# Variabilità ed insidie dell'esordio Bipolare

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# Note Storiche

**1898 Beach** descrive il caso di un ragazzo di 13 anni che "..*essendo pigro e ottenendo scarsi risultati scolastici era caduto in melanconia ed aveva provato ad uccidersi. La melanconia si alternava alla mania durante la quale il ragazzo fischiava e cantava giorno e notte… "*

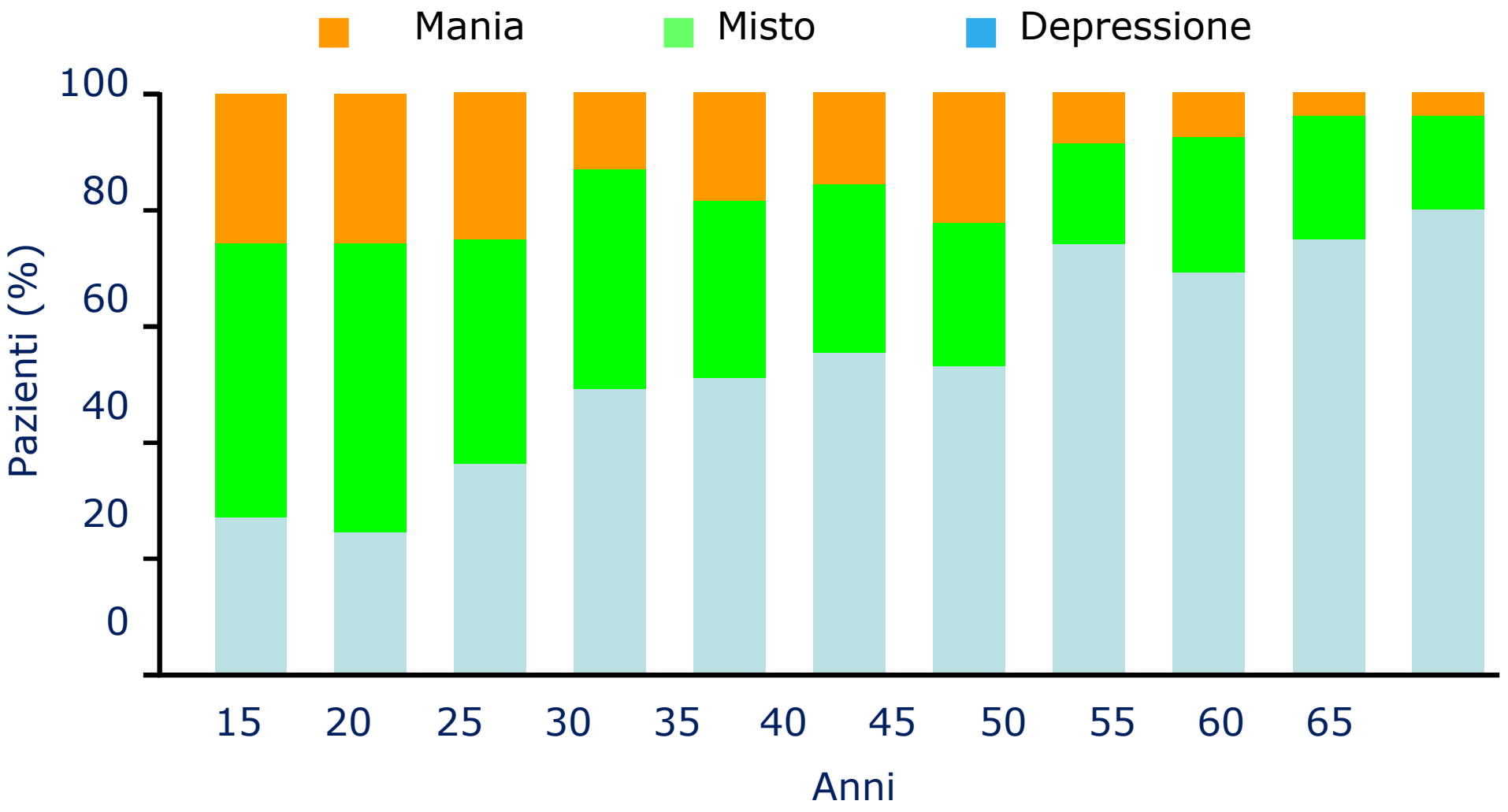
***1902-1906 Theodore Ziehen*** *in Germania effettua il primo lavoro di raccolta sistematica di dati sulla psichiatria infantile (intesa fino ai 15 anni). Descrive così i ragazzi con malattia maniaco-depressiva "tra i sintomi una particolare giocosità è il preminente…spesso i ragazzi non possono smettere di ridere per ore. Questa giocosità rimane presente anche se il ragazzo prova dolore o è corretto o criticato. Comunque non è raro che si associ con rabbia e in alcuni casi con attacchi di rabbia violenti. Il pensiero è accellerato, con fuga delle idee, il discorso continuo. […] Ogni stimolo sensoriale è fonte di distrazione dalle occupazioni. Correlata a questa aumentata attività psicomotoria vi sono disturbi del sonno, spesso insonnia completa. I deliri sono più frequenti rispetto ai disturbi della percezione, e sono spesso caratterizzati da idee di grandezza. Più spesso comunque la grandezza si presenta con atteggiamenti di sfida verso l'autorità genitoriale o nei confronti degli insegnanti con piani fantastici per il futuro.*

# Note Storiche

**1921 Kraepelin** nel suo testo “Malattia maniaco depressiva e paranoia” riferisce che la maggior parte degli esordi del disturbo (bipolare) appaiono compresi tra i 15 e i 20 anni e solo lo 0.4% appaiono precedenti ai 10 anni. Non è chiaro se fosse venuto in contatto direttamente con questi soggetti o se questi dati fossero riferiti da pazienti bipolari adulti

**1930-35 Kanner** descrive differenti pattern di malattia maniaco-depressiva in bambini e adolescenti. Effettua una differenziazione in base al decorso e all’alternanza degli episodi

# Stato dell'umore al ricovero ed età dei pazienti (N= 899)




Kraepelin E. Manic-Depressive Insanity and Paranoia. Edinburgh, Scotland: ES Livingstone, 1921:169

Eur Psychiatry. 2018 May 4;52:61-67. doi: 10.1016/j.eurpsy.2018.04.002. [Epub ahead of print]

# Secular trends in the age at onset of bipolar I disorder - Support for birth cohort effects from interational, multi-centre clinical observational studies.

Scott J[1], Etain B[2], Azorin JM[3], Bellivier F[2].

Author information

## Abstract

**OBJECTIVE:** To examine any association of birth decade, sex and exposure to alcohol and/or substance use disorders (ASUD) with age at onset (AAO) of bipolar I disorder (BD-I).

**METHODS:** Using data from a representative clinical sample of 3896 BD-I cases recruited from 14 European countries, we examined AAO distributions in individuals born in consecutive birth decades. Cumulative probabilities with Mantel-Cox log-rank tests, pairwise comparisons and Odds Ratios (OR) with 95% confidence intervals (95% CI) were employed to analyze AAO according to birth decade, sex, and presence or absence of an ASUD.

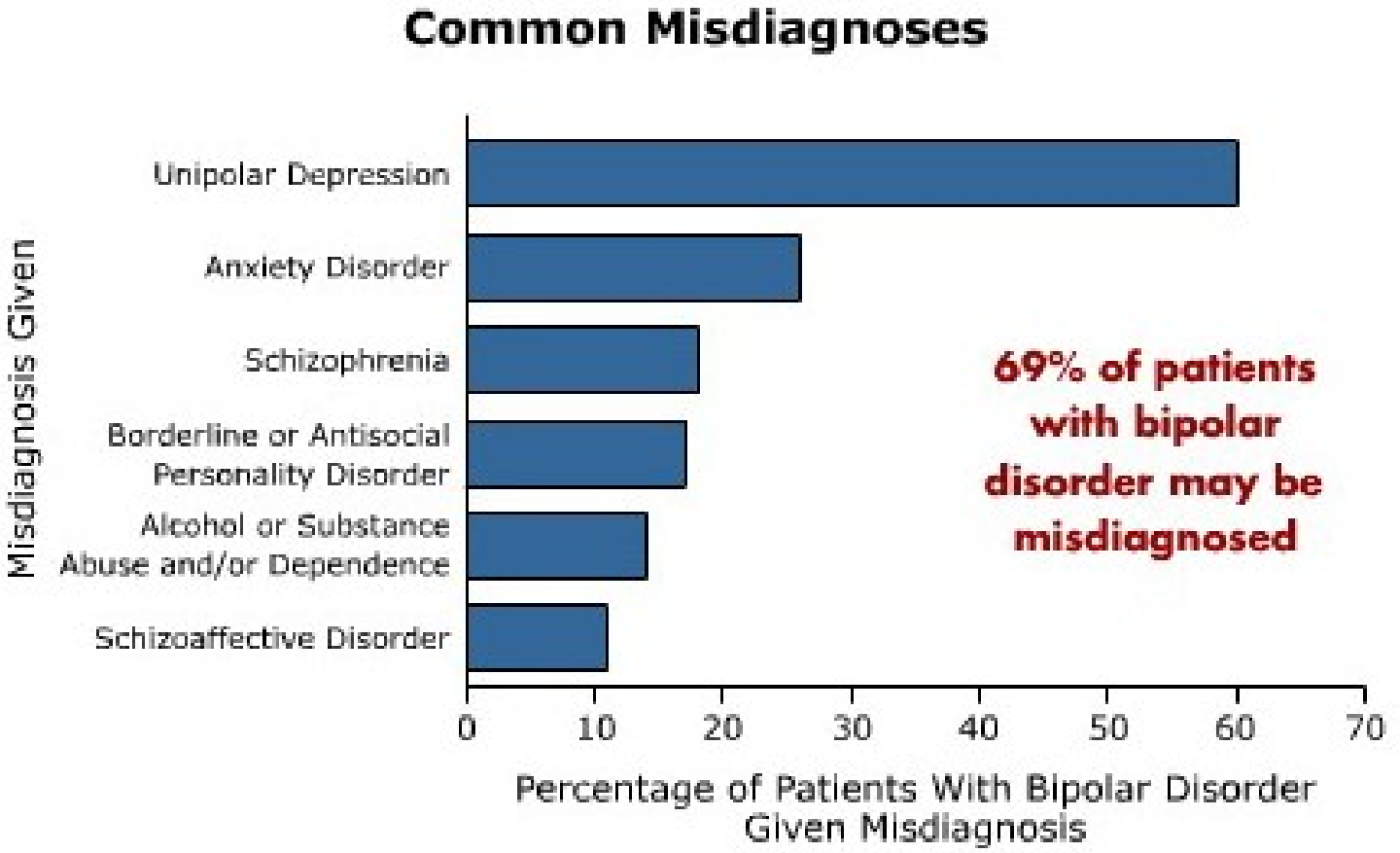
**RESULTS:** In the total sample, median AAO of BD-I decreased from about 41 years for those born in the 1930s to about 26 years for those born in the 1960s. In a sub-sample of 1247 individuals (selected to minimize confounding), AAO significantly decreased for males and females born in each consecutive decade between 1930 and 50 (OR: 0.65; 95% CI: 0.51, 0.81), and for cases with an ASUD as compared to without (OR: 0.77, 95% CI: 0.69, 0.87). The best fitting regression model identified an independent effect for each birth decade and an interaction between ASUD status and sex, with a consistently earlier AAO in males with an ASUD (OR: 0.79: 95% CI: 0.70, 0.91).

