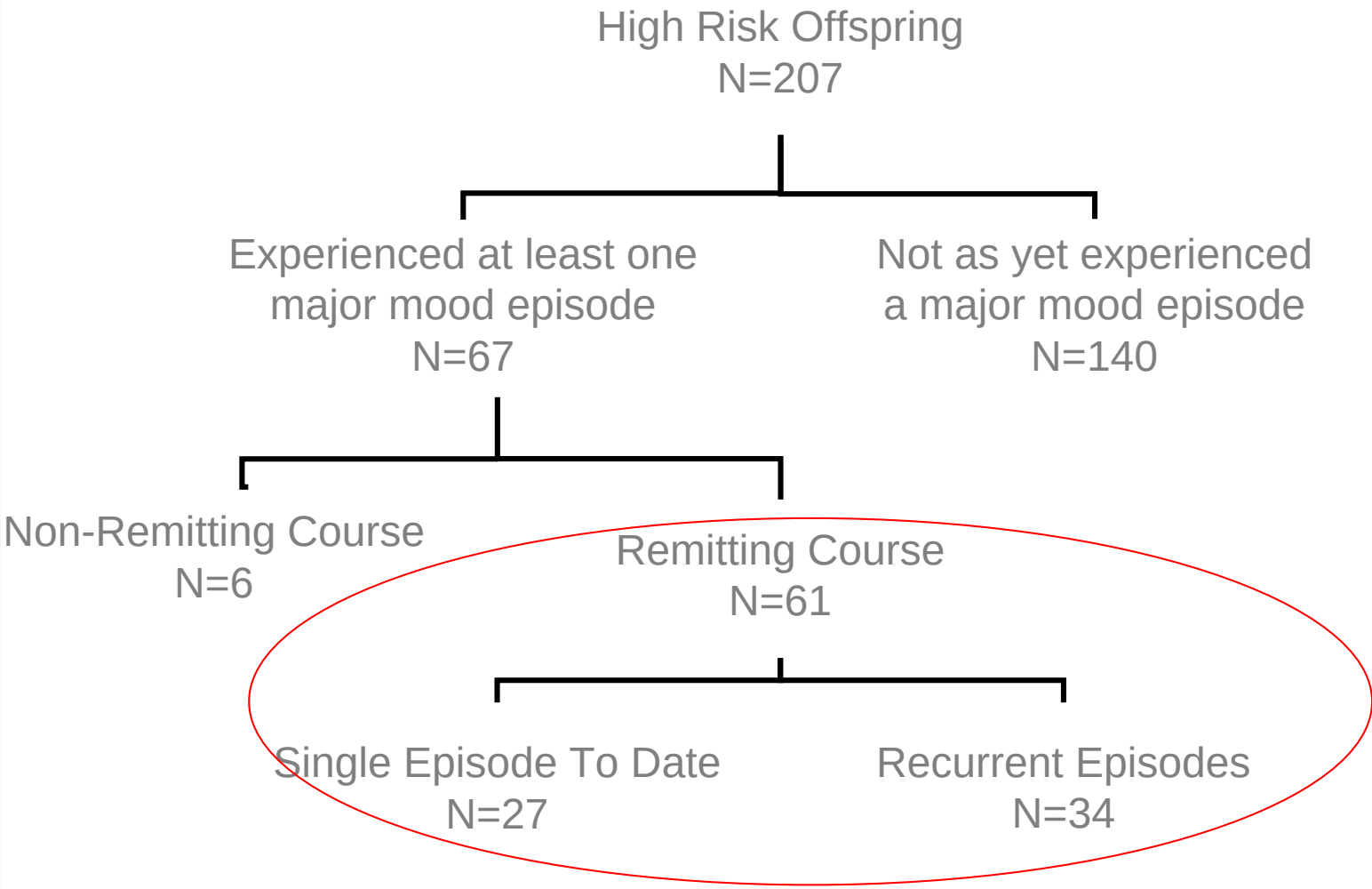

Duffy et al., in press, AJP

# Most recent:
# Bipolar disorder in HR offspring LiR vs LiNR subgroups



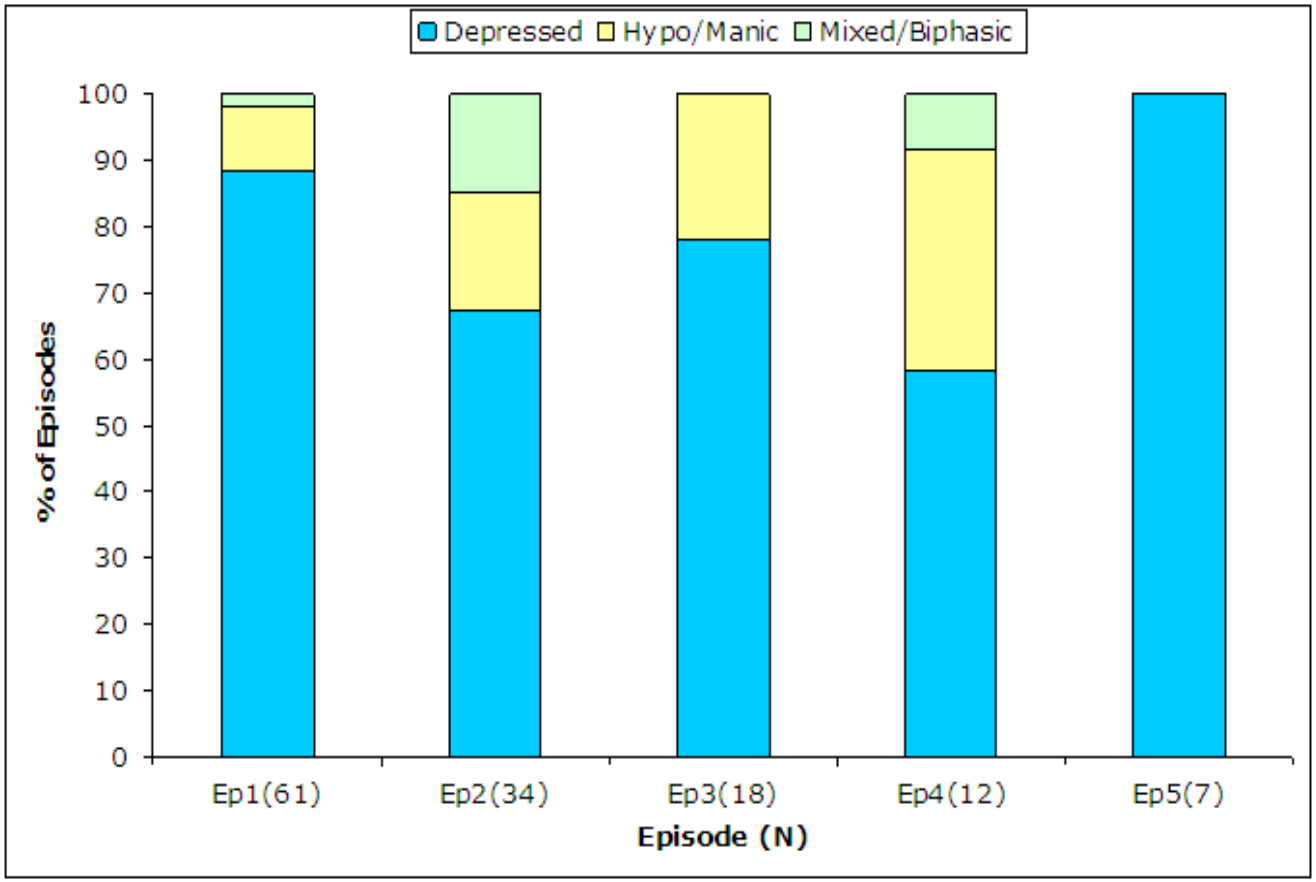

Duffy et al., in press, AJP

# Course of major mood disorder




Duffy et al., 2010

# Polarity of first mood episodes

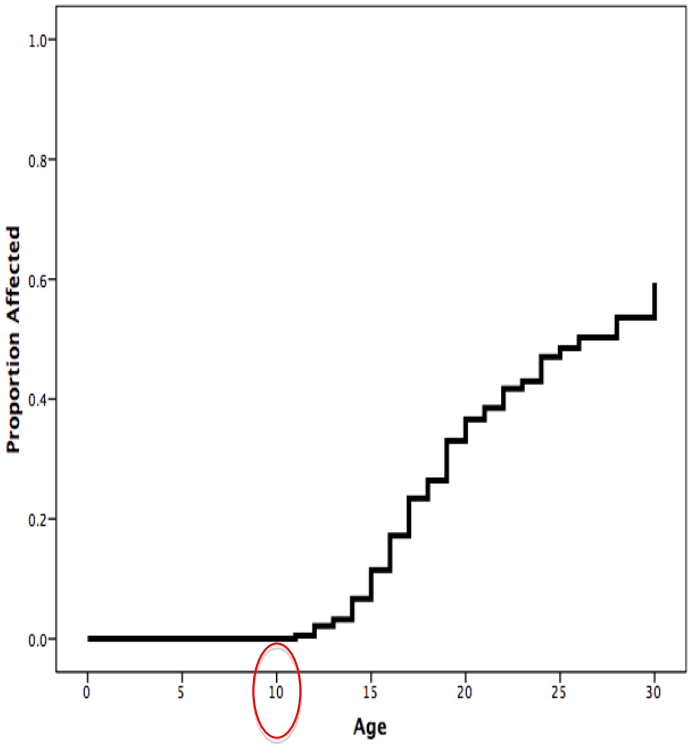



*D≈6 ¶4.8 months; m/M≈1.7¶1.3 months*

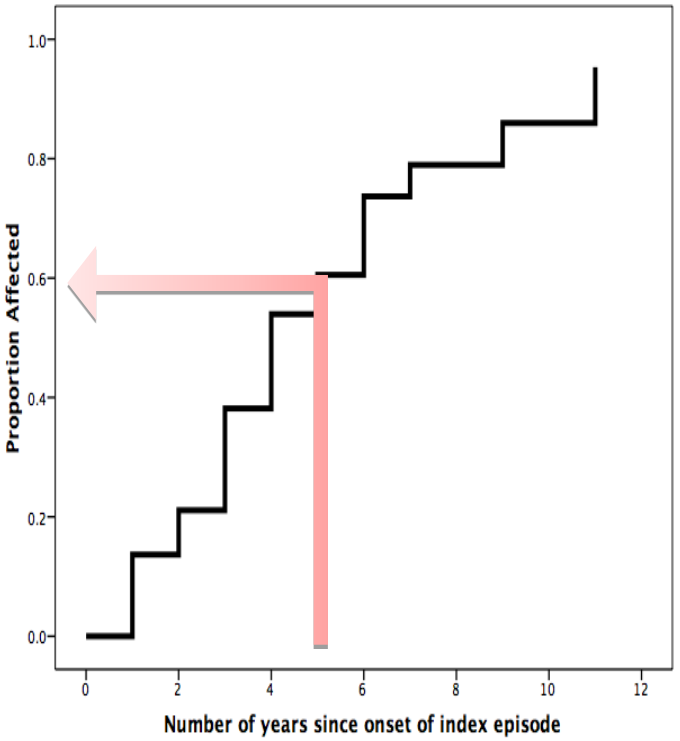
Duffy et al., 2010

# Risk of mood disorder onset and recurrence

## Risk of illness onset as a function of age




## Risk of recurrence as a function of age




Duffy et al., 2010

# Course of major mood disorder

| | Offspring of LiR (n = 26) | Offspring of LiNR (n = 27) |
|---|---|---|
| Episodic [a] | 25 | 4 |
| Non-Episodic [b] | 1 | 23 |

$\chi^2$ (1)= 35.4, p< .001

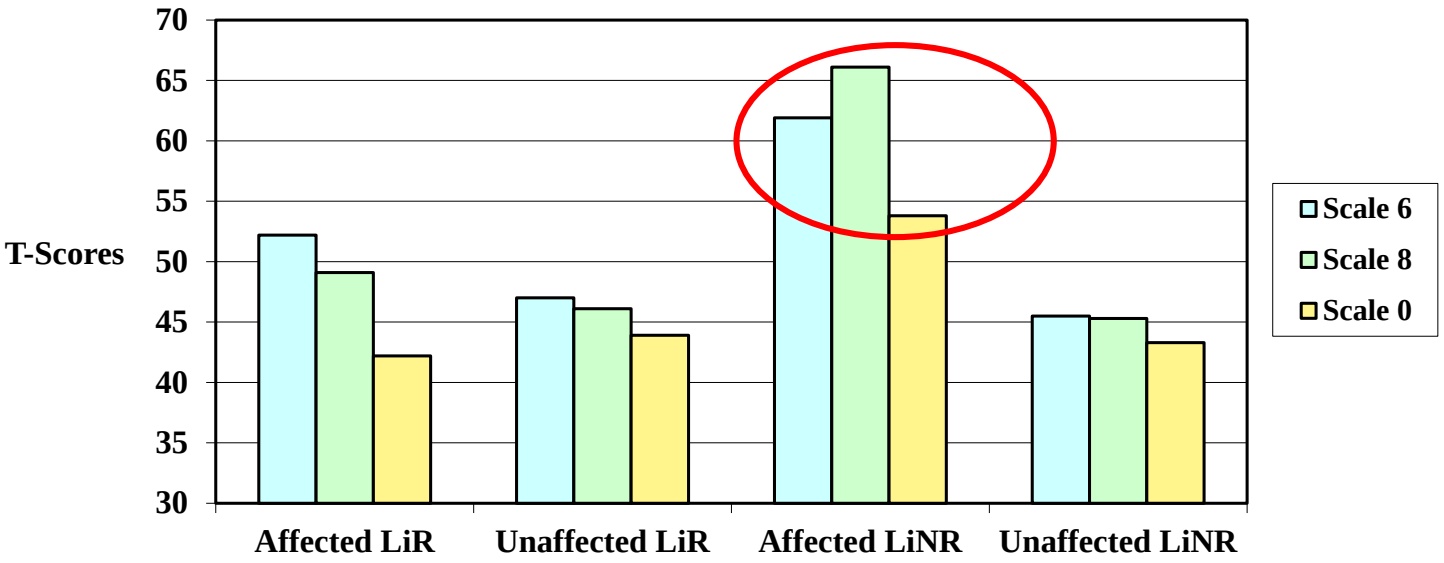
[a] Episodic= episodic course with full remission