**CONCLUSIONS:** In BD-I cases diagnosed according to internationally recognized criteria and recruited to pan-European clinical observational studies, the AAO distributions are compatible with a birth cohort effect. A potentially modifiable risk factor, namely ASUD status, was associated with the observed reduction in AAO, especially in males.

# SFIDE DIAGNOSTICHE NEL DISTURBO BIPOLARE

Spesso non riconosciuto
Spesso mal diagnosticato
Spesso inadeguatamente trattato
Spesso aggravato da trattamenti sbagliati

# Errata diagnosi di Disturbo Bipolare




ECM Seminar, J Clin Psychiatr 2009

# Diagnosi differenziale, l'età critica


Why do many psychiatric disorders emerge during adolescence?

***T. Paus et al., Nature Rev. December 2008***

Received: 10 March 2017 | Accepted: 9 December 2017

DOI: 10.1111/bdi.12604

REVIEW

WILEY BIPOLAR DISORDERS

# Clinical staging model in offspring of parents with bipolar disorder: a systematic review

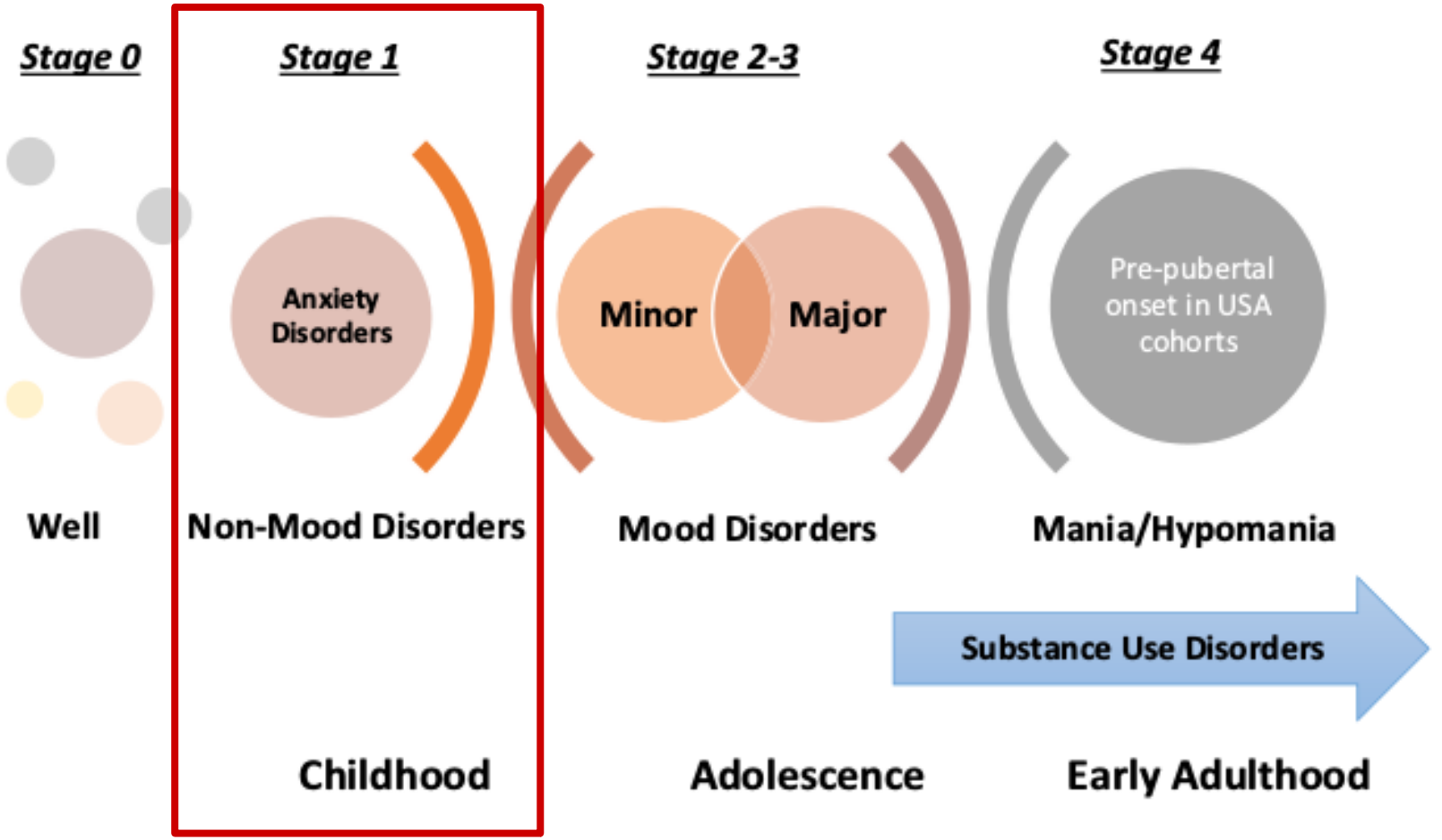
Aigli Raouna | Cemre Su Osam | Angus MacBeth

Review sistematica di 26 studi per identificare i rischi ed i sintomi precoci dello sviluppo di disturbo bipolare nella prole di pazienti affetti da disturbo bipolare.

In letteratura, studi su familiarità (parenti primo grado, gemelli mono/dizigoti, adottati) indicano un grado di ereditarietà fino all'85% nei gemelli monozigoti ed una prevalenza 5-10 volte più alta di DB nei figli di pz affetti da disturbo bipolare (un solo genitore affetto), rispetto alla popolazione generale.

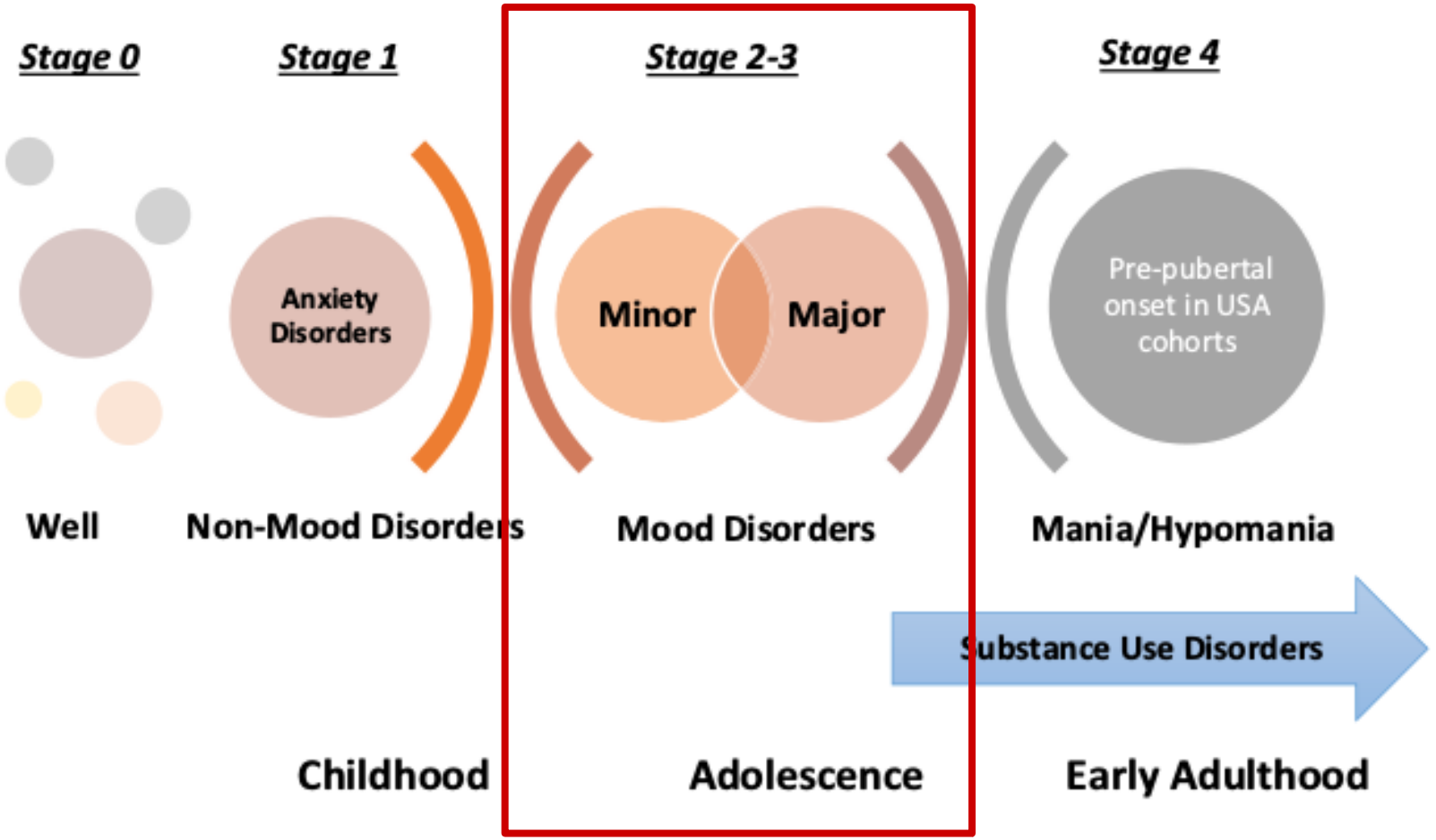
I figli con entrambi i genitori con diagnosi di disturbo bipolare mostrano un rischio di 5,7 volte maggiore di sviluppare DB rispetto a coloro con un solo genitore affetto. **Rispetto alla popolazione generale il rischio appare essere 51,9 volte più elevato.**

Raouna et al., 2017



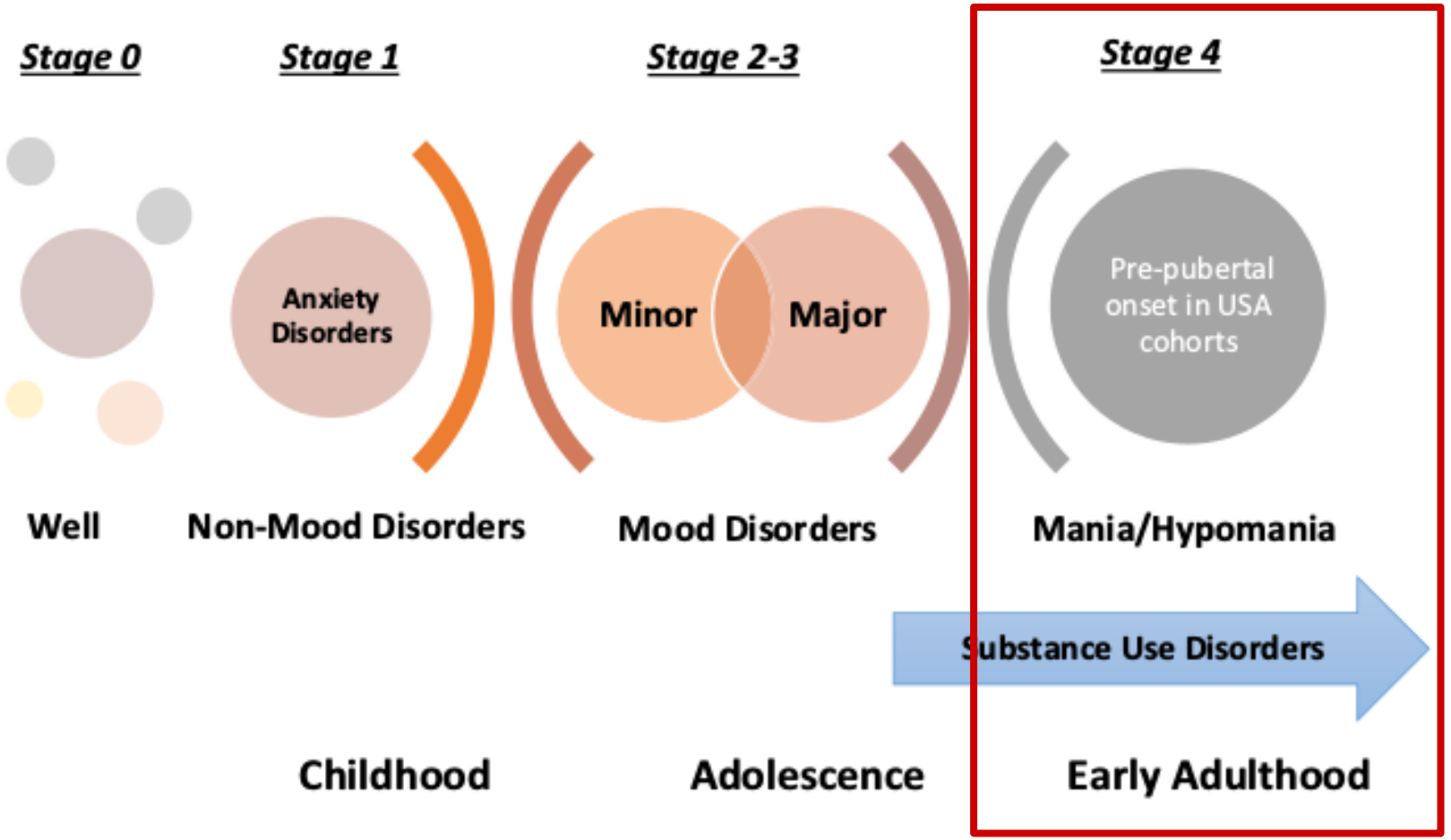

**Stage 1: sviluppo di disturbi d'ansia nella prima-media infanzia. I dati longitudinali indicano come lo sviluppo di disturbi d'ansia in questa fase sia predittivo di successivo esordio i DB nella prole di pz affetti da DB. Non tutti i ragazzi con dist. d'ansia in questa fase svilupperanno poi DB**

Raouna et al., 2017




**Stage 2-3: differentenmente rispetto a precedenti dati, emerge come lo sviluppo di una ampia gamma i disturbi dell'umore, minori e maggiori, sia predittivo di successiva comparsa di DB.**
**Fra questi, distimia, disturbi dell'adattamento,depressione NAS.**

Raouna et al., 2017




**Stage 4 : sviluppo di sintomi maniacali/ipomaniacali**

Il ruolo delle sostanze d'abuso è certamente rilevante sin dalla tarda infanzia ma non strettamente legato causalmente e temporalmente al successivo esordio. Il meccanismo appare essere biunivoco: sicuramente l'utilizzo di SS provoca una slatentizzazione di alcuni sintomi sottosoglia ma, d'altra parte, è possibile come l'utilizzo di SS possa essere esso stesso un meccanismo di coping alla comparsa di iniziali disturbi affettivi NAS.

Raouna et al., 2017

Duffy et al. Int J Bipolar Disord (2017) 5:37
DOI 10.1186/s40345-017-0106-4

International Journal of Bipolar Disorders

REVIEW Open Access

# The clinical trajectory of emerging bipolar disorder among the high-risk offspring of bipolar parents: current understanding and future considerations

A. Duffy[1*], C. Vandeleur[2], N. Heffer[3] and M. Preisig[2]

- Il disturbo bipolare non esordisce tipicamente con un episodio maniacale ma è di solito preceduto da **disturbi nell'infanzia** e da **anni di episodi depressivi** con il **crescente rischio di episodi ipomaniacali**
- I disturbi del sonno ed i sintomi internalizing hanno diversa rilevanza nei gruppi di giovani con elevato rischio familiare rispetto a coloro senza.
- Episodi depressivi in adolescenza in ragazzi con rischio familiare possono rappresentare l'esordio del DB o comunque la conferma di elevata predisposizione.
- Esordi con sintomatologia maniacale in bambini (prepubere) in popolazioni senza rischio familiare confermato per bipolarità, possono rappresentare l'esordio di disturbi o problemi NON collegati al disturbo bipolare.
- Sintomi psicotici e deficit cognitivi risultano invece presenti solo dopo l'esordio conclamato della patologia.

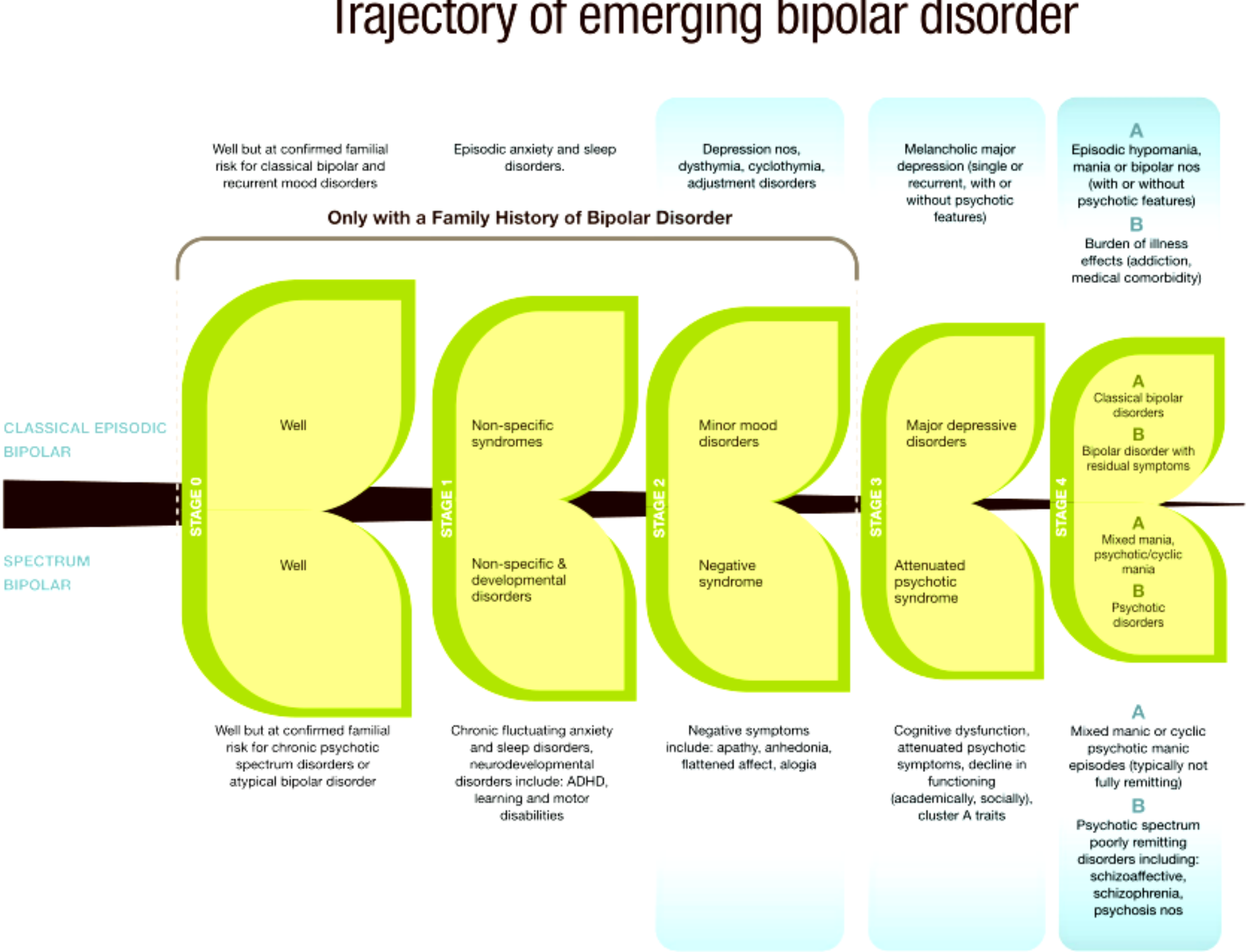



**Fig. 1** The trajectory of emerging bipolar disorder in two subtypes of high-risk offspring

# Toward the Definition of a Bipolar Prodrome: Dimensional Predictors of Bipolar Spectrum Disorders in At-Risk Youths

Danella M. Hafeman, M.D., Ph.D., John Merranko, M.A., David Axelson, M.D., Benjamin I. Goldstein, M.D., Ph.D., Tina Goldstein, Ph.D., Kelly Monk, B.S.N., R.N., Mary Beth Hickey, B.A., Dara Sakolsky, M.D., Ph.D., Rasim Diler, M.D., Satish Iyengar, Ph.D., David Brent, M.D., David Kupfer, M.D., Boris Birmaher, M.D.