[b] Non-episodic= chronic, chronic fluctuating, episodic with residual symptoms

Duffy et al., 2007

# MMPI –Quality of remission in LiR vs LiNR offspring



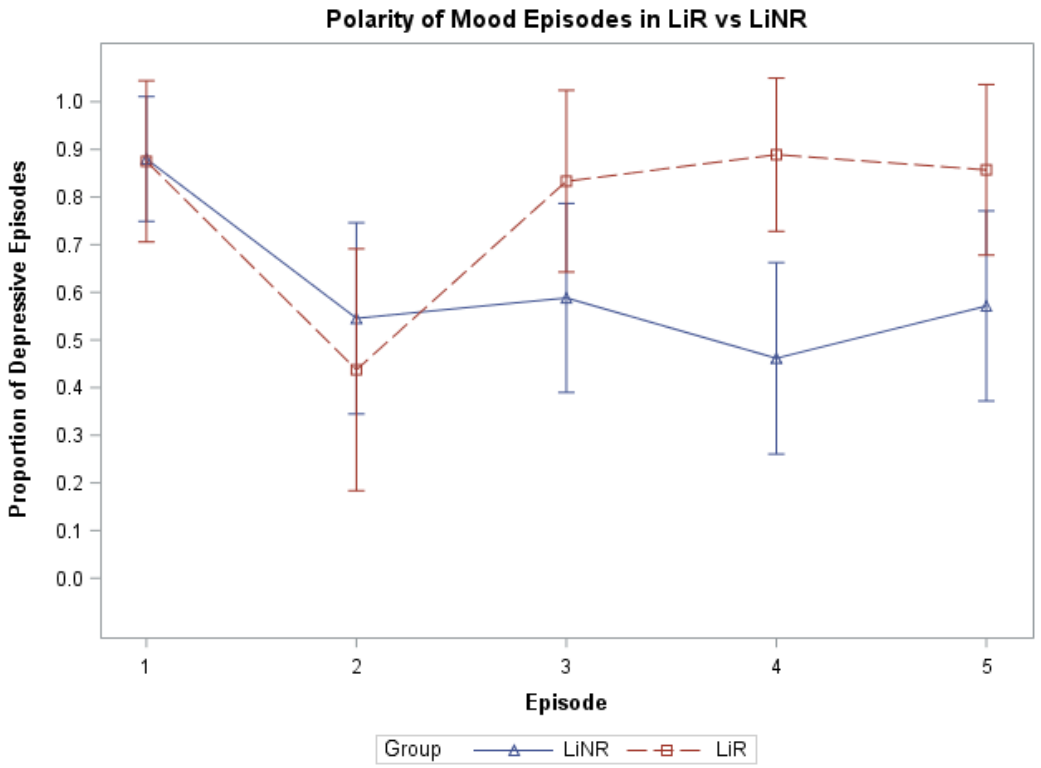



Scale 6 p= 0.01 Paranoid

Scale 8 p= 0.009 Psychotic

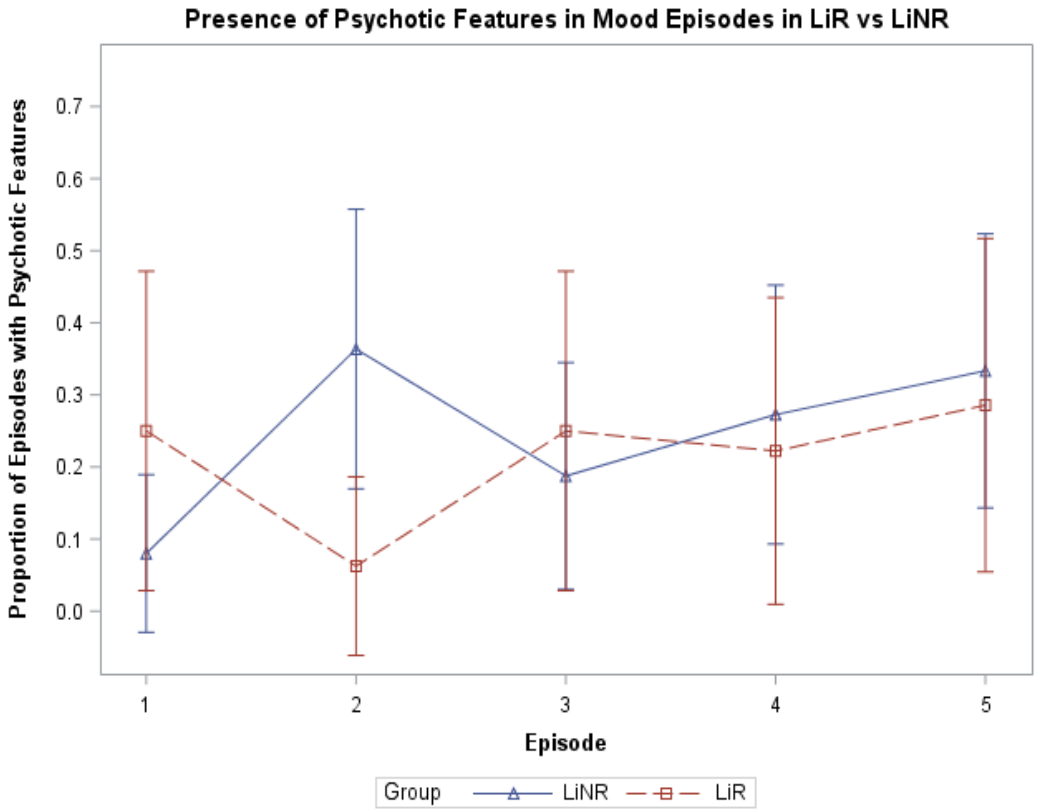
Scale 0 p= 0.034 Social Introversion

# Most recent:
# Proportion episodes in depressive polarity over the first five in HR with bipolar disorder



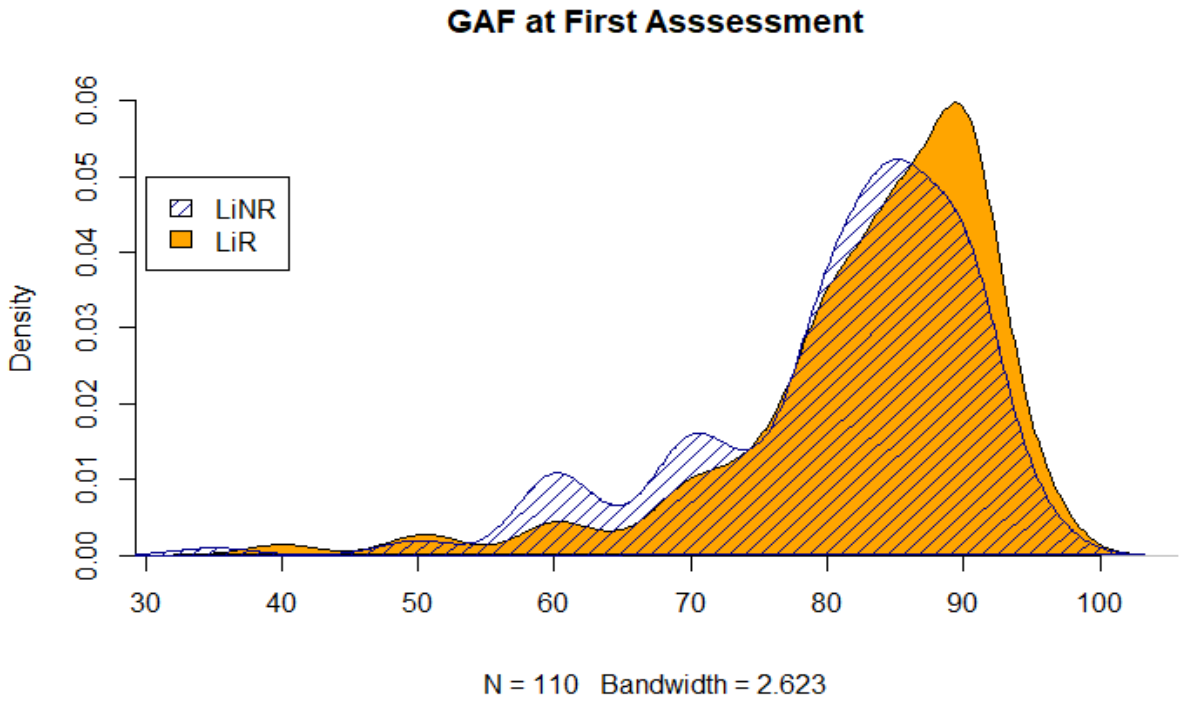

Duffy et al., in press, AJP

# Most Recent:
# Psychotic features in mood episodes in HR offspring with bipolar disorder




Duffy et al., in press, AJP

# Global Assessment of Functioning (GAF) at Baseline in LiR vs LiNR



# Global assessment of functioning (GAF) over observation period

| Table S2. Differences in GAF Scores Among Offspring | | | | | |
|---|---|---|---|---|---|
| | Controls (n=87) | High-Risk from LiR Family (n=117) | C vs LiR p-value | High-Risk from LiNR Family (n=162) | C vs LiNR p-value |
| **GAF (recruitment)** | | | | | |
| Median (min, max) | 90 (50, 100) | 85 (40, 95) | <0.0001[d] | 85 (35, 95) | <0.0001[d] |
| | | | | | |
| **GAF (most recent)** | | | | | |
| Median (min, max) | 90 (55, 95) | 85 (50, 100) | 0.0727[d] | 80 (30, 95) | <0.0001[d] |

# Parent and child mood disorder features

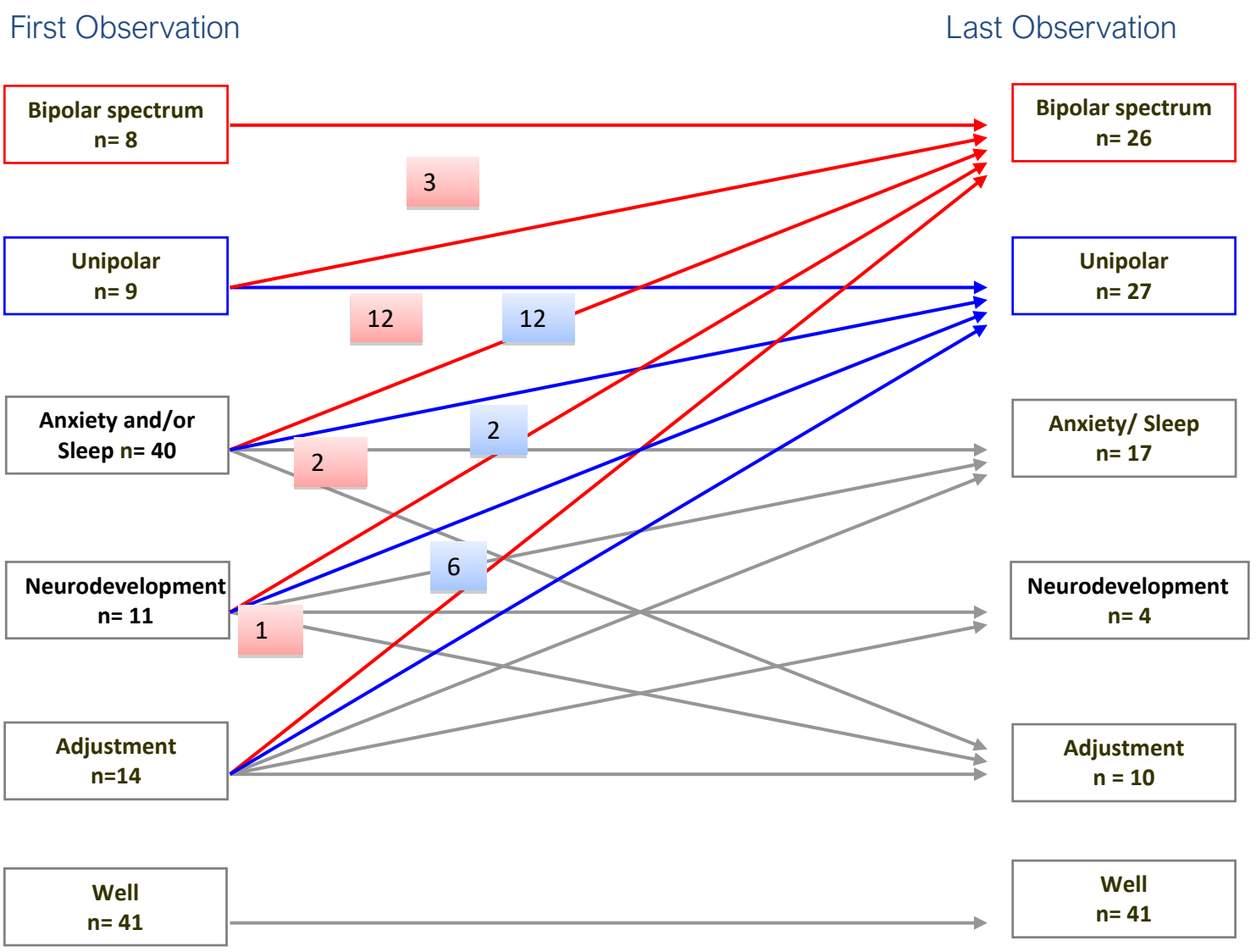
- Earlier age of onset of parent illness was associated with earlier age of offspring onset (p=.0137)

- Earlier parent onset was associated with increased risk of BD in offspring (p=0.0527)

- Parent course was associated with child mood disorder course ie parent with fully remitting course more likely to have a child with fully remitting course compared to remitting with residual symptoms (p=.0090) or chronic fluctuating (p=.0189)

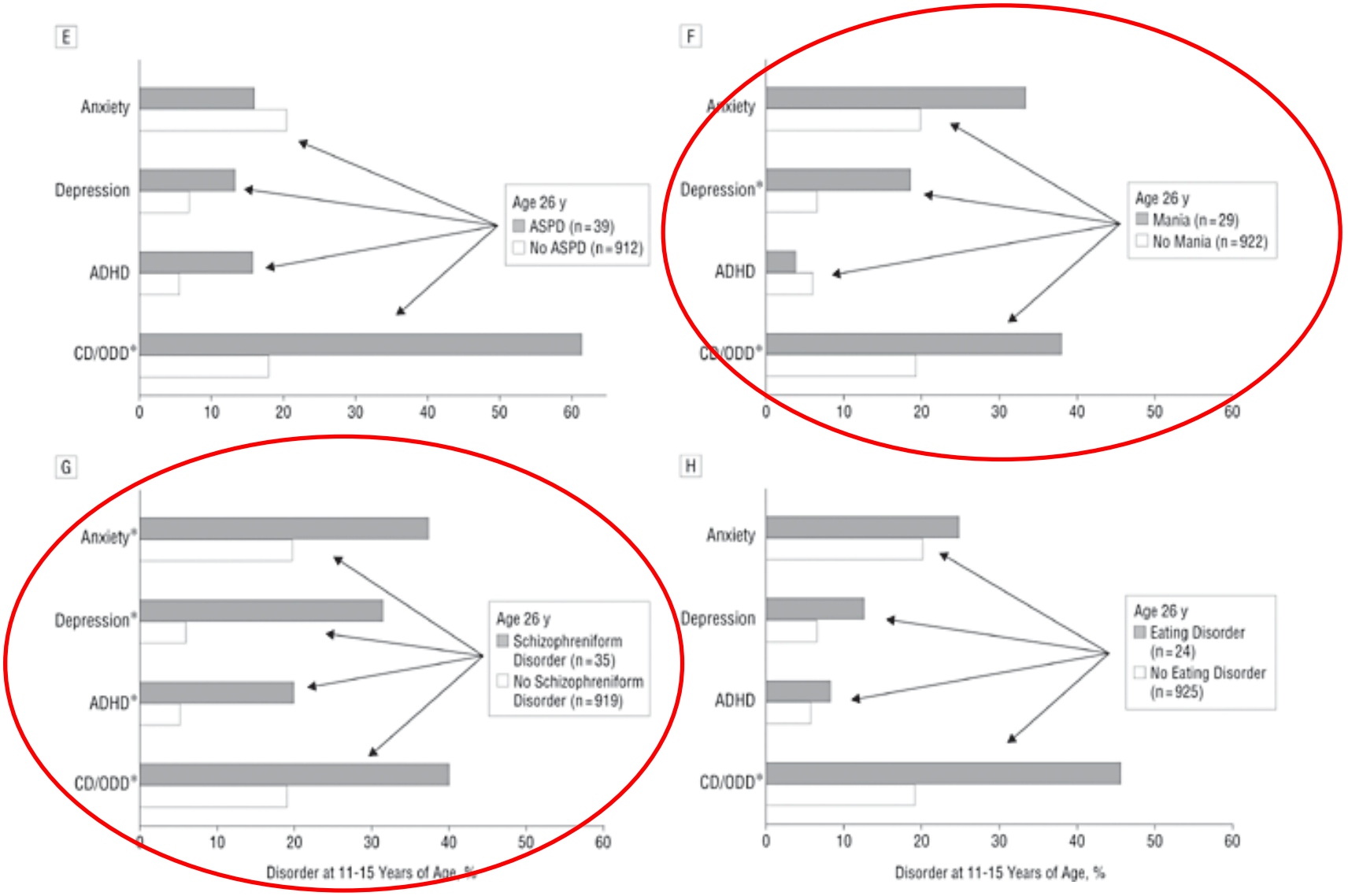
Duffy et al., in press, AJP

# Evolution of psychopathology high risk offspring



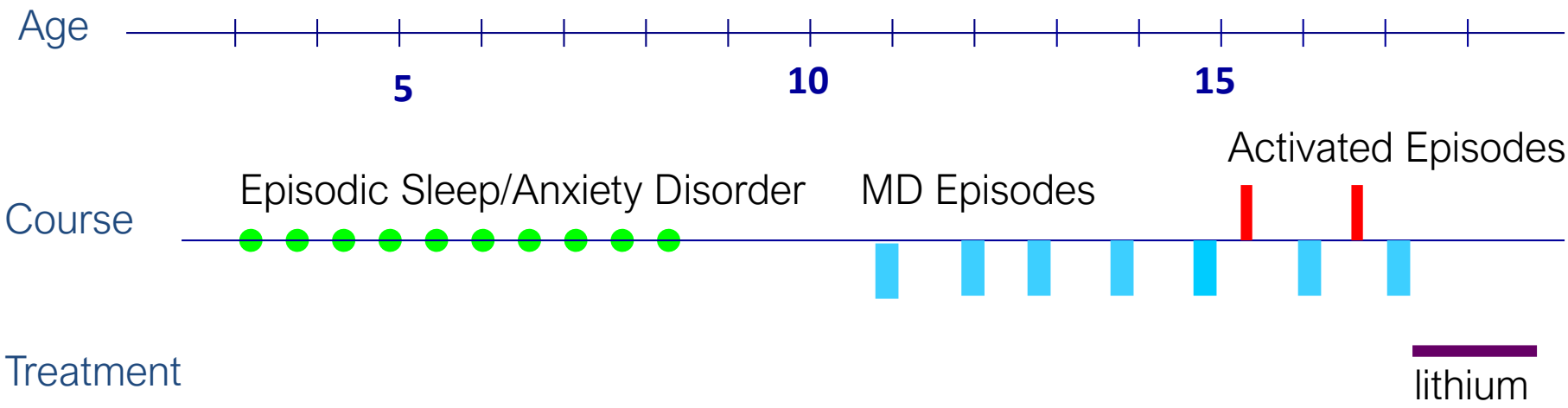

Duffy et al., 2007

# Proportion of Adult Cases with Juvenile Diagnoses- Dunedin Study




Kim-Cohen J et al., 2003

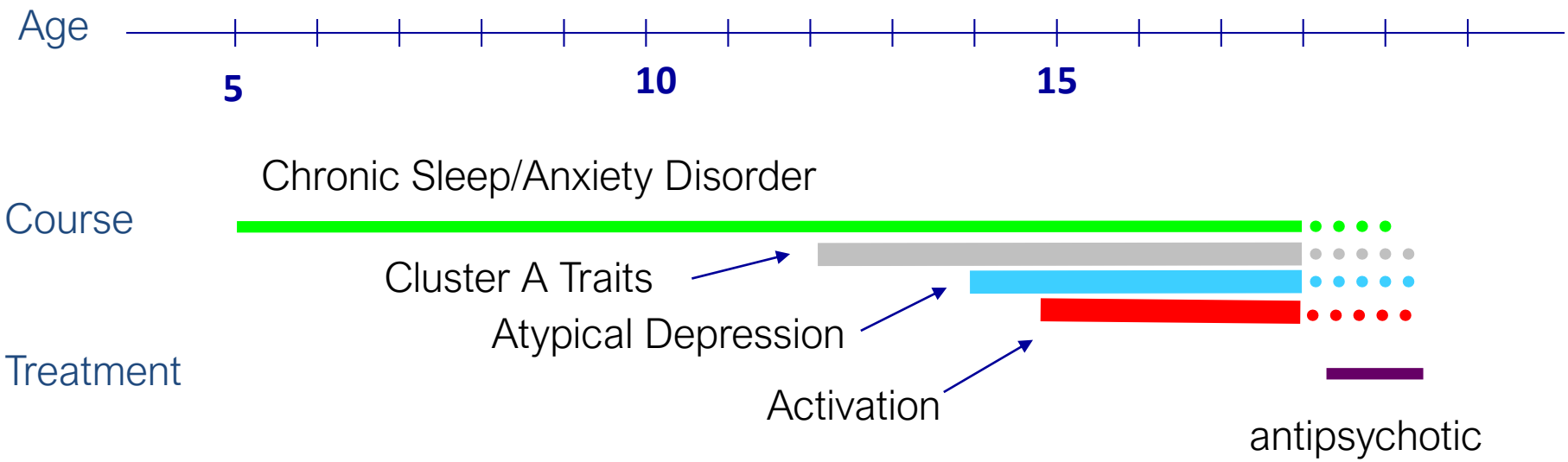
# Child of LiR Bipolar Parent – Emerging Illness Course




"Sequential comorbidity"

Duffy, A., 2002

# Child of LiNR Bipolar Parent- Emerging Illness Course




"Concurrent comorbidity"

Duffy, A. et al. 2002

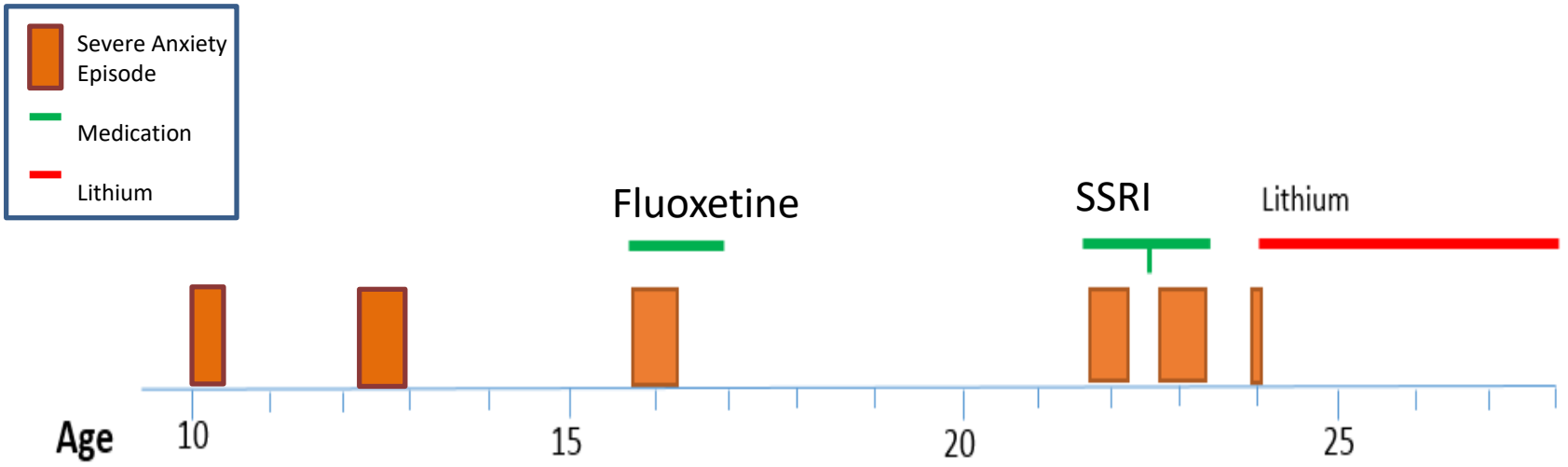
# Son responds to medication effective for LIR BD mother

## not to a medication recommended for his diagnosis

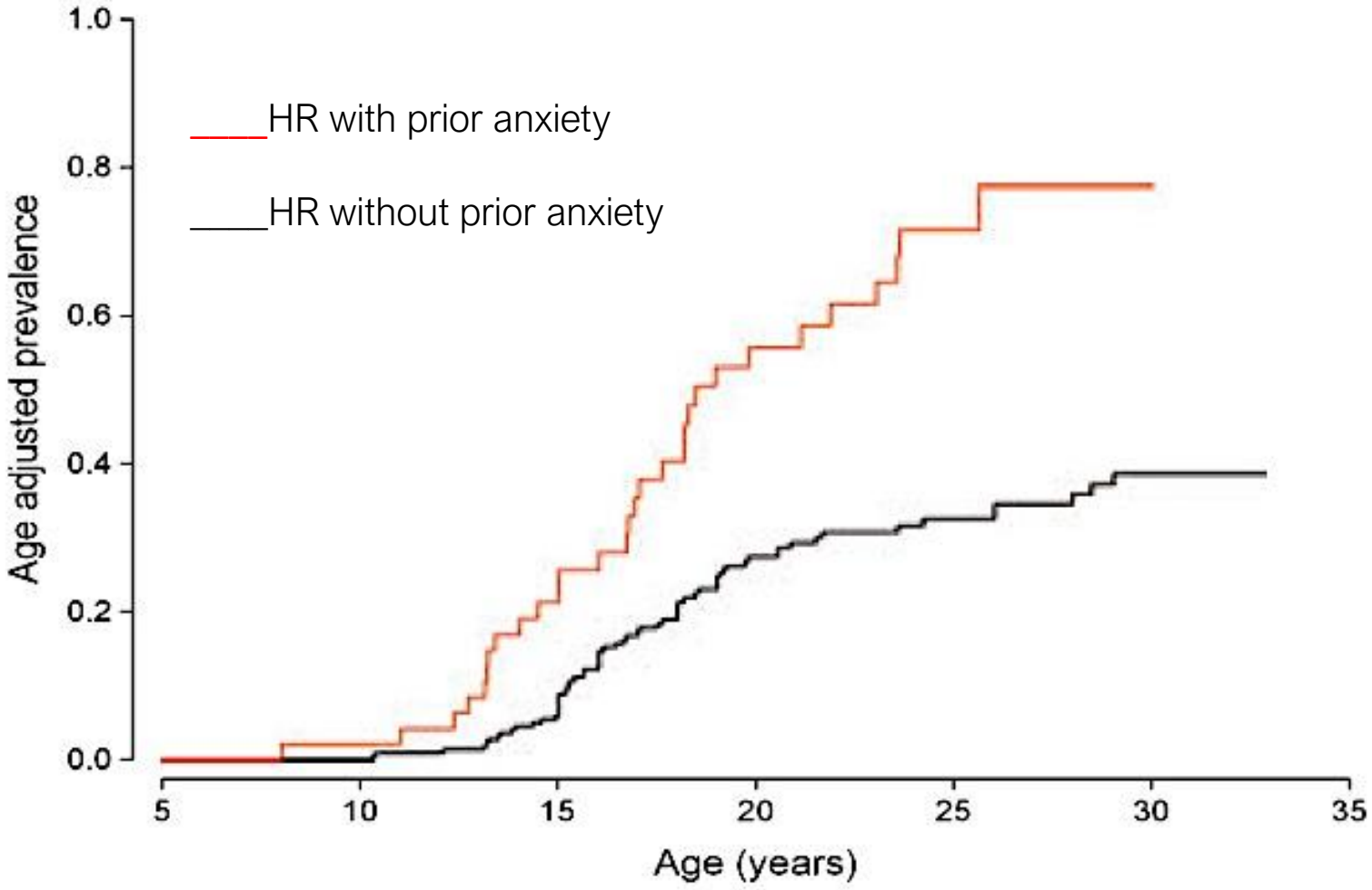
**Symptoms:**

- Feelings of anxiety
- Constant excessive worries
- Panic attacks
- Feeling overwhelmed
- Palpitations
- Pressure on the chest
- Insomnia