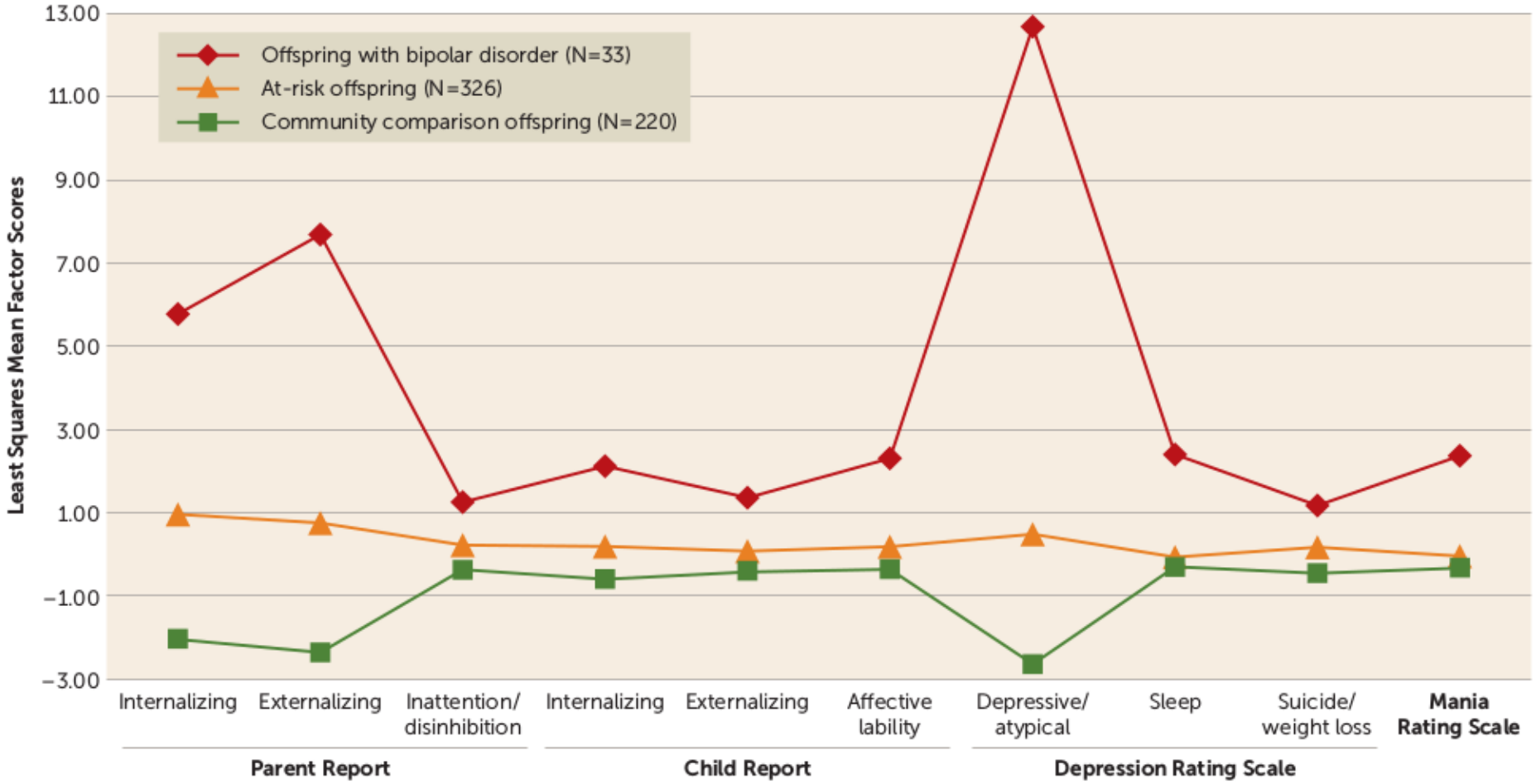
Reclutati figli di età compresa fra i 6-18 anni (tot. 359) di pazienti bipolari (almeno 1 genitore) confrontati con 220 controlli.

Al baseline  già l'8,4% del campione mostrava sintomatologia dello spettro bipolare.

Negli 8 anni successivi il 14% del campione per cui erano ancora disponibili dati (44 pz) aveva sviluppato disordini dello spettro bipolare.


American Journal of Psychiatry, 2016

**FIGURE 1. Baseline Differences in Each Factor Across Groups, Adjusting for Demographic Characteristics, in a Study of Dimensional Predictors of Bipolar Spectrum Disorders in At-Risk Youths[a]**




[a] All two-group comparisons between at-risk and comparison offspring were significant ($p<0.05$) except sleep scores.

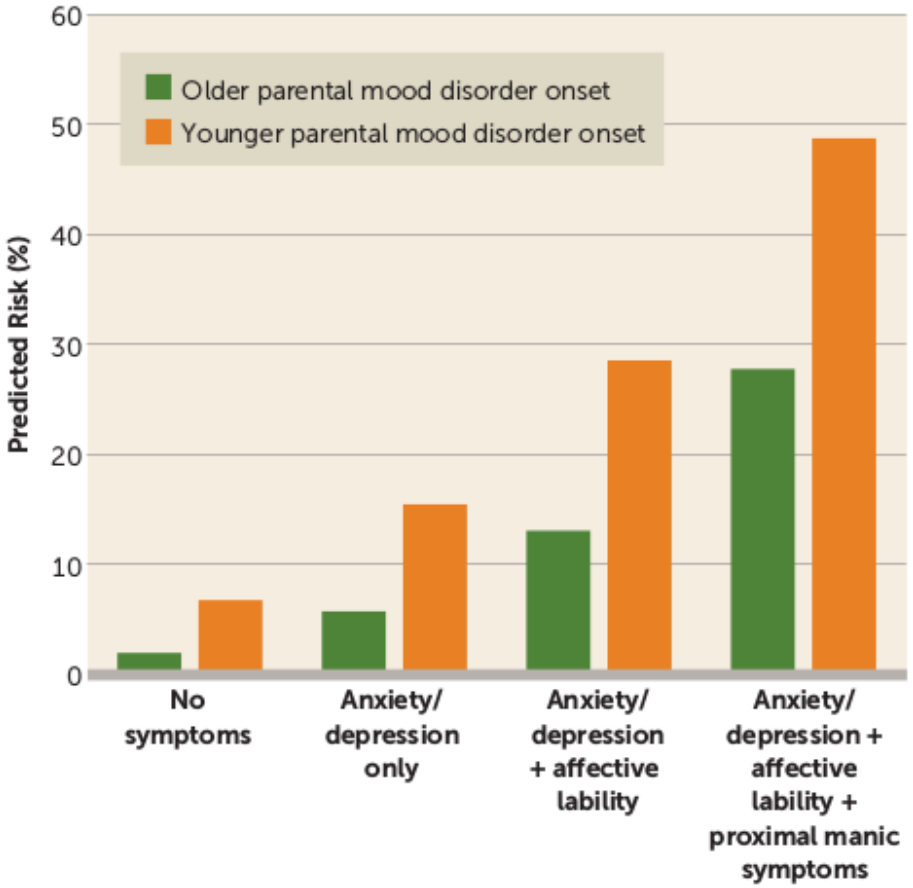
Sintomi *internalizing* ed *externalizing* (comportamenti distruttivi, irritabilità, dist. della condotta, etc) e *labilità emotiva* risultavano predittivi di conversione verso disturbo bipolare nel confronto fra At risk (giallo) e popolazione generale (verde).

American Journal of Psychiatry, 2016

# Toward the Definition of a Bipolar Prodrome: Dimensional Predictors of Bipolar Spectrum Disorders in At-Risk Youths

Danella M. Hafeman, M.D., Ph.D., John Merranko, M.A., David Axelson, M.D., Benjamin I. Goldstein, M.D., Ph.D., Tina Goldstein, Ph.D., Kelly Monk, B.S.N., R.N., Mary Beth Hickey, B.A., Dara Sakolsky, M.D., Ph.D., Rasim Diler, M.D., Satish Iyengar, Ph.D., David Brent, M.D., David Kupfer, M.D., Boris Birmaher, M.D.

**FIGURE 4. Predicted Probability of New-Onset Bipolar Spectrum Disorders for Risk Profiles Defined by Significant Predictors in the Overall Probit Model[a]**




Il rischio di successivo sviluppo di DB nel campione risultava inoltre correlato con l'età d'esordio del disturbo genitoriale (esordio più precoce>>>maggior rischio).

American Journal of Psychiatry, 2016

Bipolar Disord. 2018 May 20. doi: 10.1111/bdi.12658. [Epub ahead of print]

# Double trouble: weekend sleep changes are associated with increased impulsivity among adolescents with bipolar I disorder.

Gershon A[1], Johnson SL[2], Thomas L[1], Singh MK[1].

**Abstract**

**OBJECTIVES:** Both sleep disruption and impulsivity are important predictors of the course of bipolar disorder (BD). Although sleep disruption has been shown to intensify impulsivity, little research has considered how these two important domains interact within BD. Adolescence is a critical period for the onset of BD, and is often associated with increases in impulsivity and substantial changes in sleep. We tested the hypothesis that disruptions in sleep would increase impulsivity among adolescents, and that this effect would be more pronounced among those with BD.

**METHODS:** Thirteen- to nineteen-year-olds diagnosed with BD-I (n = 33, age [mean ± standard deviation (SD)] 16.2 ± 1.66 years, 54.5% female) and psychiatrically healthy controls (n = 26, age [mean ± SD] 15.5 ± 1.45 years, 55.6% female) reported their past-week bedtime, rise time, and sleep duration, separately for school days and weekends, and completed a self-report questionnaire on impulsivity. Stepwise regression was used to examine the effects of sleep on impulsivity, and the moderation of this effect by BD status.

**RESULTS:** Adolescents with BD reported significantly higher impulsivity, later and more variable rise time, and more variable time in bed and sleep duration on school days than did controls. Greater change in sleep duration between school days and weekends was associated with significantly more impulsivity among adolescents with BD as compared to controls.

**CONCLUSIONS:** These findings highlight the important effect of sleep on impulsivity among adolescents with BD and add to the growing evidence that establishing sleep routines may be an important therapeutic target for youth with BD.

Studio effettuato su 33 bipolari di età compresa fra 13 e 19 anni confrontati con 26 controlli sani di pari età.
È stata valutata la qualità del sonno, l'ora di addormentamento e risveglio, la durata totale, distinguendo fra giorni di scuola e weekend. I ragazzi sono stati sottoposti a questionari per la valutazione dell'impulsività.

I ragazzi affetti DB mostravano maggior impulsività, maggior variabilità dell'ora di risveglio, maggior variabilità fra tempo di sonno dei giorni feriali rispetto ai festivi.
Maggior variabilità fra la durata del sonno feriale/weekend risultava associata a maggior grado di impulsività (significatività statistica) nei ragazzi con DB rispetto ai controlli sani.