**Diagnosis** → Anxiety Disorder

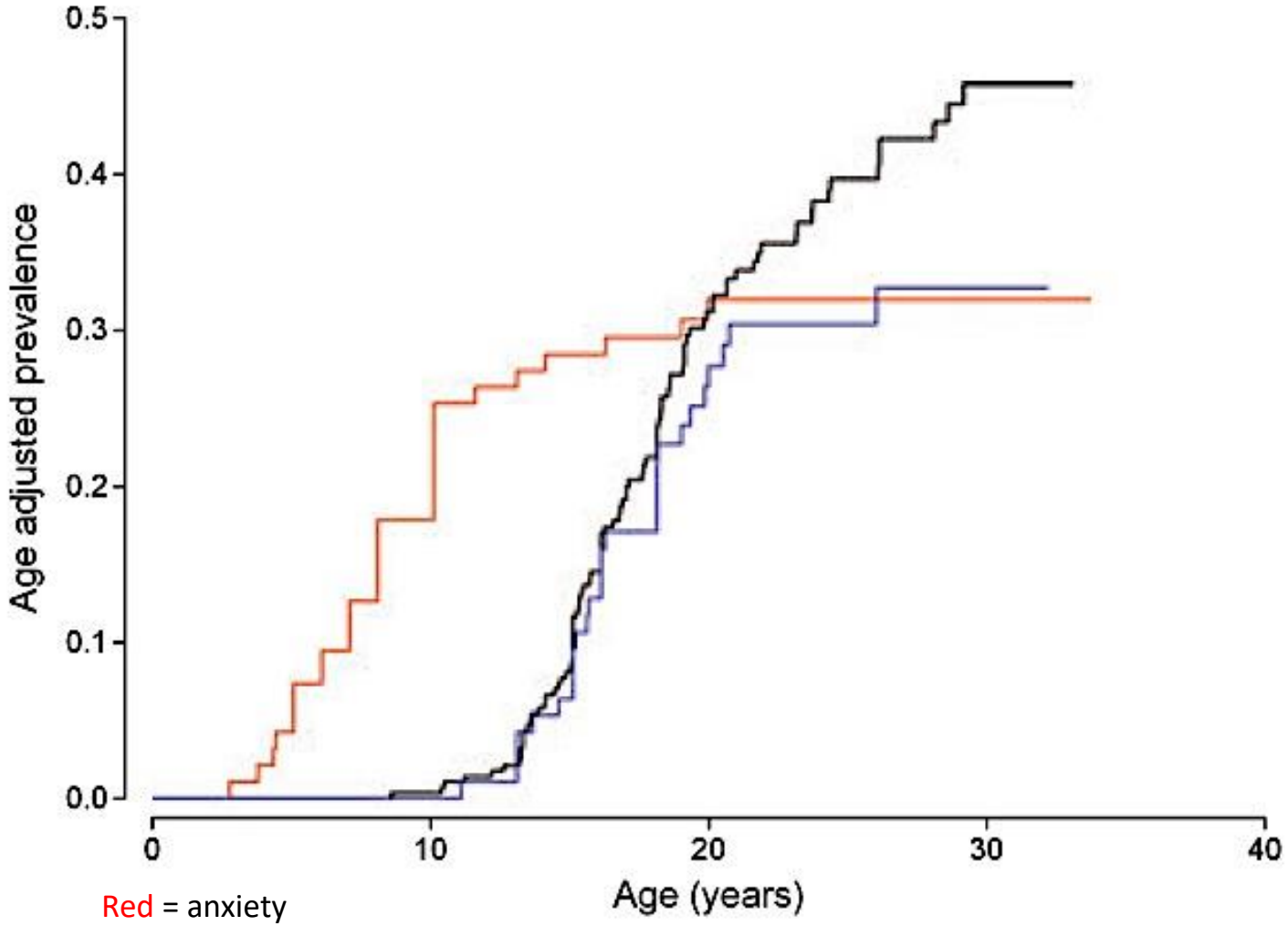


# Risk of mood disorder in high-risk offspring increased by pre-existing anxiety disorder




Duffy et al., 2010

# Age of onset of mood disorder in relation to anxiety disorder and substance abuse in high-risk offspring

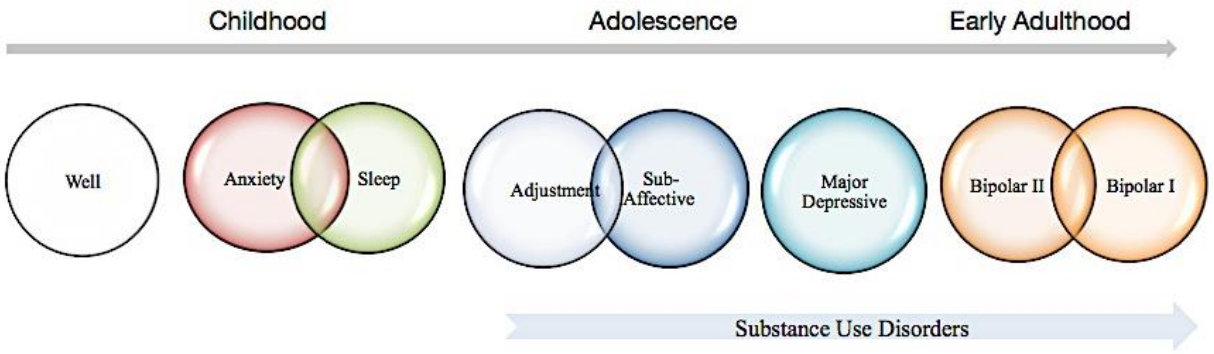



Red = anxiety
Blue=substance use
Black=mood

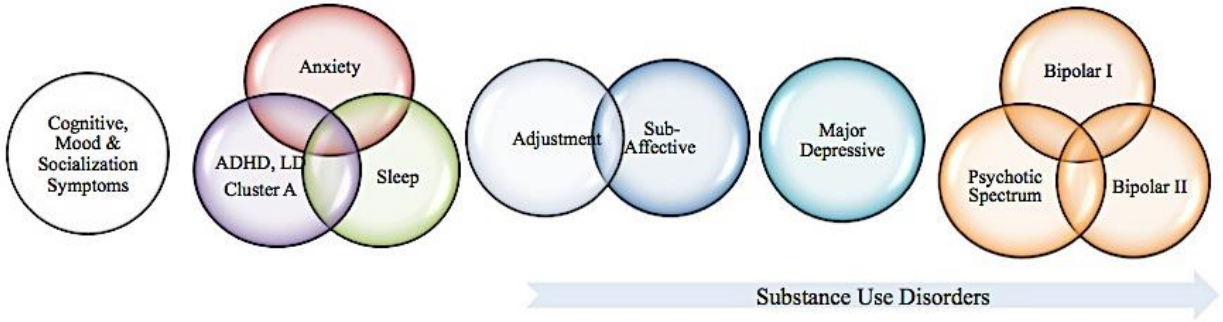
Duffy et al., 2010

# Clinical trajectory into BD by subtype

## Offspring of Lithium Responsive BD Parents




## Offspring of Lithium Non-Responsive BD Parents




Duffy et al., BJP 2014

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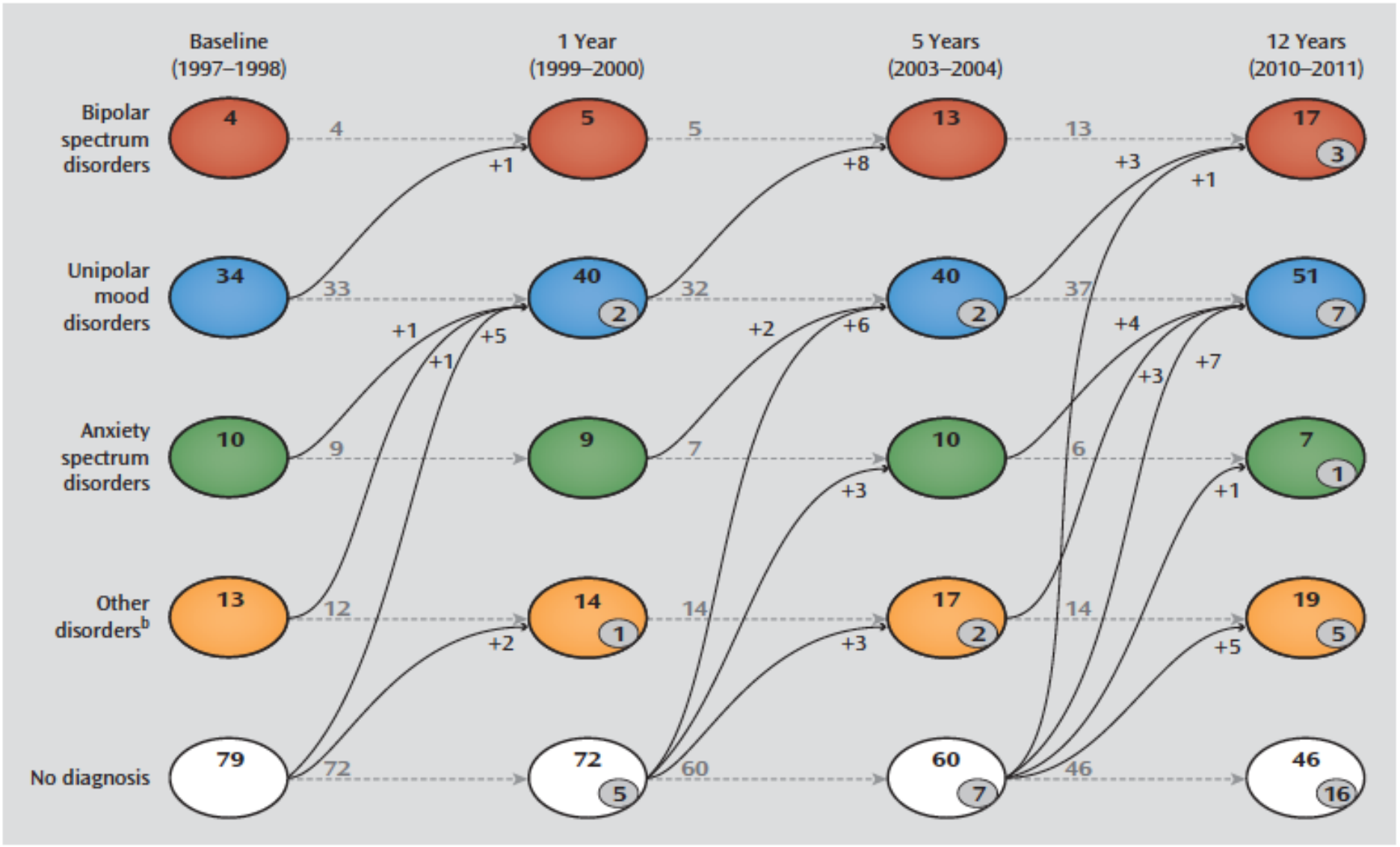
# Independent offspring studies from around the world

| Study | Risk of Bipolar Disorder | Polarity of index BD episode | Age onset Bipolar Disorder | Risk of Pre-pubertal Hypo/mania |
|---|---|---|---|---|
| ***Duffy et al., 2014*** | 13.5% BD:<br>7.3% BDnos<br>9.7% BDI/II<br>4.8% SchizoBD | 84% depressive<br>16 ± 4 years | BDII<br>17 years<br>BDI<br>19 years | 0% < 12 years earliest<br>15 years BDI/II<br>13 years BDNos |
| ***Mesman et al., 2013*** | 13% BD:<br>11% BDI/II<br>1% SchizoBD<br>1% Cyclothymia | 88% depressive<br>15 ± 5 years | Hypomania<br>17 years<br>Mania<br>20 years | 0% < 12 years earliest 13y |
| ***Egeland et al., 2012*** | 7% BDI<br>39% risk +ve | 100% anxiety & depressive | Hypomania<br>18 years | 0% <12 years earliest 13y |
| ***Axelson et al., 2015*** | 19.1%BD:<br>8.4% BDI/II<br>10.7% BDNOS | 69% depressive<br>12.5 ± 4.6 years | Hypomania<br>13 years<br>BDNos<br>12 years | 53% < 12years<br>33% < 10 years<br>earliest 8 years |
| ***Nurnberger et al., 2011*** | 9% BDII, NOS | depression onset<br>12 year<br>(10.5-15.5) | Hypomania<br>16 y<br>Mania<br>13 years | 5%≤ 12years |
| ***Preisig et al. 2016*** | 12% BDII<br>17% BDS | 70% onset with depression | Hypo/mania<br>16 years | 19%≤ 12 years *<br>*5/6 cases had witnessed trauma |

Duffy et al., 2017

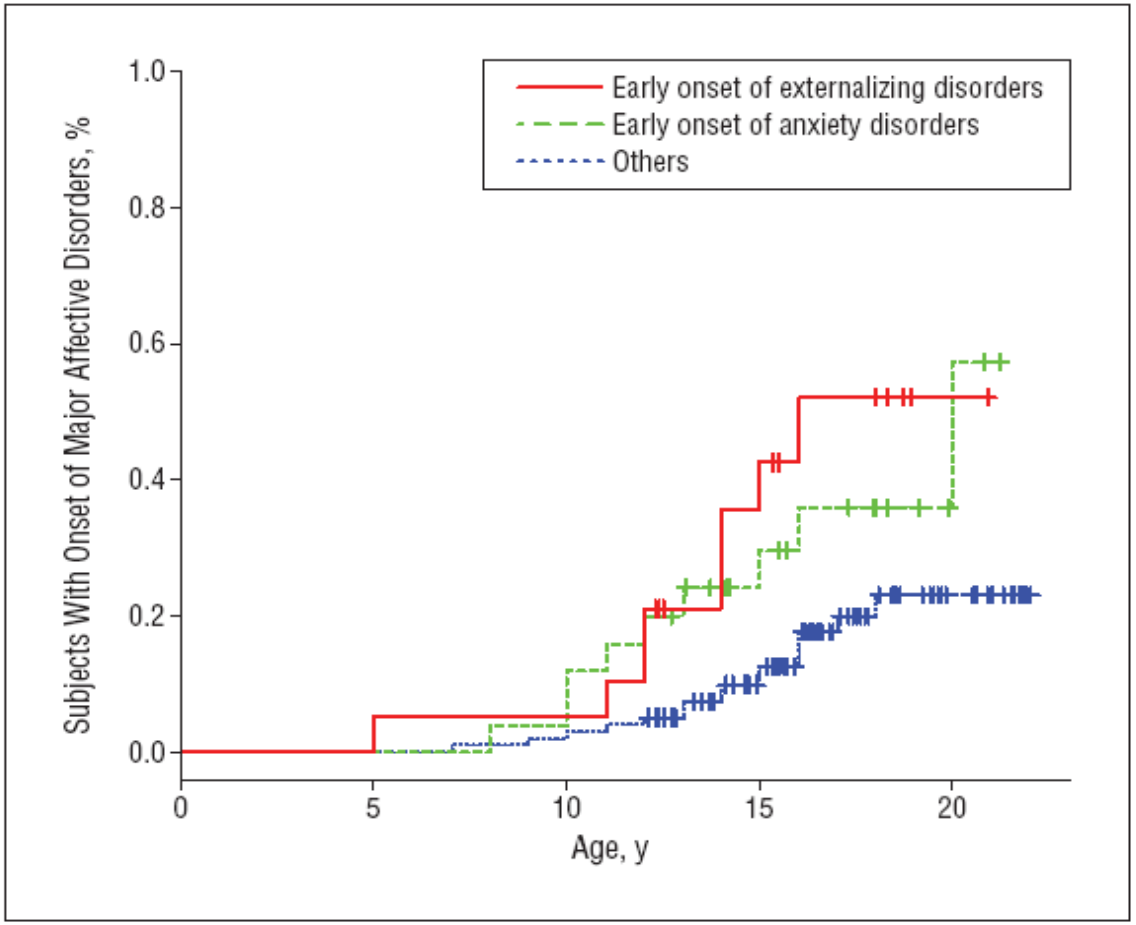
# Trajectory of psychopathology Dutch high-risk study

**FIGURE 2. Transition to Mood Disorders in the Dutch Bipolar Offspring Cohort (N=140)[a]**




Mesmen et al., 2013

# Risk of mood disorder in HR offspring with antecedent diagnoses dx




Nurnberger et al., 2011

# Early vs later age of onset parental BD and risk of bipolar disorder – Swiss offspring study

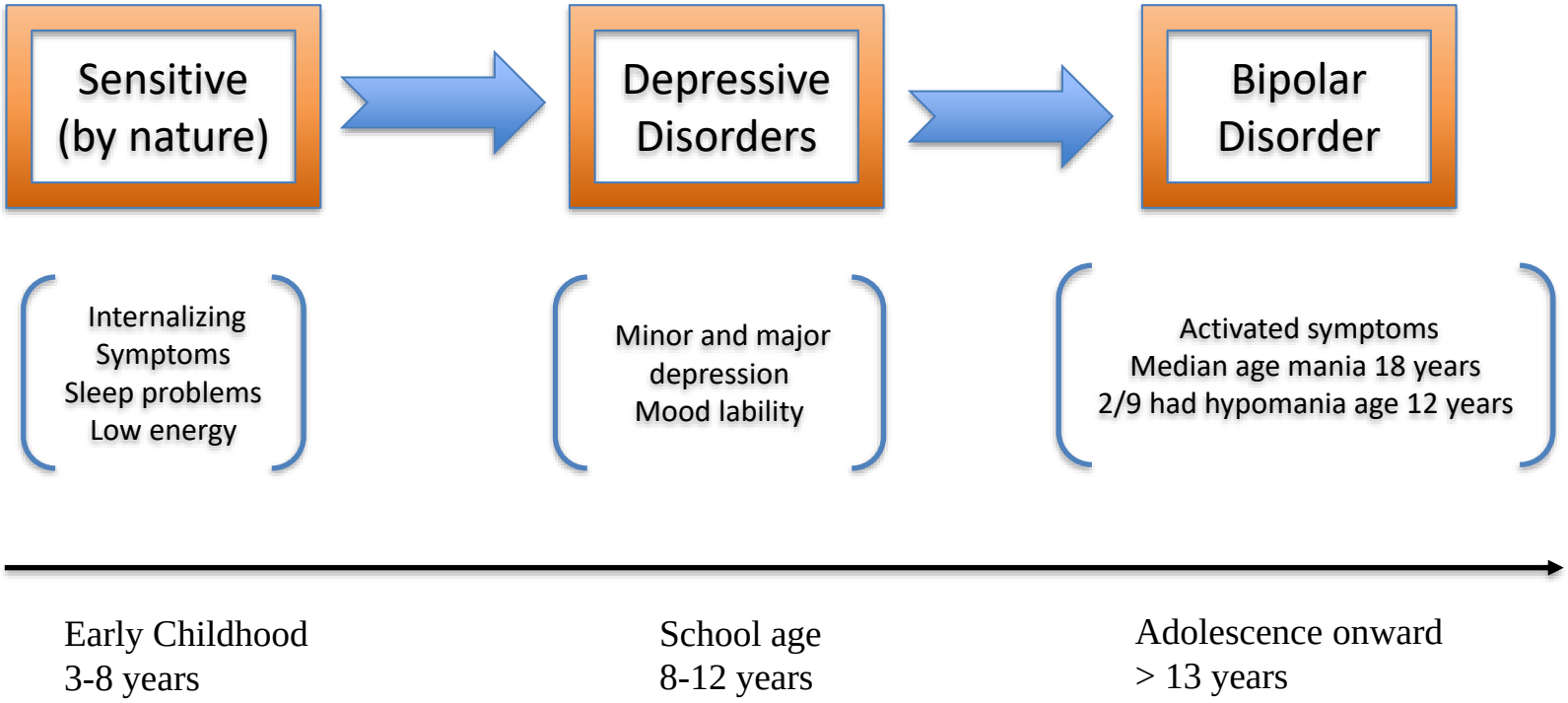
Rates (%) and risk (HR, 95CI) of lifetime psychiatric disorders in offspring ($N$=372) by proband mood disorder subtype.

| | **Proband disorder BPD subtypes** | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **Onset BPD < 21 yrs** | | | | **Onset BPD > 21 yrs** | | | |
| **Offspring *N*** | 52 | | | | 93 | | | |
| **Offspring disorder** | % | Model 1 HR 95CI | Model 2 HR 95CI | Model 3 HR 95CI | % | Model 1 HR 95CI | Model 2 HR 95CI | Model 3 HR 95CI |
| **Any mood disorder** | 65.4 | 1.3 (0.7,2.2) | 1.1 (0.6,1.9) | 1.1 (0.6,2.0) | 61.3 | 0.9 (0.6,1.4) | 0.8 (0.5,1.3) | 0.8 (0.5,1.3) |
| **Any BPD** | 26.9 | **15.3*** (3.3,70.2)** | **7.9* (1.6,39.1)** | **7.9** (1.8,34.6)** | 11.8 | 2.3 (0.5,9.9) | 1.8 (0.4,8.3) | 1.4 (0.3,6.1) |
| BPD | 21.2 | **15.3*** (3.3,70.2)** | **7.9* (1.6,39.1)** | **7.9** (1.8,34.6)** | 7.5 | 2.3 (0.5,9.9) | 1.8 (0.4,8.3) | 1.4 (0.3,6.1) |
| OSBARD[b] | 5.8 | – | – | – | 4.3 | – | – | – |

Preisig et al., 2016

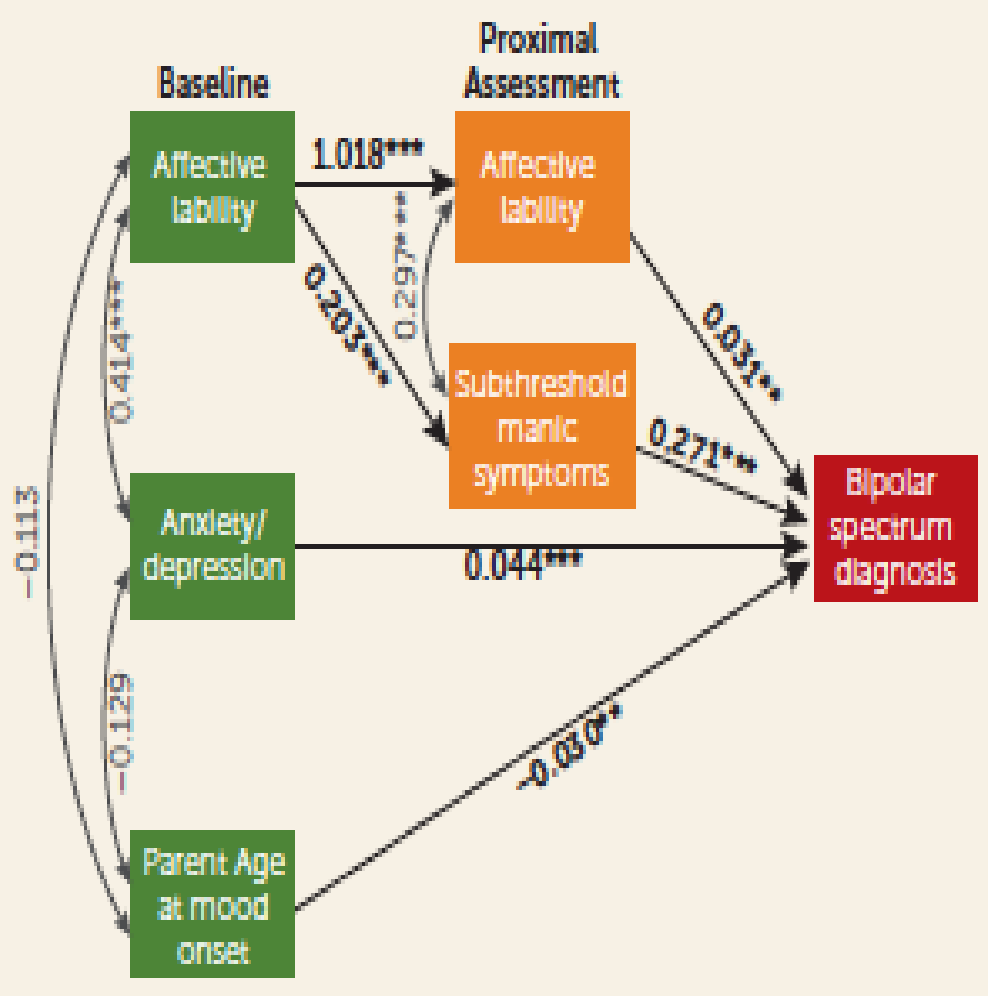
Flourish
Mood Disorders Research

# Trajectory into bipolar disorder
# Amish offspring of bipolar parents study



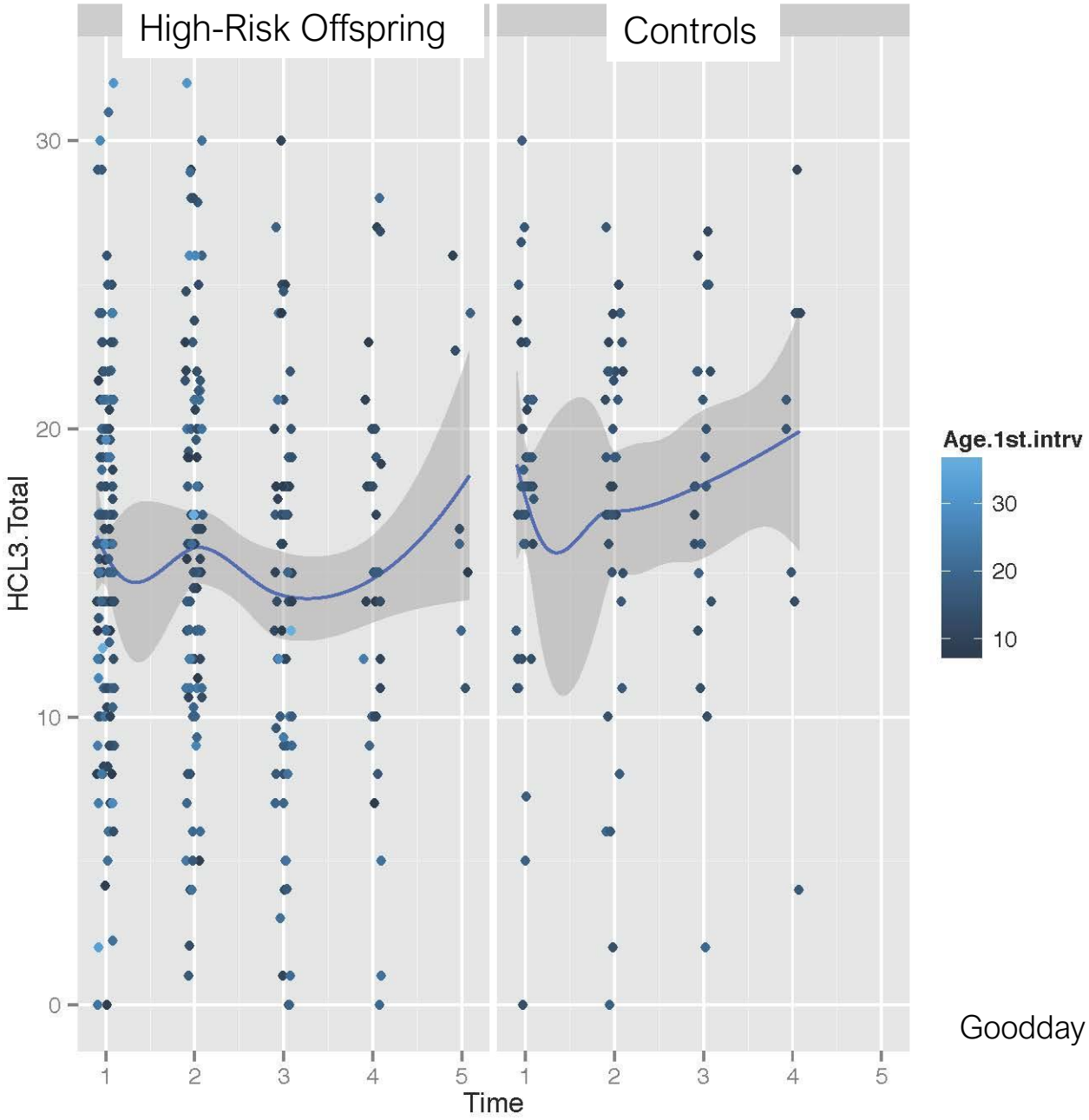

Egeland et al., 2013

# Significant predictors of new onset BD spectrum disorders in high-risk offspring BIOS



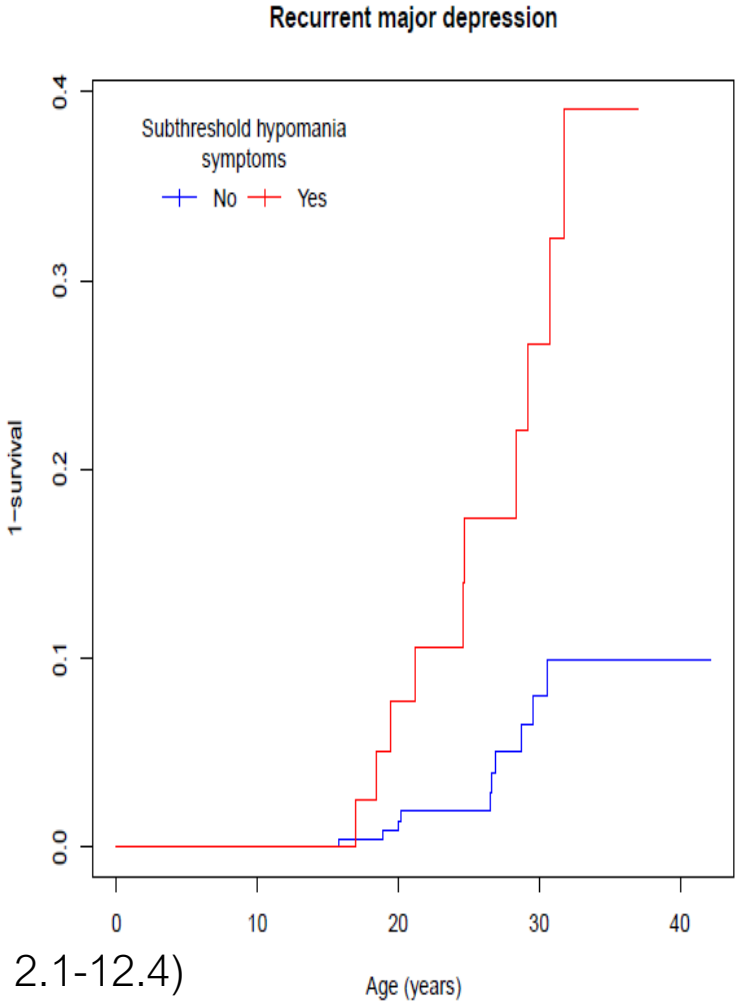

Hafeman et al., 2016

# Self-report manic symptoms




Goodday et al., 2017

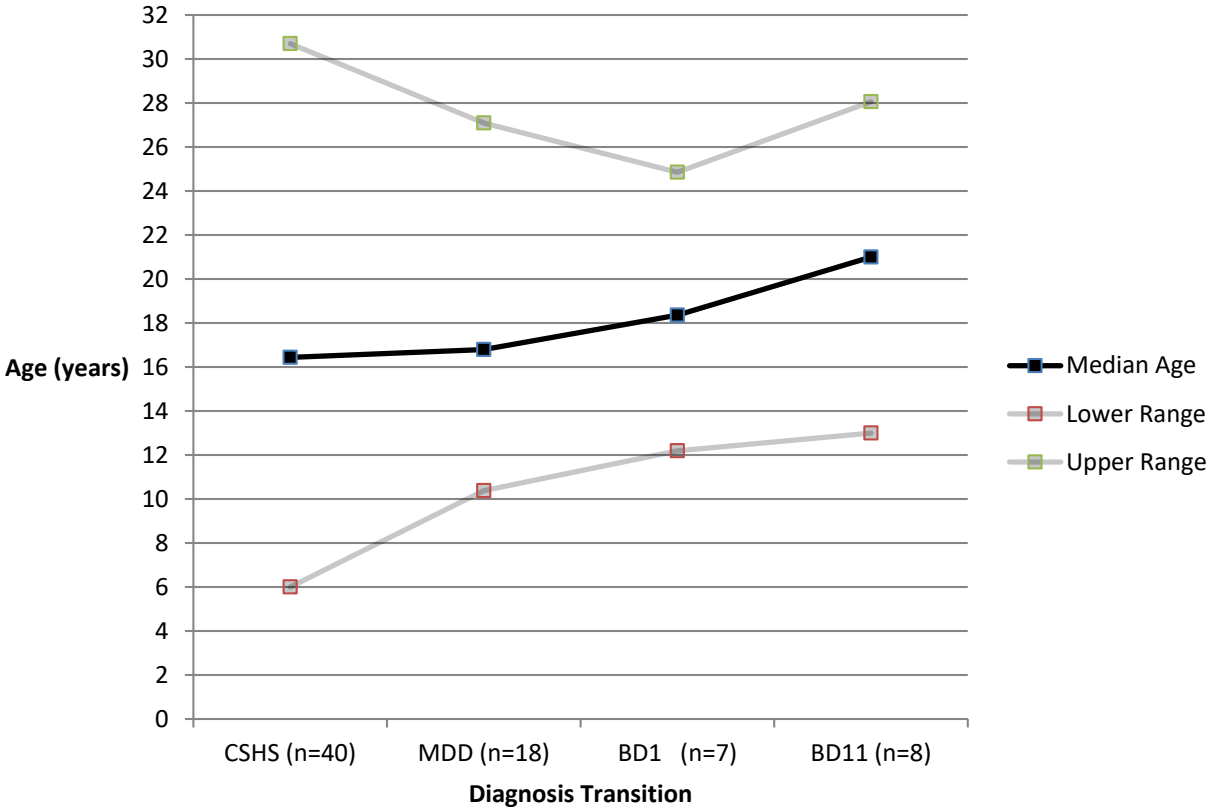
# The hazard of recurrent major depression in high-risk offspring with and without clinically significant hypomanic symptoms