Acta Psychiatrica Scandinavica

Acta Psychiatr Scand 2015: 132: 389–399

DOI: 10.1111/acps.12426


ACTA PSYCHIATRICA SCANDINAVICA

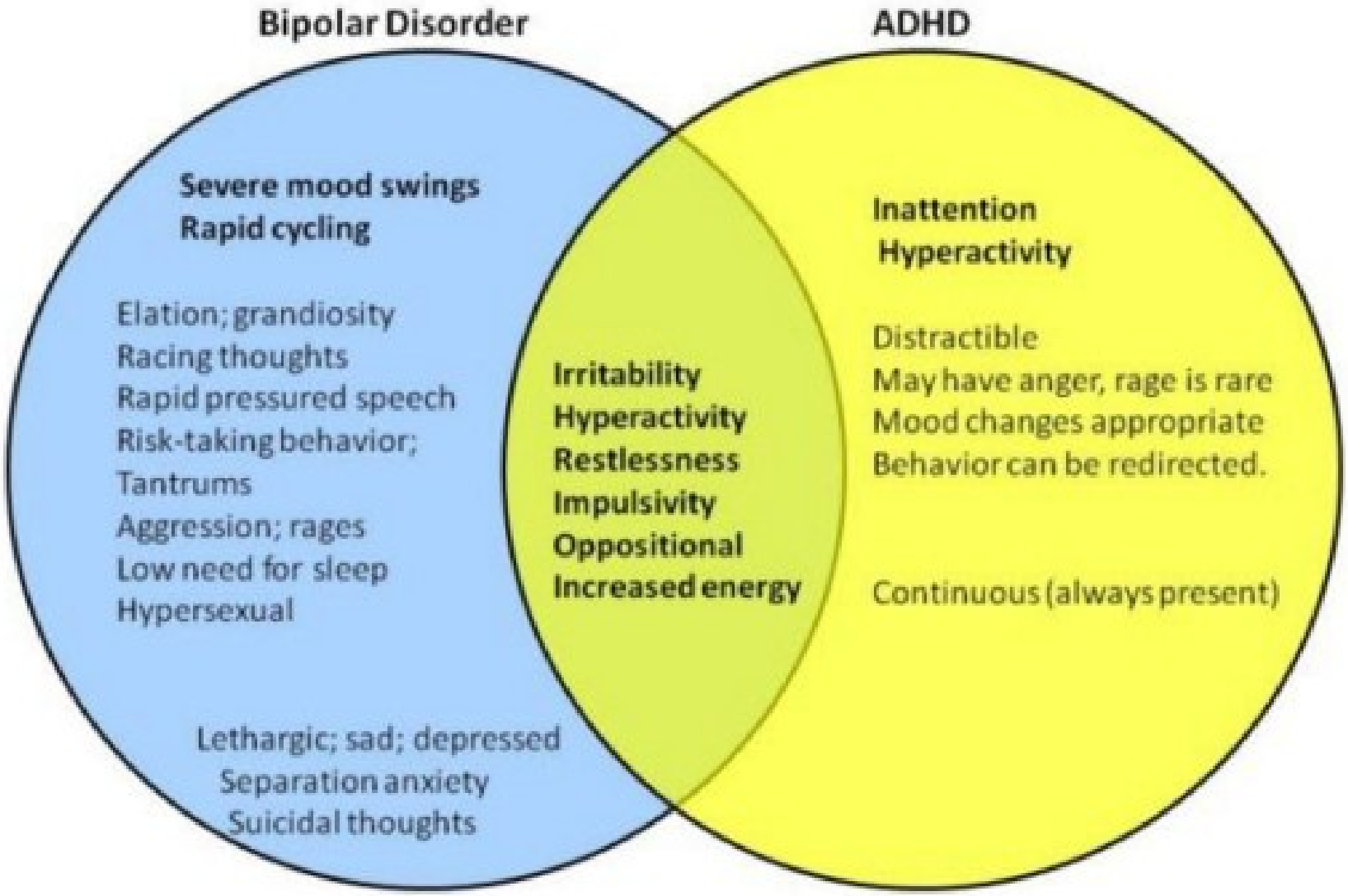
# Bipolar disorder with comorbid attention-deficit and hyperactivity disorder. Main clinical features and clues for an accurate diagnosis

In adult patients with bipolar disorder (BD) lifetime prevalence of comorbid attention-deficit and hyperactivity disorder (ADHD) was 17.9% (10.5% for adult ADHD and 7.4% for childhood ADHD). The BD + ADHD group showed more suicidal behaviour although less severe.

Comorbidity was also more common, especially regarding substance use disorders.

**Significant outcomes**

- Comorbidity with ADHD is common in bipolar patients, although possibly not as high as seen in previous studies.
- Bipolar patients with ADHD show an extremely high prevalence of substance use disorders.
- The ASRS-V1.1 has poor specificity when used in-patients with bipolar disorder; new screening tools are necessary.




*"the major differentiation is in the abnormal mood. There is nothing in the defining features of ADHD that speak to abnormal mood. Bipolar children have very, very dysregulated mood (J.Biederman)"*

PLOS | ONE

RESEARCH ARTICLE

# Delays before Diagnosis and Initiation of Treatment in Patients Presenting to Mental Health Services with Bipolar Disorder

**Rashmi Patel[1]*, Hitesh Shetty[2], Richard Jackson[3], Matthew Broadbent[2], Robert Stewart[3], Jane Boydell[1], Philip McGuire[1], Matthew Taylor[1]**

1 King's College London, Department of Psychosis Studies, Institute of Psychiatry, Psychology &

Studio retrospettivo su 1364 pazienti diagnosticati bipolari fra il 2007 ed il 2012 all'interno del database di South London and Maudsley.
È stato valutato il tempo necessario per effettuare la diagnosi (*diagnostic delay*) ed impostare corretto trattamento (treatment delay) dopo il primo contatto con specialista psichiatra.

Il *diagnostic delay* mediano risultava essere di 62 giorni (range interquartile: 17–243) ed il *treatment delay* mediano di 31 giorni (4–122).

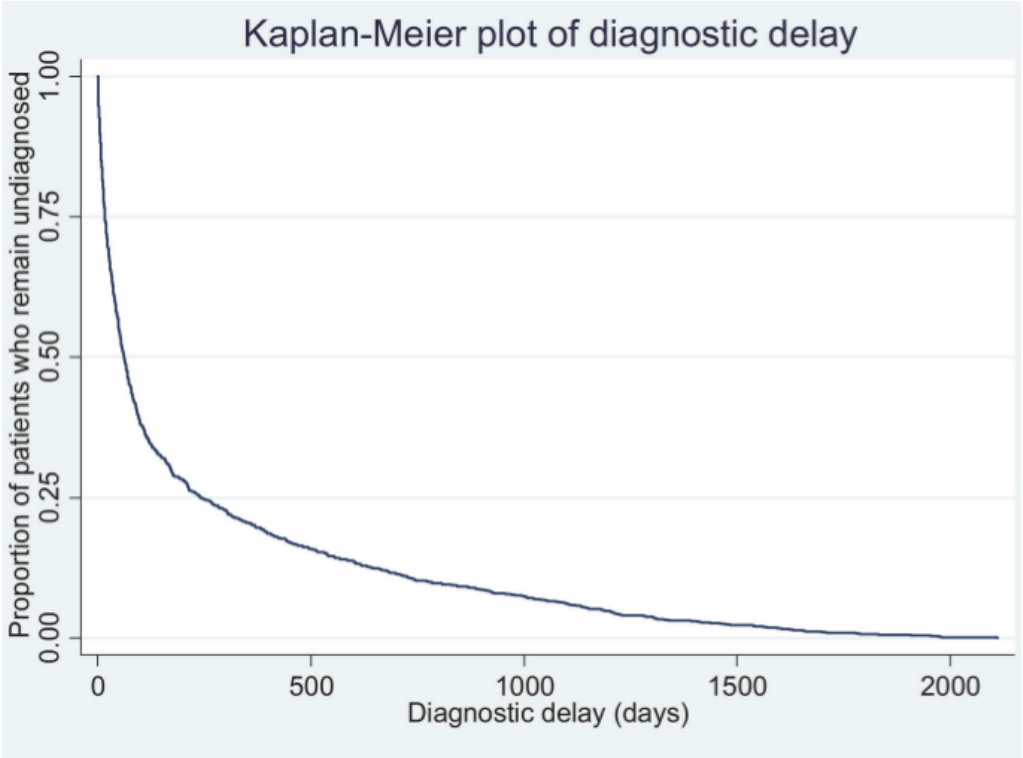
Il ricovero coatto era associato a significativa riduzione di entrambi i tempi.
Precedenti diagnosi psichiatriche, speciificamente dipendenza/abuso di alcol o sostanze causavano invece aumento del diagnostic delay.

Patel et al., 2015

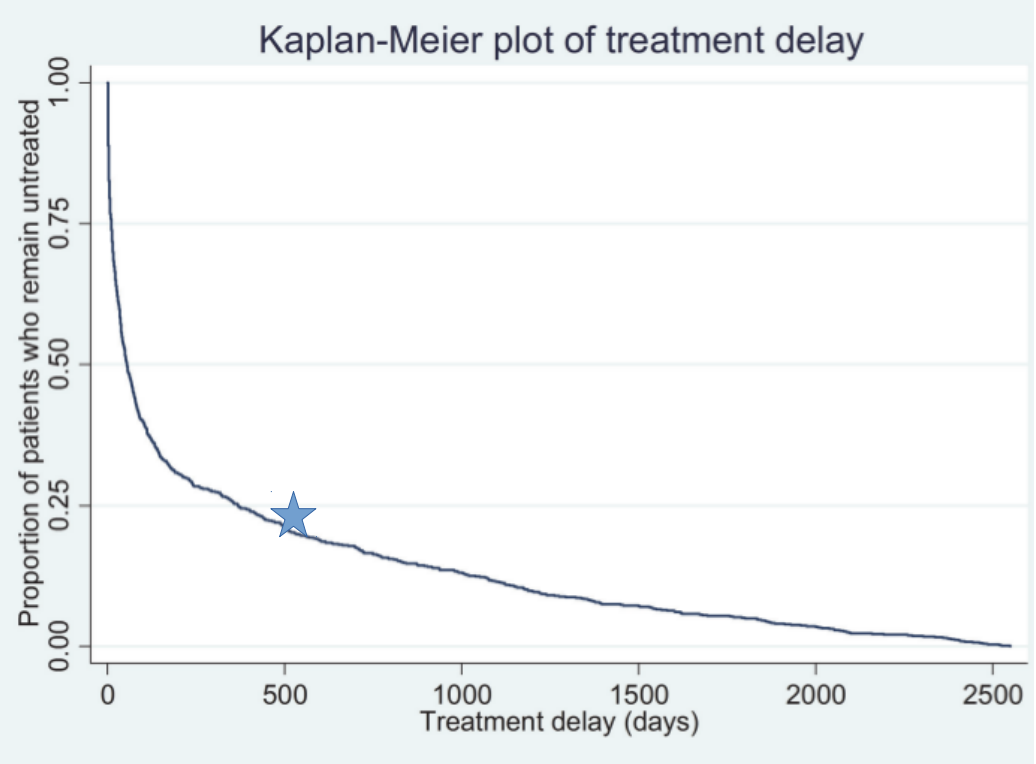
PLOS ONE

RESEARCH ARTICLE

# Delays before Diagnosis and Initiation of Treatment in Patients Presenting to Mental Health Services with Bipolar Disorder




Diagnostic delay




Treatment delay

Patel et al., 2015

# Primo, non nuocere

*CNS Spectrums* (2017), **22**, 118–119. 
doi:10.1017/S1092852917000086

EDITORIAL

## Do no harm: a paradigm shift in the unchecked use of antidepressants

*Debbi Ann Morrissette**

Neuroscience Education Institute, Carlsbad, California, USA

With our newly published guidelines for diagnosis and treatment of mood disorders all along the spectrum,[1] we (myself along with the top mood-disorder experts from around the world) are advocating that every patient who presents with symptoms of depression be thoroughly screened for family history of bipolar disorders and symptoms of (hypo)mania. I would argue that our in nature is young age of onset. When *any* patient under the age of 18 presents with symptoms of depression, mixed features or bipolarity should actually be expected and screened for thoroughly, intensely, and with no stone left unturned. If evidence that symptoms fall outside the realm of unipolar are suspected, antidepressant monotherapy should probably *not* be the treatment of choice.