Hazard ratio: 5.1 (95%CI: 2.1-12.4)

Goodday et al, 2017

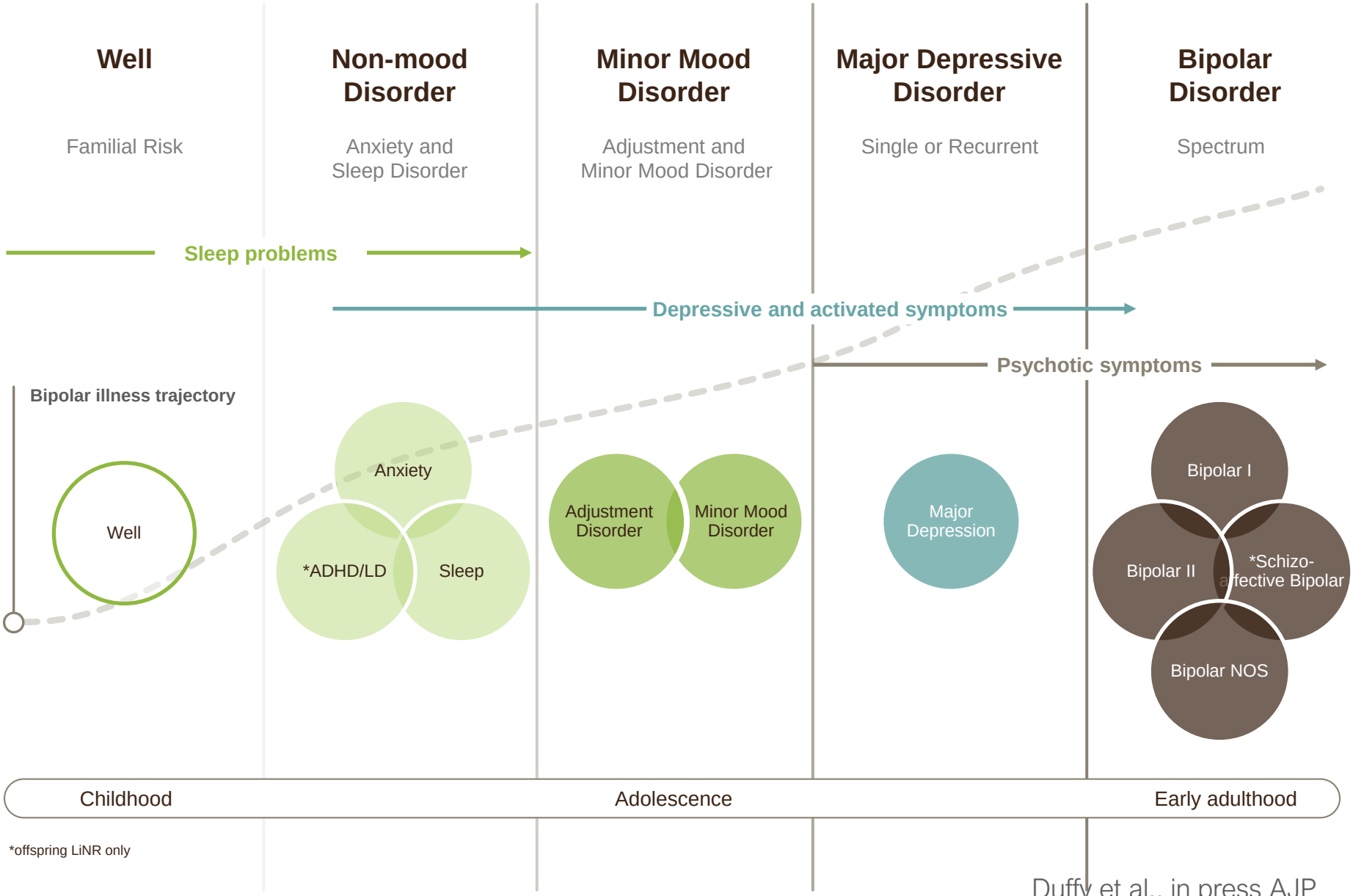
# Median age of onset of clinically determined hypomanic symptoms, MDD, and BD in high-risk offspring




Median age onset CSHS 16.4 yrs (6-30 years)

Goodday et al. 2017

# Trajectory of emerging bipolar disorder in high-risk offspring




*offspring LiNR only

Duffy et al., in press AJP

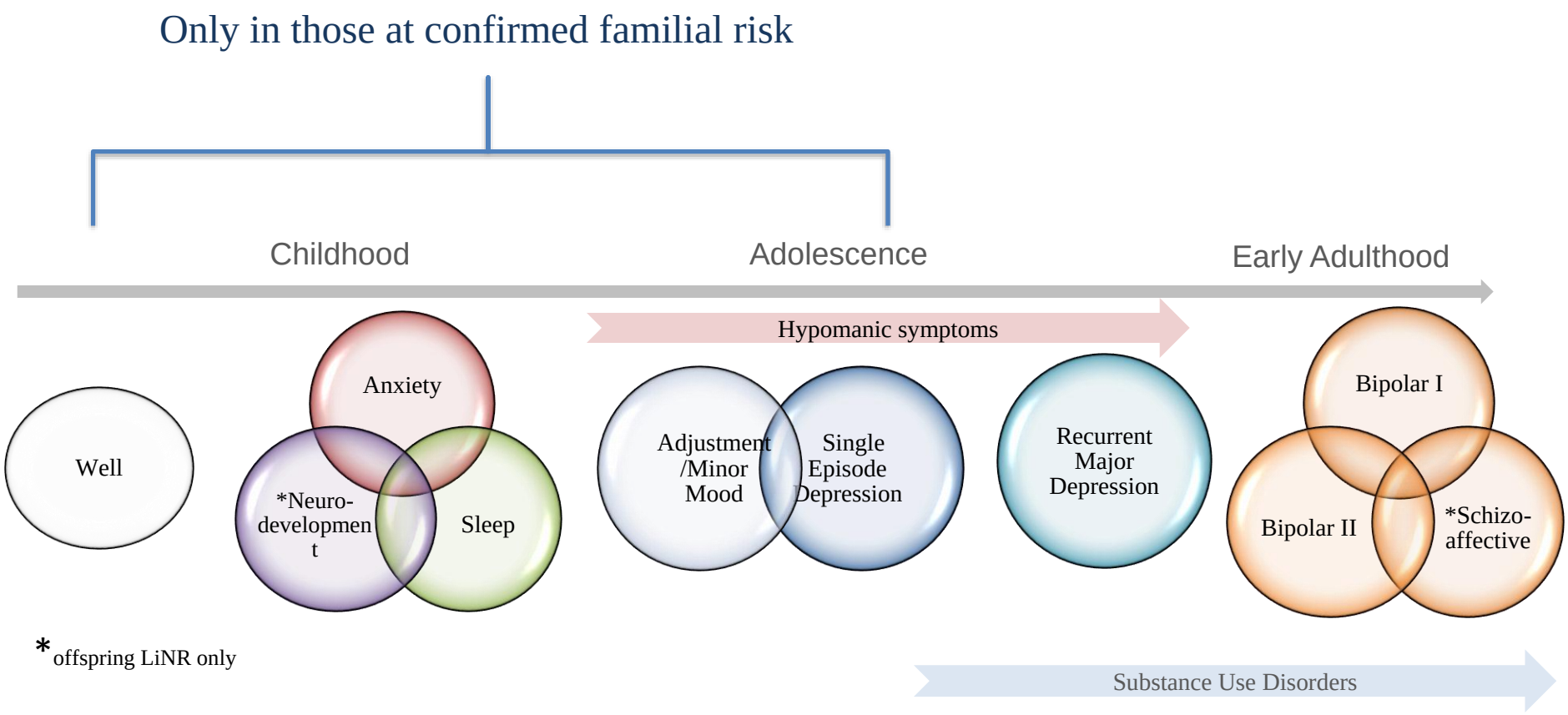
## Learning Objectives

1. Highlight background rationale for high-risk studies

2. Present findings from high-risk studies that advance understanding of the trajectory of emerging bipolar disorder

3. Discuss implications & future directions

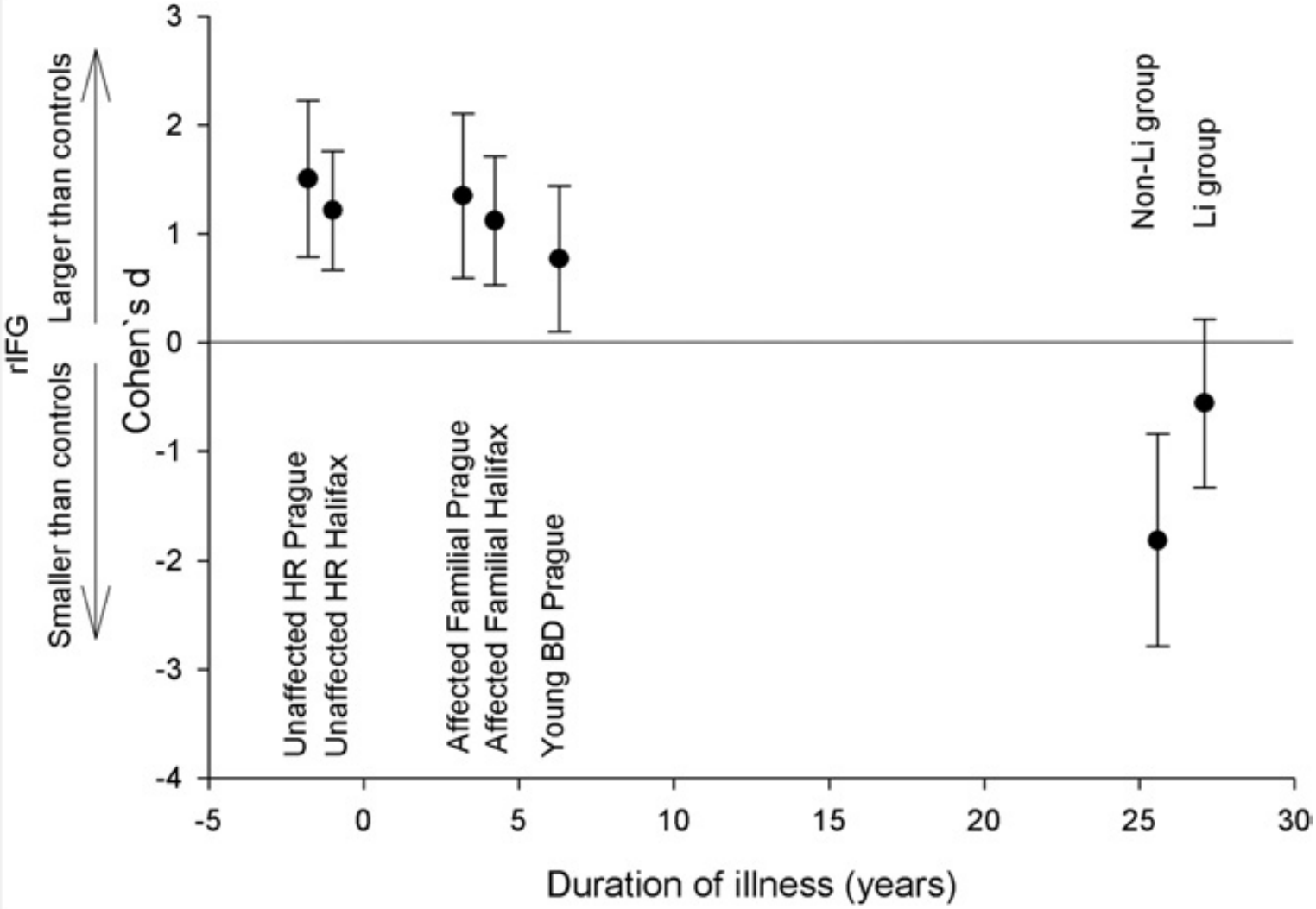
# Developmental approach: Mapping the trajectory of bipolar disorder




-map changes in biological markers and risk processes
-identifying prevention and intervention opportunities
-risk prediction

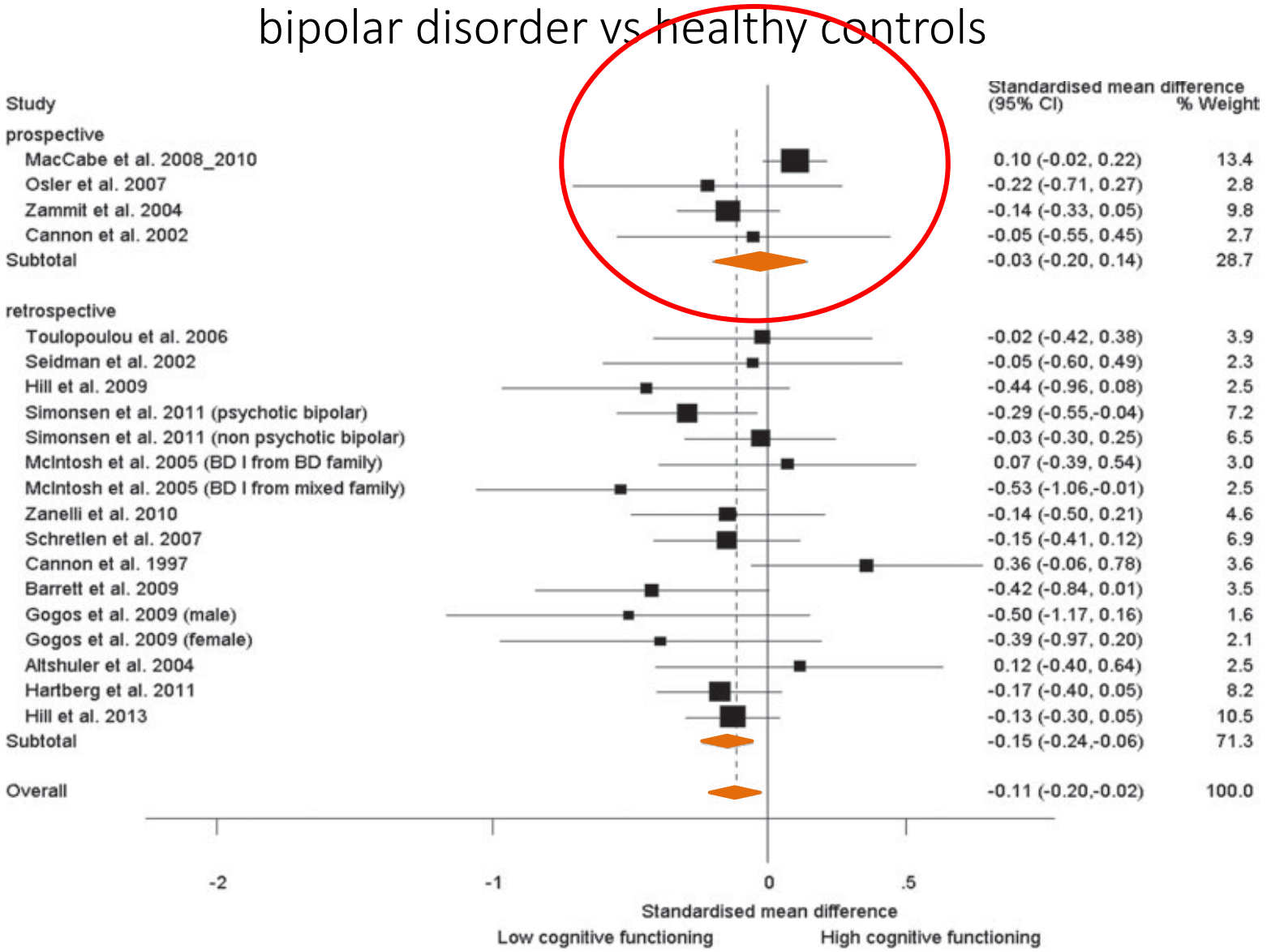
Duffy, EBMH 2015

# Differences in the rIFG volumes between high-risk and clinical groups



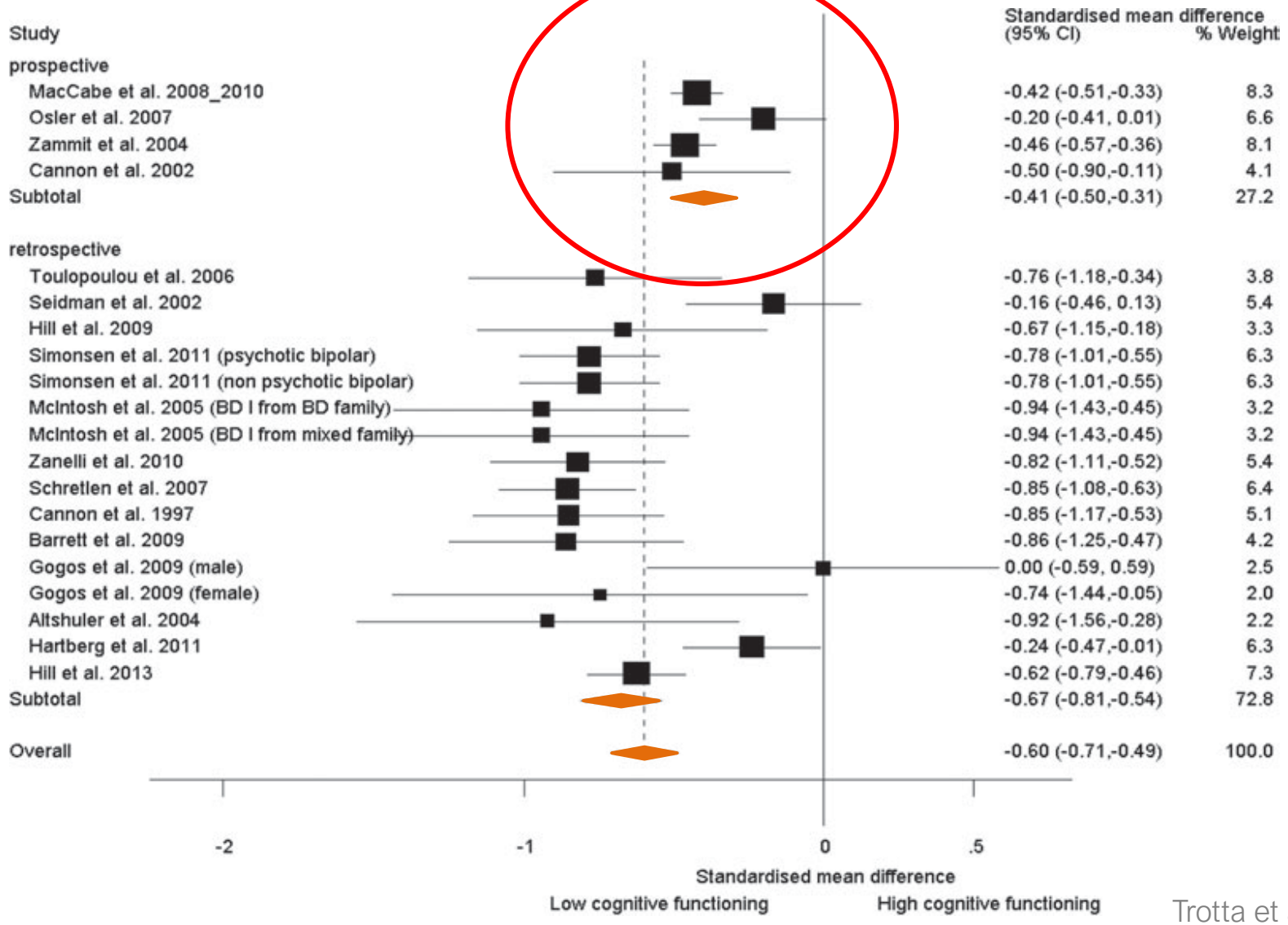

Hajek et al., 2013

# Premorbid cognitive functioning in children who develop bipolar disorder vs healthy controls



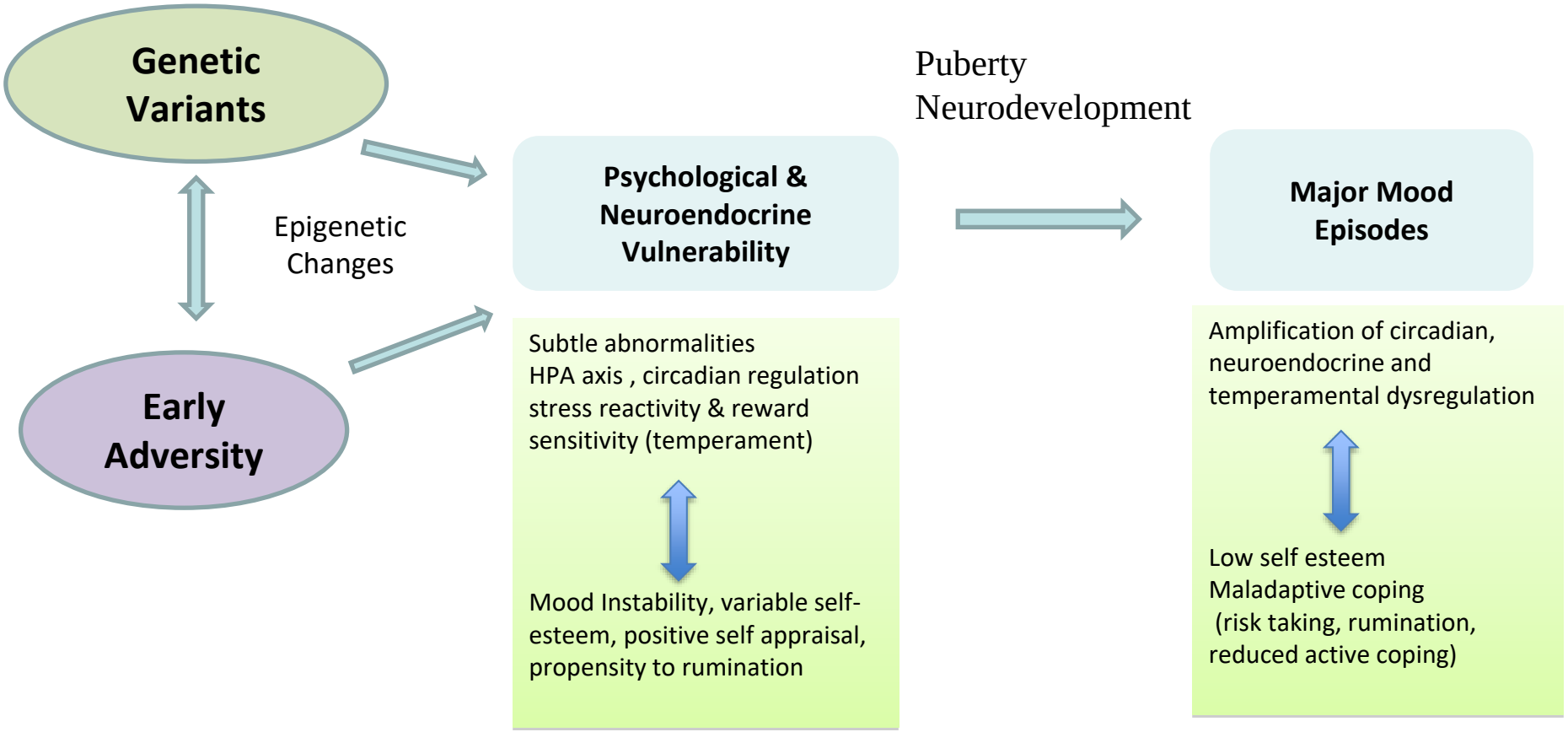

Trotta et al., 2015

# Pre-morbid cognitive functioning in children who develop schizophrenia vs healthy controls

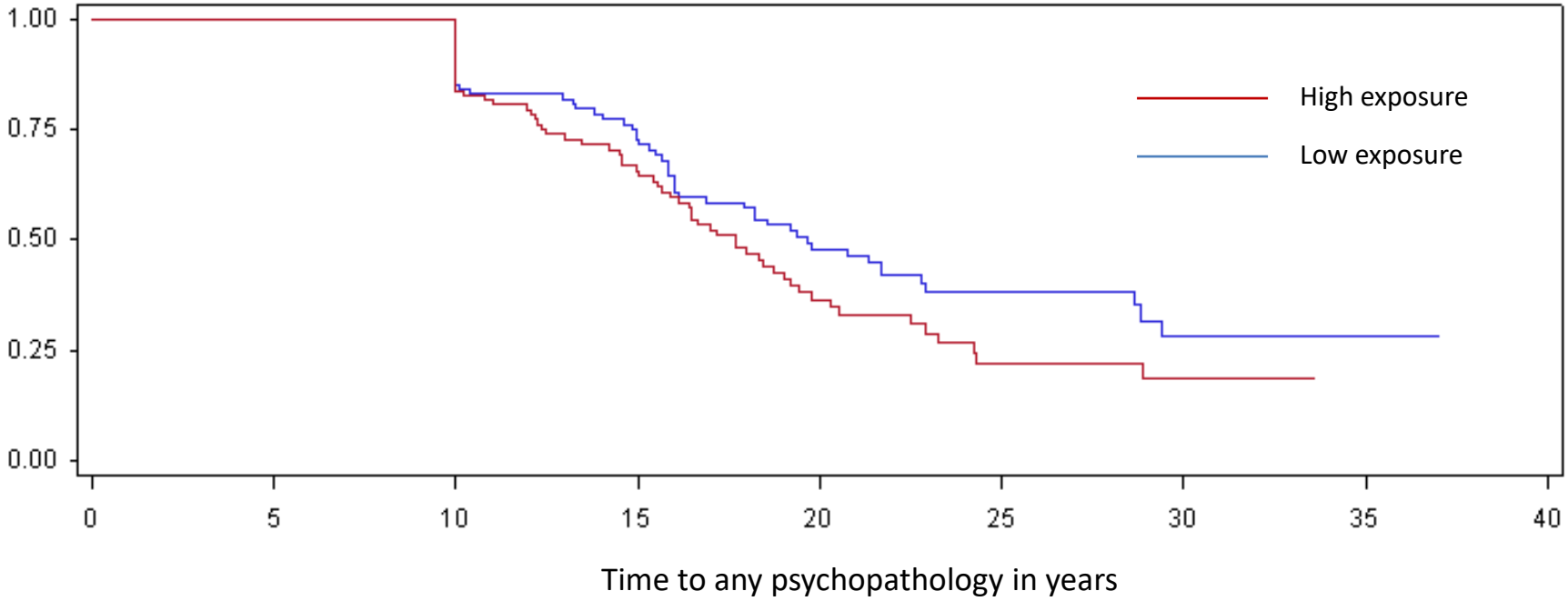



Trotta et al., 2015

# Biological and psychological risk factors determining mood disorder in high-risk offspring



# Time to any psychopathology* with high vs low exposure to parental bipolar illness during childhood




*High exposure 0-2 years of life significantly associated with mood disorder

Goodday et al., 2016

# Early environmental and psychosocial predictors of mood disorder in HR offspring

| | | Unadjusted | | Adjusted+ | |
|---|---|---|---|---|---|
| | | HR | 95%CI | HR | 95%CI |
| Affected Parent | | 1.3 | 0.9-2.1 | 0.9 | 0.5-1.5 |
| Lithium Response | | | | | |
| High Exposure | | 1.2 | 0.8-1.8 | 1.1 | 0.7-2.0 |
| Life Events | | 1.2 | 1.0-1.4 | 1.2 | 1.0-1.5* |
| Parental Neglect | Mother | 1.1 | 1.1-1.2 | 1.1 | 1.0-1.2* |
| Score* | Father | 1.0 | 1.0-1.1 | 1.0 | 0.9-1.0 |
| Parental Antipathy | Mother | 1.0 | 1.0-1.1 | 1.0 | 0.9-1.0 |
| Scored | Father | 1.0 | 1.0-1.1 | 1.0 | 1.0-1.1 |
| Offspring emotionality** | | 1.9 | 1.3-2.8 | 1.7 | 1.0-3.1* |