BMJ Open

# Do antidepressants increase the risk of mania and bipolar disorder in people with depression? A retrospective electronic case register cohort study

Rashmi Patel,[1] Peter Reiss,[1] Hitesh Shetty,[2] Matthew Broadbent,[2] Robert Stewart,[3] Philip McGuire,[1] Matthew Taylor[1]

[1]Department of Psychosis Studies, King's College London, Institute of Psychiatry, Psychology & Neuroscience, London, UK
[2]Biomedical Research Centre Nucleus, South London and Maudsley NHS Foundation Trust, London, UK
[3]Department of Psychological Medicine, King's College London, Institute of Psychiatry, Psychology & Neuroscience, London, UK

**Table 1** Cox regression analysis of factors associated with mania/bipolar disorder (n=21 012)

| Factor | Group | Number in sample (%) | Incidence rate of mania/bipolar disorder (per 1000 person-years) |
|---|---|---|---|
| Age (years) | 16–25 | 4586 (21.8) | 10.1 |
| | 26–35 | 5406 (25.7) | 12.3 |
| | 36–45 | 5353 (25.5) | 11.2 |
| | 46–55 | 3798 (18.1) | 10.7 |
| | 56–65 | 1869 (8.9) | 8.3 |
| Gender | Female | 12 767 (60.8) | 11.1 |
| | Male | 8245 (39.2) | 10.5 |
| Prior antidepressant treatment | MAOi | 37 (0.2) | 14.1 |
| | Mirtazapine | 1977 (9.4) | 13.7 |
| | SSRI | 7468 (35.5) | 13.2 |
| | TCA | 993 (4.7) | 13.1 |
| | Trazodone | 160 (0.8) | 19.1 |
| | Venlafaxine | 1184 (5.6) | 14.9 |
| | Duloxetine | 248 (1.2) | 13.8 |
| | Other antidepressant | 101 (0.5) | 13.7 |

L'incidenza complessiva di switch maniacale/bipolare risulta essere di 10.9 per 1000 pz/anno.
Il picco si osserva fra pz di età compresa fra 26 e 35 anni.
Precedenti trattamenti con AD sono associati con ulteriore aumento dell'incidenza (fra 13.1 e 19.1 per 1000 pz/anno).Analisi multivariate indicano una associazione significativa con SSRI (HR 1.34, 95% CI 1.18 to 1.52) e
venlafaxina (1.35, 1.07 to 1.74)

Patel et al., 2015

Acta Psychiatrica Scandinavica

2017

# Manic switches induced by antidepressants: an umbrella review comparing randomized controlled trials and observational studies

N. Allain, C. Leven, B. Falissard, J.-S. Allain, J.-M. Batail, E. Polard, F. Montastruc, D. Drapier, F. Naudet

Metanalisi di RCT e studi osservazionali (rispettivamente 35 e 22 studi).

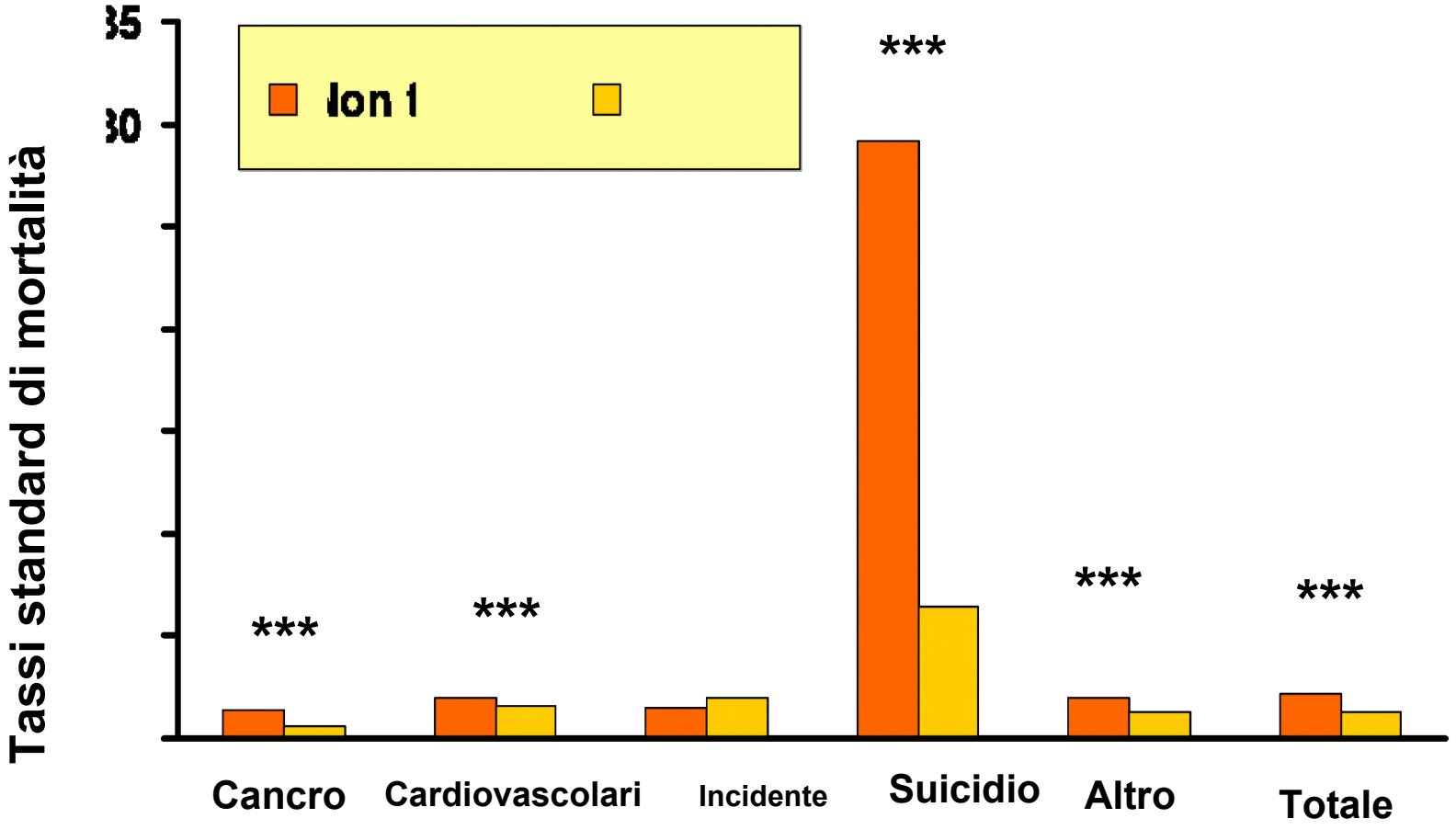
Il rischio di switch maniacale risulta sottostimato dai RCT rispetto agli studi osservazionali (tempo di osservazione ridotto? Bias di campionamento).

Aumentato rischio di switch in pz con abuso di sostanze, soprattutto alcol (popolazione generalmente esclusa da RCT).

Aumentato rischio di switch con SNRI e triciclici.

Allain et al., 2017

# Mortalità nel disturbo bipolare




**220 bipolari seguiti durante 22 anni**
*****p<0.001**

**Angst et al 2002**

# Suicidality in Pediatric Bipolar Disorder

Tina R. Goldstein, PhD

**KEYWORDS**

• Suicide • Suicidal behavior • Suicidal ideation
• Self-injurious behavior • Pediatric bipolar disorder

Risk for completed suicide in bipolar disorder (BP) is among the highest of all psychiatric disorders;[1] between 25% and 50% of adults with BP make at least one suicide attempt in their lifetime, and between 8% and 19% of individuals with BP will die from suicide.[2] Research indicates that between 20% and 65% of adults with BP experience onset in childhood,[3,4] and those adults with early illness onset are at higher risk for suicidal behavior.[4,5] Given the relative infancy of the field of clinical research examining the phenomenology and course of pediatric BP, it is not surprising that little is known about suicidal behavior in this population despite the apparent link between early illness onset and suicidality.

**Schizophrenia Bulletin**
doi:10.1093/schbul/sbx158

# Cannabis Use and Hypomania in Young People: A Prospective Analysis

**Steven Marwaha*[,1,2], Catherine Winsper[1], Paul Bebbington[3], and Daniel Smith[4]**

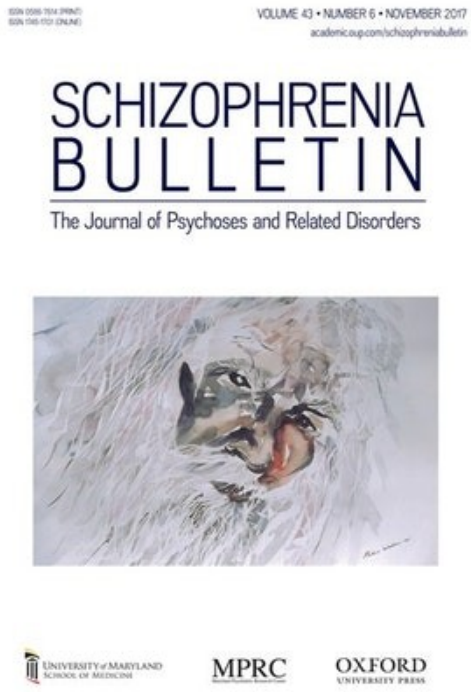
[1]Unit of Mental Health and Wellbeing, Warwick Medical School, University of Warwick, Coventry, UK; [2]Affective Disorders Service, Caludon Centre, Coventry, UK; [3]Division of Psychiatry, University College London, London, UK; [4]University of Glasgow, Gartnavel Royal Hospital, Glasgow, UK

L'utilizzo di THC in età adolescenziale è, come noto, estremamente frequente; tuttavia l'associazione con il disturbo bipolare, nello specifico con l'insergenza di mania/ipomania risulta poco studiata.

L'utilizzo di cannabis al baseline (almeno 2-3 volte settimana) è associato con successivo sviluppo di ipomania (OR = 2.21, 95% CI = 1.49–3.28). Riscontrata relazione dose risposta (occasionale vs settimanale).

La cannabis inoltre è risultato il mediatore fra abusi sessuali nell'infanzia e ipomania.

Il link fra cannabis ed ipomania non risulta invece mediato da depressione o da sintomi psicotici




Schizophr Bull. 2017 Nov 28

Article

# Longitudinal Trajectories and Associated Baseline Predictors in Youths With Bipolar Spectrum Disorders

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**Objective:** The authors sought to identify and evaluate longitudinal mood trajectories and associated baseline predictors in youths with bipolar disorder.

**Method:** A total of 367 outpatient youths (mean age, 12.6 years) with bipolar disorder with at least 4 years of follow-up were included. After intake, participants were interviewed on average 10 times (SD=3.2) over a mean of 93 months (SD=8.3). Youths and parents were interviewed for psychopathology, functioning, treatment, and familial psychopathology and functioning.

**Results:** Latent class growth analysis showed four different longitudinal mood trajectories: "predominantly euthymic" (24.0%), "moderately euthymic" (34.6%), "ill with improving course" (19.1%), and "predominantly ill" (22.3%). Within each class, youths were euthymic on average 84.4%, 47.3%, 42.8%, and 11.5% of the follow-up time, respectively. Multivariate analyses showed that better course was associated with higher age at onset of mood symptoms, less lifetime family history of bipolar disorder and substance abuse, and less history at baseline of severe depression, manic symptoms, suicidality, subsyndromal mood episodes, and sexual abuse. Most of these factors were more noticeable in the "predominantly euthymic" class. The effects of age at onset were attenuated in youths with lower socioeconomic status, and the effects of depression severity were absent in those with the highest socioeconomic status.

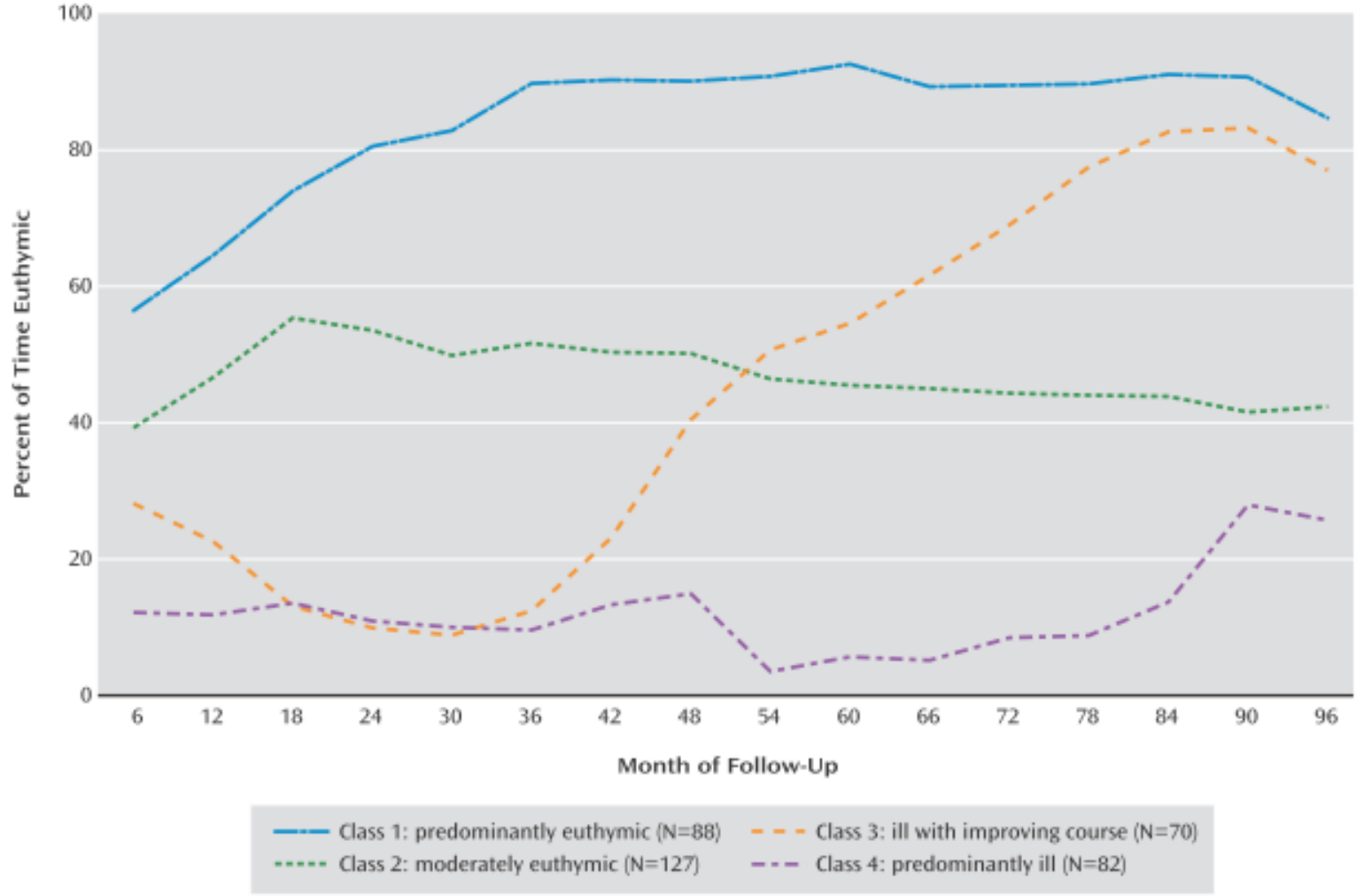
**Conclusions:** A substantial proportion of youths with bipolar disorder, especially those with adolescent onset and the above-noted factors, appear to be euthymic over extended periods. Nonetheless, continued syndromal and subsyndromal mood symptoms in all four classes underscore the need to optimize treatment.

*(Am J Psychiatry 2014; 171:990–999)*

367 pazienti, **età media 12.6 anni**, affetti da dist. Bipolare. Seguiti in follow-up per almeno 4 anni.
Sono state identificate 4 differenti traiettorie del disturbo: ***predominantly euthymic*** **(24%),** ***moderately euthymic*** **(34,6%),** ***ill with improving course*** **(19,1%)** ***predominantly ill*** **(22,3).**
Un follow up migliore risultava associato a: età d'esordio più elevata, ridotta familiarità per DB e abuso di sostanze, ridotta presenza al baseline di depressione grave, sintomi maniacali, suicidalità, abusi sessuali

# Longitudinal Trajectories and Associated Baseline Predictors in Youths With Bipolar Spectrum Disorders

FIGURE 1. Latent Class Growth Analysis Based on Percentage of Time Euthymic for Youths With Bipolar Disorder Who Had at Least 4 Years of Follow-Up



Open Access Protocol

BMJ Open

# The Bipolar Illness Onset study: research protocol for the BIO cohort study

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BMJ, 2017

- Protocollo in corso per la valutazione longitudinale di pazienti con esordio bipolare.
- 300 pazienti con esordio bipolare, 200 dei loro familiari sani (o figli), 100 controlli sani senza evidenza di disturbi dell'umore.
- Saranno effettuati **test ematici** seriati (fra cui BDNF, citochine, beta-amiloide, marker d'infiammazione, PCR, DNA/RNA), **neuroimaging** (RMN basale e funzionale in eutimia), **test cognitivi**, valutazioni autosomministrate tramite **smartphone** (sia valutazione giornaliera del timismo che dati sull'utilizzo stesso dello smartphone e della socialità).
- Follow-up: 5-10 anni

Kessing et al., 2017

# Le critiche al modello di diagnosi precoce di Schizofrenia

## A critique of the "ultra-high risk" and "transition" paradigm

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*The transdiagnostic expression of psychotic experiences in common mental disorder (anxiety/depression/substance use disorder) is associated with a poorer prognosis, and a small minority of people may indeed develop a clinical picture that meets criteria for schizophrenia. However, it appears neither useful nor valid to observe early states of multidimensional psychopathology in young people through the "schizo"-prism, and apply misleadingly simple, unnecessary and inefficient binary concepts of "risk" and "transition". A review of the "ultra-high risk" (UHR) or "clinical high risk" (CHR) literature indicates that UHR/CHR samples are highly heterogeneous and represent individuals diagnosed with common mental disorder (anxiety/depression/substance use disorder) and a degree of psychotic experiences. Epidemiological research has shown that psychotic experiences are a (possibly non-causal) marker of the severity of multidimensional psychopathology, driving poor outcome, yet notions of "risk" and "transition" in UHR/CHR research are restrictively defined on the basis of positive psychotic phenomena alone, ignoring how baseline differences in multidimensional psychopathology may differentially impact course and outcome. The concepts of "risk" and "transition" in UHR/CHR research are measured on the same dimensional scale, yet are used to produce artificial diagnostic shifts. In fact, "transition" in UHR/CHR research occurs mainly as a function of variable sample enrichment strategies rather than the UHR/CHR "criteria" themselves. Furthermore, transition rates in UHR/CHR research are inflated as they do not exclude false positives associated with the natural fluctuation of dimensional expression of psychosis. Biological associations with "transition" thus likely represent false positive findings, as was the initial claim of strong effects of omega-3 polyunsatured fatty acids in UHR samples. A large body of UHR/CHR intervention research has focused on the questionable outcome of "transition", which shows lack of correlation with functional outcome. It may be more productive to consider the full range of person-specific psychopathology in all young individuals who seek help for mental health problems, instead of "policing" youngsters for the transdiagnostic dimension of psychosis. Instead of the relatively inefficient medical high-risk approach, a public health perspective, focusing on improved access to a low-stigma, high-hope, small scale and youth-specific environment with acceptable language and interventions may represent a more useful and efficient strategy.*

**Key words:** Ultra-high risk, transition, psychotic experiences, common mental disorder, transdiagnostic expression of psychosis, public health perspective

***(World Psychiatry 2017;16:200–206)***

# La difficoltà a differenziare le patologie e identificare predittori

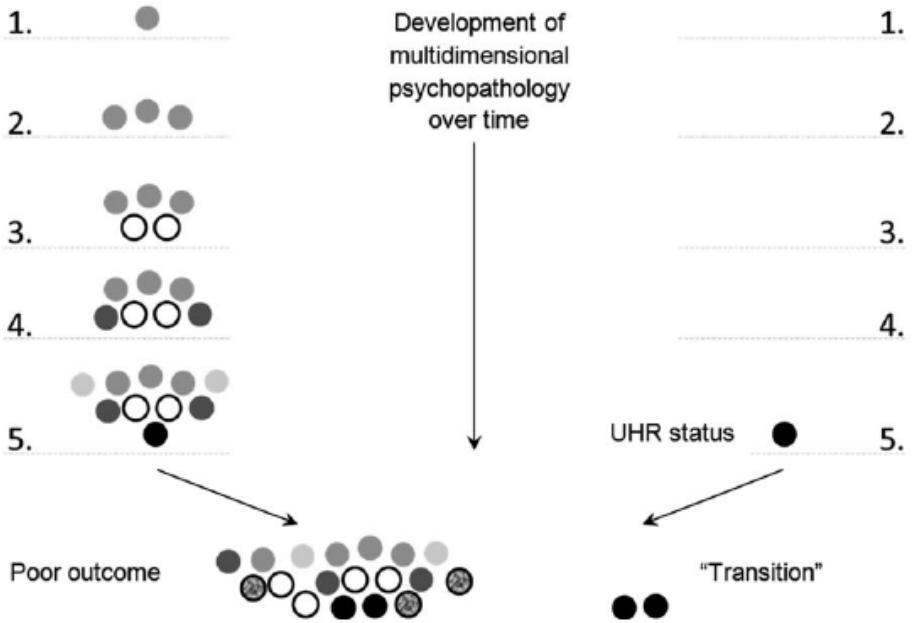


**Figure 1** Relative "blindness" of the ultra-high risk (UHR)/transition paradigm. On the left, the natural development of multidimensional psychopathology over time. Black circles indicate (attenuated) positive psychotic symptoms. Other gray-scale circles indicate other psychopathology. As the UHR paradigm ignores multidimensional psychopathology, it remains "blind" and only "sees" psychotic phenomena as precursors of schizo-"transition" (i.e., more severe psychosis; below on the right), while these phenomena are in fact a marker of relative poor outcome of multidimensional psychopathology (below on the left). The restricted focus on positive symptoms in the UHR paradigm means that considerable potential for prevention in phases 1-4 is missed.