+ adjusted for sibling correlation and sex

- <5% moderate-severe neglect – mostly mild

** interaction between perceived neglect x temperament predicting mood disorder

Doucette et al., 2014

Flourish Mood Disorders Research

# Effect of mood and self-esteem on response style

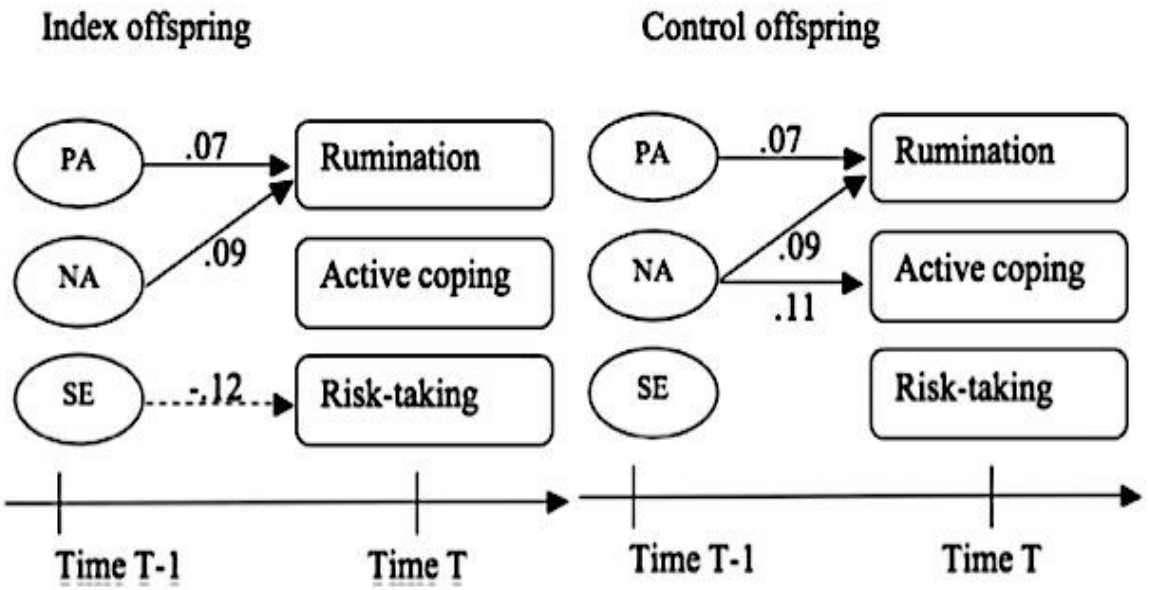
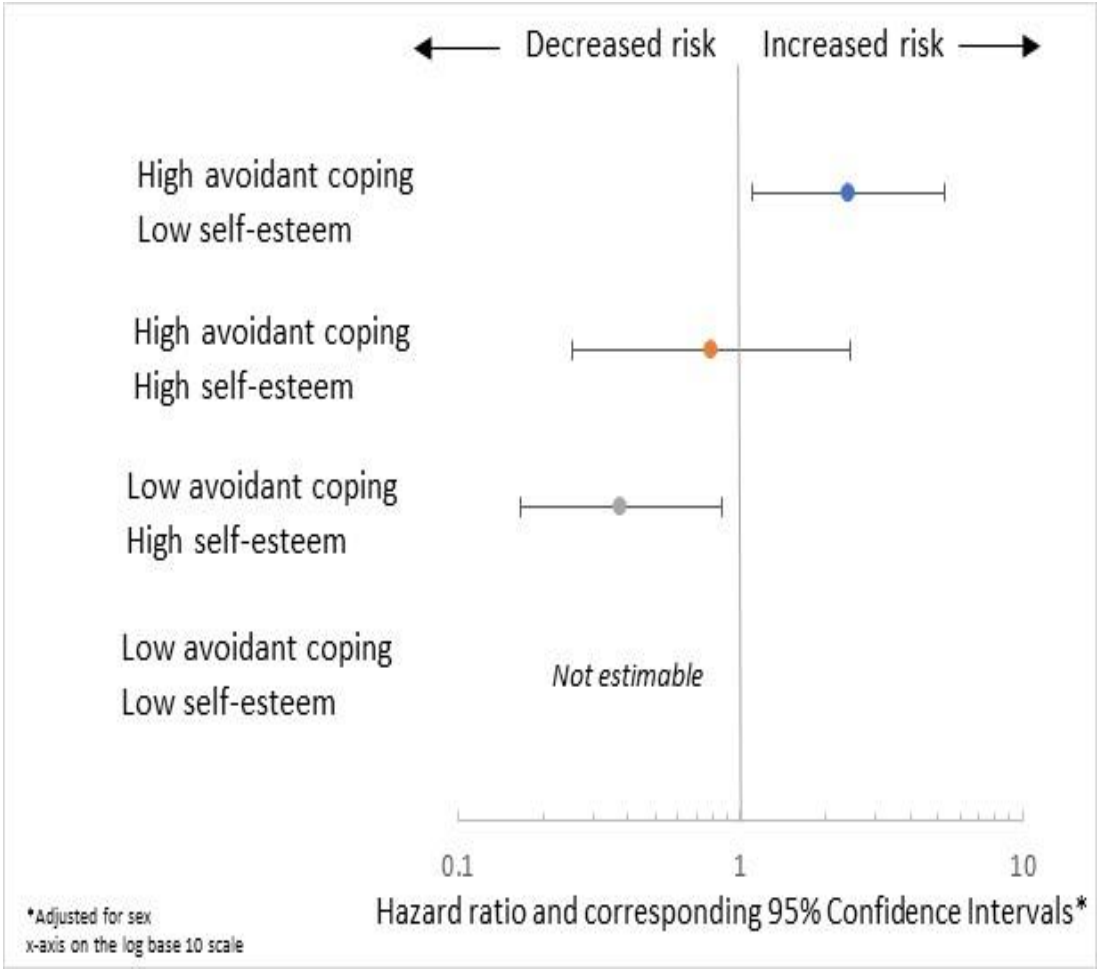



**Fig. 1.** Effect ($\beta$) of mood and self-esteem on response styles at the subsequent time point in index and control offspring. Full line indicates positive relationship, dashed line indicates negative relationship. PA=positive affect; NA=negative affect; and SE=Self-esteem.

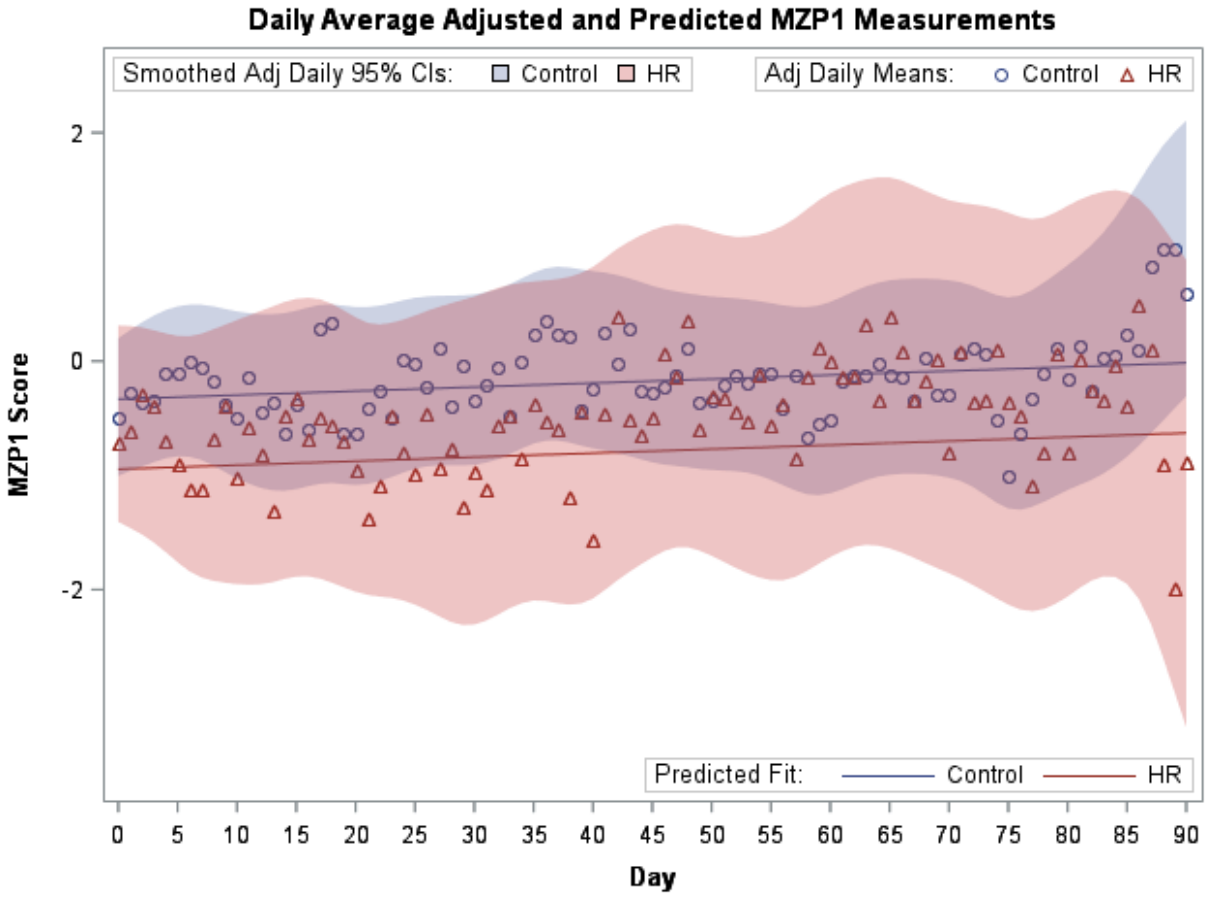
Pavilickova et al., 2015

# Risk of mood disorder in high-risk offspring associated with self-esteem and avoidant coping




Goodday et al., in press

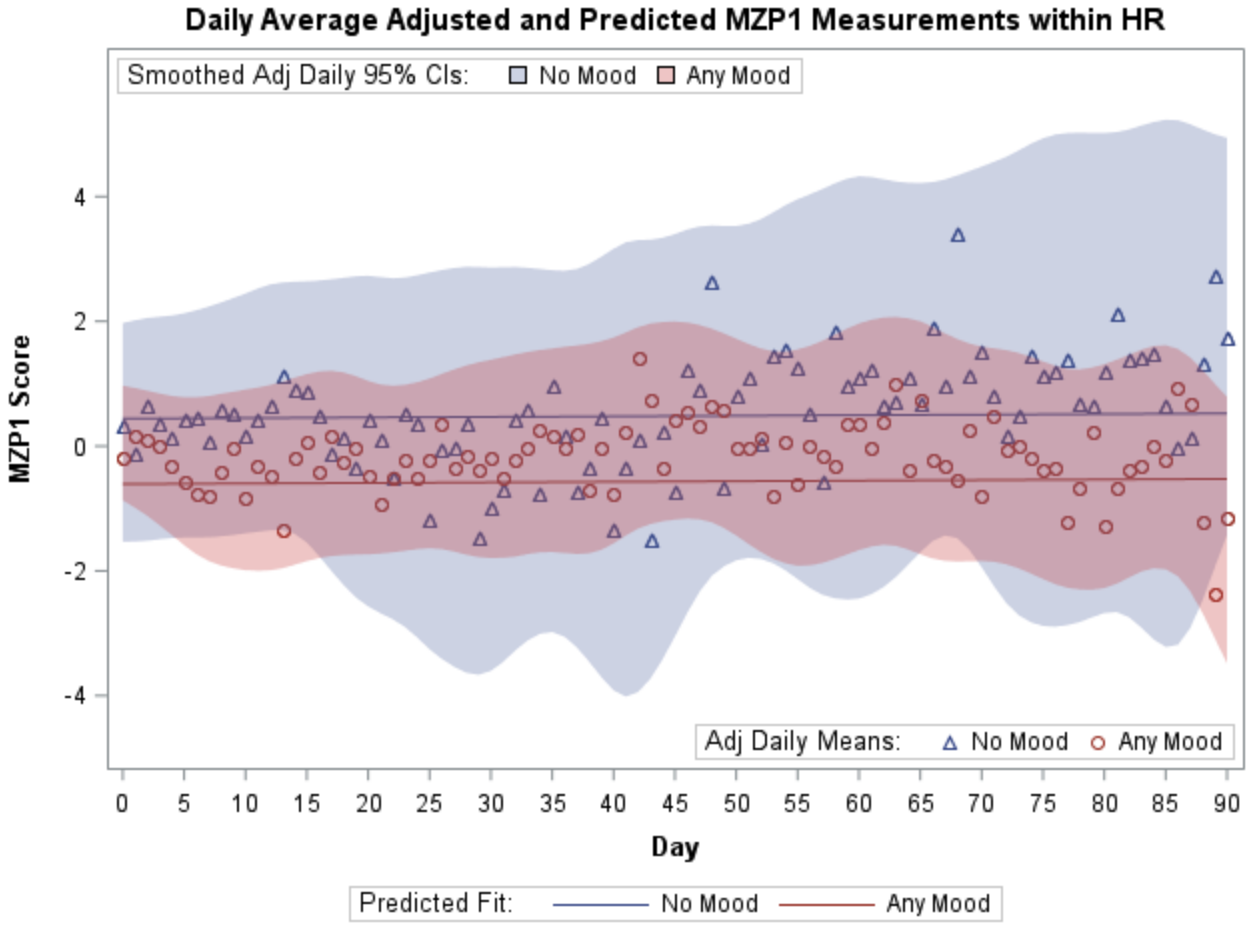
# Adjusted daily ratings* in high-risk offspring compared to controls over 90 days




*higher score: higher positive affect, lower negative affect and higher self-esteem adjusted for day of week, season, age and sex

Duffy et al, submitted

# Adjusted daily ratings* in HR offspring with compared to those without prior mood diagnosis




higher score: higher positive affect, lower negative affect and higher self-esteem
adjusted for day of week, season, age and sex

Duffy et al, submitted

# Stepped approach to intervention mapping to bipolar illness trajectory

| | | |
|---|---|---|
| 0 | Well at genetic risk | ○ Optimize nutrition, sleep, exercise and relaxation routines<br>○ Education*<br>○ Healthy coping strategies** |
| 1 | Non-specific anxiety & sleep disorders | ○ Cognitive and supportive psychotherapy<br>○ Healthy coping strategies**<br>○ Consider nutraceuticals (ie omega fatty acids)/ antioxidants<br>○ Consider short term sleep aids (ie. melatonin) |
| 2 | Subaffective & adjustment disorders | ○ Psychotherapy***<br>○ Optimize nutrition, sleep, exercise and relaxation routines<br>○ Healthy coping strategies**<br>○ Nutraceuticals (ie. omega 3 fatty acids)/antioxidants |
| 3 | Major depression | ○ Psychotherapy***<br>○ Substance use avoidance<br>○ Healthy coping strategies<br>○ Nutraceuticals/antioxidants<br>○ For refractory or moderate to severe depression consider either short-term closely monitored antidepressant<br>If psychosis add short-term low dose atypical<br>OR<br>Consider selected mood stabilizer****<br>○ If prominent suicidal thoughts consider lithium either as adjunct or monotherapy |
| 4 | Bipolar Disorder | ○ Selected mood stabilizer****<br>○ Psychotherapy***<br>○ Psychoeducation<br>○ Family education & support<br>○ Healthy coping strategies**<br>○ Long-term follow-up in specialty clinic |

Duffy, 2014

# Response to maintenance treatment in BD offspring

| Clinical Course | Mood Disorder Onset (Yrs.) | Major Lifetime Episodes | Start of Treatment (age in yrs) | Start of Adequate Treatment (age in yrs) | Parent Treatment Response | Stabilizing Offspring Treatment |
|---|---|---|---|---|---|---|
| Episodic | 19 | 4 | 25 | 32 | LiR | Li |
| Episodic | 18 | 3 | 20 | 21 | LiR | Li |
| Episodic | 16 | 3 | 18 | 19 | LiR | Li |
| Episodic | 16 | 5 | 19 | 19 | LiR | Li |
| Episodic | 15 | 7 | 22 | 27 | LiR | Li |
| Episodic | 13 | 5 | 23 | 25 | LiR | Li |
| Episodic | 25 | 2 | 25 | 27 | LiR | ANC |
| Episodic | 11 | 6 | 17 | 19 | LiR | Li |
| Episodic | 16 | 4 | 17 | 19 | LiR | Li |
| Episodic | 16 | 3 | 24 | 24 | LiR | Li |
| Chronic | 15 | Chronic | 22 | 24 | LiNR | ATP |
| Chronic | 13 | Chronic | 14 | 19 | LiNR | ATP |
| Chronic | 18 | Chronic | 21 | 21 | LiNR | ATP |
| Chronic | 18 | Chronic | 20 | 20 | LiNR | ATP |
| Chronic | 18 | Chronic | 19 | 24 | LiNR | ANC |

Duffy et al, 2007

# Summary Remarks

- Longitudinal studies of high-risk offspring have advanced understanding of bipolar illness onset
- The illness evolves over development in a predictable sequence - but is heterogeneous
- Trajectory of classical bipolar disorder (ie LiR) is different from schizophrenia, although there is overlap in more psychotic BD subtypes (ie LiNR)
- There maybe a prototypical trajectory in more homogenous subtypes essential for research into etiology and to identify specific intervention targets
- Individualized risk prediction and treatment are a work in progress as is the question of staging

Towards Optimal Brain and Psychosocial Development

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