# La risposta e la formulazione di nuovi modelli

## Beyond the "at risk mental state" concept: transitioning to transdiagnostic psychiatry

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*The "at risk mental state" for psychosis approach has been a catalytic, highly productive research paradigm over the last 25 years. In this paper we review that paradigm and summarize its key lessons, which include the valence of this phenotype for future psychosis outcomes, but also for comorbid, persistent or incident non-psychotic disorders; and the evidence that onset of psychotic disorder can at least be delayed in ultra high risk (UHR) patients, and that some full-threshold psychotic disorder may emerge from risk states not captured by UHR criteria. The paradigm has also illuminated risk factors and mechanisms involved in psychosis onset. However, findings from this and related paradigms indicate the need to develop new identification and diagnostic strategies. These findings include the high prevalence and impact of mental disorders in young people, the limitations of current diagnostic systems and risk identification approaches, the diffuse and unstable symptom patterns in early stages, and their pluripotent, transdiagnostic trajectories. The approach we have recently adopted has been guided by the clinical staging model and adapts the original "at risk mental state" approach to encompass a broader range of inputs and output target syndromes. This approach is supported by a number of novel modelling and prediction strategies that acknowledge and reflect the dynamic nature of psychopathology, such as dynamical systems theory, network theory, and joint modelling. Importantly, a broader transdiagnostic approach and enhancing specific prediction (profiling or increasing precision) can be achieved concurrently. A holistic strategy can be developed that applies these new prediction approaches, as well as machine learning and iterative probabilistic multimodal models, to a blend of subjective psychological data, physical disturbances (e.g., EEG measures) and biomarkers (e.g., neuroinflammation, neural network abnormalities) acquired through fine-grained sequential or longitudinal assessments. This strategy could ultimately enhance our understanding and ability to predict the onset, early course and evolution of mental ill health, further opening pathways for preventive interventions.*

**Key words:** At risk mental state, psychosis, ultra high risk, transition, transdiagnostic psychiatry, clinical staging, CHARMS, prediction strategies, network theory, dynamical systems theory, joint modelling

***(World Psychiatry 2018;17:133–142)***

# Da un modello di diagnosi precoce per la Schizofrenia…

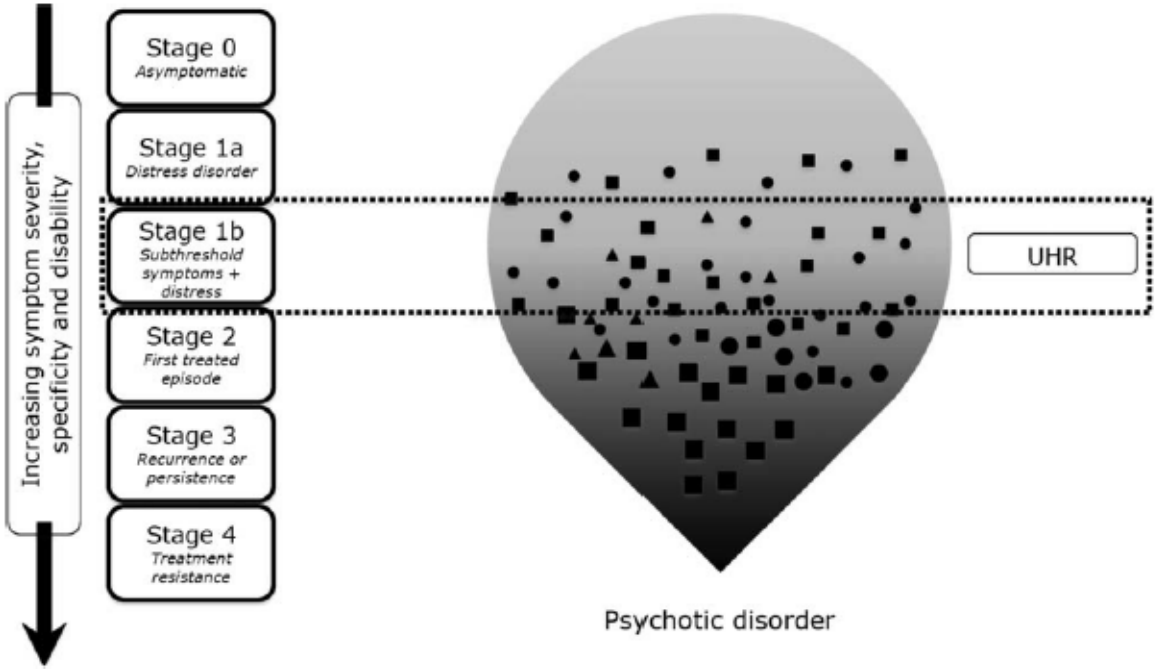


**Figure 1** Traditional ultra high risk (UHR) paradigm in the context of clinical staging. The shapes represent different types of symptoms

# Ad un modello rivolto a "Stati Mentali a Rischio"

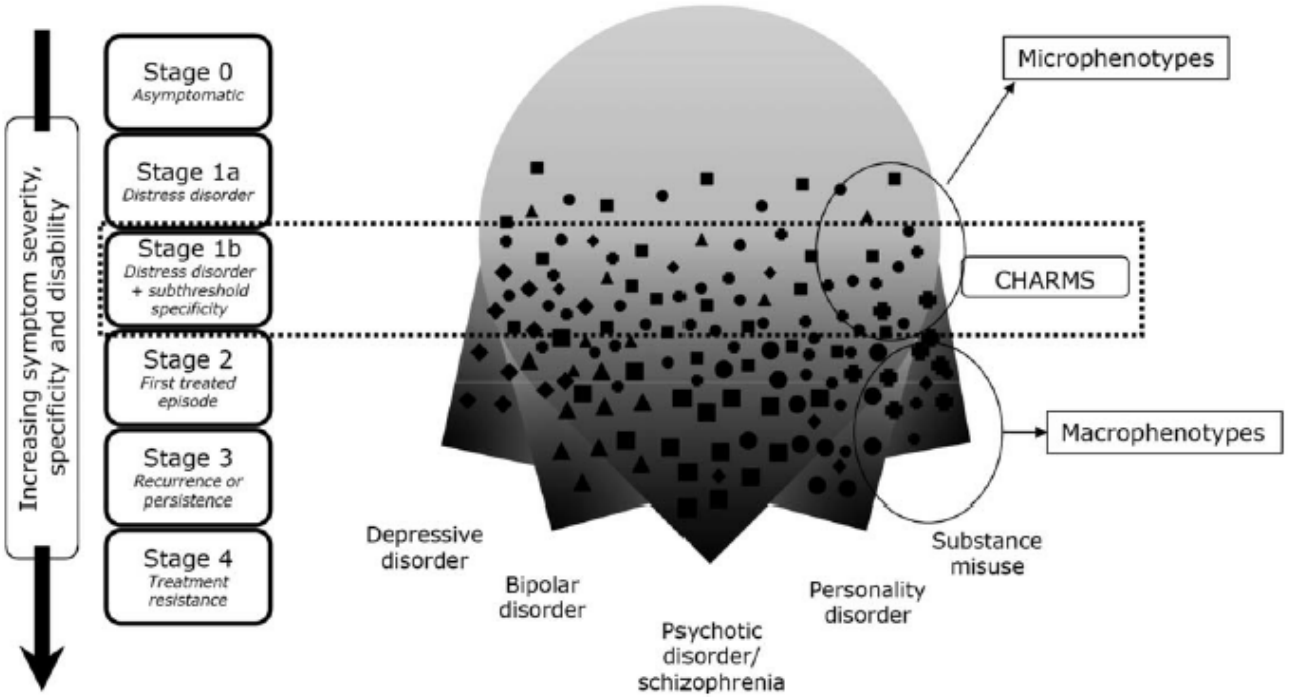


**Figure 2** New transdiagnostic Clinical High At Risk Mental State (CHARMS) paradigm in the context of clinical staging. The shapes represent different types of symptoms

# La necessità di un modello di diagnosi ed intervento nuovo

La complessità del Disturbo Bipolare e le modalità di presentazione dei Disturbi Psichiatrici all'esordio (Stati Mentali a Rischio)rendono necessario ripensare a modelli di valutazione e presa in carico nei servizi capaci di effettuare interventi valutativi longitudinali che permettano un processo di stadiazione adeguato alla formulazione di adeguati percorsi di cura.


# Grazie per l'attenzione

| | |
|---|---|
| *Psychotic-Like Experiences* (**PLE**): | anomali vissuti cognitivo-percettivi che echeggiano i sintomi psicotici ma con minori livelli di intrusività e disagio |
| *At-Risk Mental State* (**ARMS**): | stato mentale a rischio, comprendente anche i primi stadi di disfunzione (fase premorbosa) |
| *Ultra-High Risk* (**UHR**): | condizione prodromica caratterizzata da sintomi e deficit cognitivi sottosoglia per durata e/o intensità, possibilmente revertibile attraverso un intervento precoce. |
| *Cognitive Basic Symptoms* (**BS**): | disturbi soggettivi del processo cognitivo |
| *Attenuated Psychotic Symptoms* (**APS**): | sintomi psicotici attenuati o sottosoglia per durata/intensità |
| *Brief Limited Intermittent Psychotic Symptoms* (**BLIPS**): | sintomi psicotici a bassa pervasività per ridotta frequenza (limitati nel tempo e/o intermittenti) |
| *First Episode of Psychosis* (**FEP**): | **esordio psicotico - comparsa di disturbi di forma e/o contenuto del pensiero, senso percezione e comportamento** |