



# **How do we Differentiate Bipolar from Unipolar Depression?**

**Andrew A. Nierenberg, MD**

**Thomas P. Hackett, MD, Endowed Chair in Psychiatry, MGH**

**Director, Dauten Family Center for**

**Bipolar Treatment Innovation,**

**Massachusetts General Hospital**

**Professor of Psychiatry, Harvard Medical School**

# Disclosures

**If you have disclosures, state:**

“My spouse/partner and I have the following relevant financial relationship with a commercial interest to disclose:” followed by disclosures

or

**If you do not have disclosures, state:**

“Neither I nor my spouse/partner has a relevant financial relationship with a commercial interest to disclose.”

**(Note: Disclosures must match the information provided on your disclosure form.)**

# Challenges in Depression

---

**Bipolar or Unipolar**

**Mixed features**

**Convert from unipolar to bipolar**



**Write (at least) two things to  
differentiate bipolar from  
unipolar depression.**

# Bipolar or Unipolar

---

**Demographics**

**Family history**

**Symptoms**

**Course**

**Biomarkers**

# Bipolar or Unipolar

---

**Genetics**

**Screening tools**

# Unipolar or Bipolar

---

## Demographics

# Unipolar or Bipolar

---

**Family history**





**Will a first degree relative of  
someone who has bipolar  
disorder be more likely to  
have bipolar or unipolar  
depression?**

# Familial Risks

Condition	Lifetime Prevalence	First-Degree Relative Risk*
Autism	1-2%	25x
Schizophrenia	1%	10x
Bipolar Disorder	2-3%	7-10x
ADHD	8%	2-6x
Alcohol/SUDs	3-13%	3-8x
Eating Disorders	3%	10x
Anxiety Disorders	2-12%	5x
Depression	15-20%	3x

\* Increased risk to siblings or children of affected individual

# Heritability of Conditions (Twin Studies)

---

<b>Autism</b>	<b>60 - 90%</b>
<b>Bipolar Disorder</b>	<b>80%</b>
<b>Schizophrenia</b>	<b>80%</b>
<b>ADHD</b>	<b>76%</b>
<b>Alcoholism</b>	<b>55%</b>
<b>Eating Disorders</b>	<b>55%</b>
<b>Depression</b>	<b>40%</b>
<b>Parkinson's Disease</b>	<b>34%</b>
<b>Breast Cancer</b>	<b>27%</b>

# Weighted Summary Risks of Mood Disorders From Family Studies of Bipolar Disorder

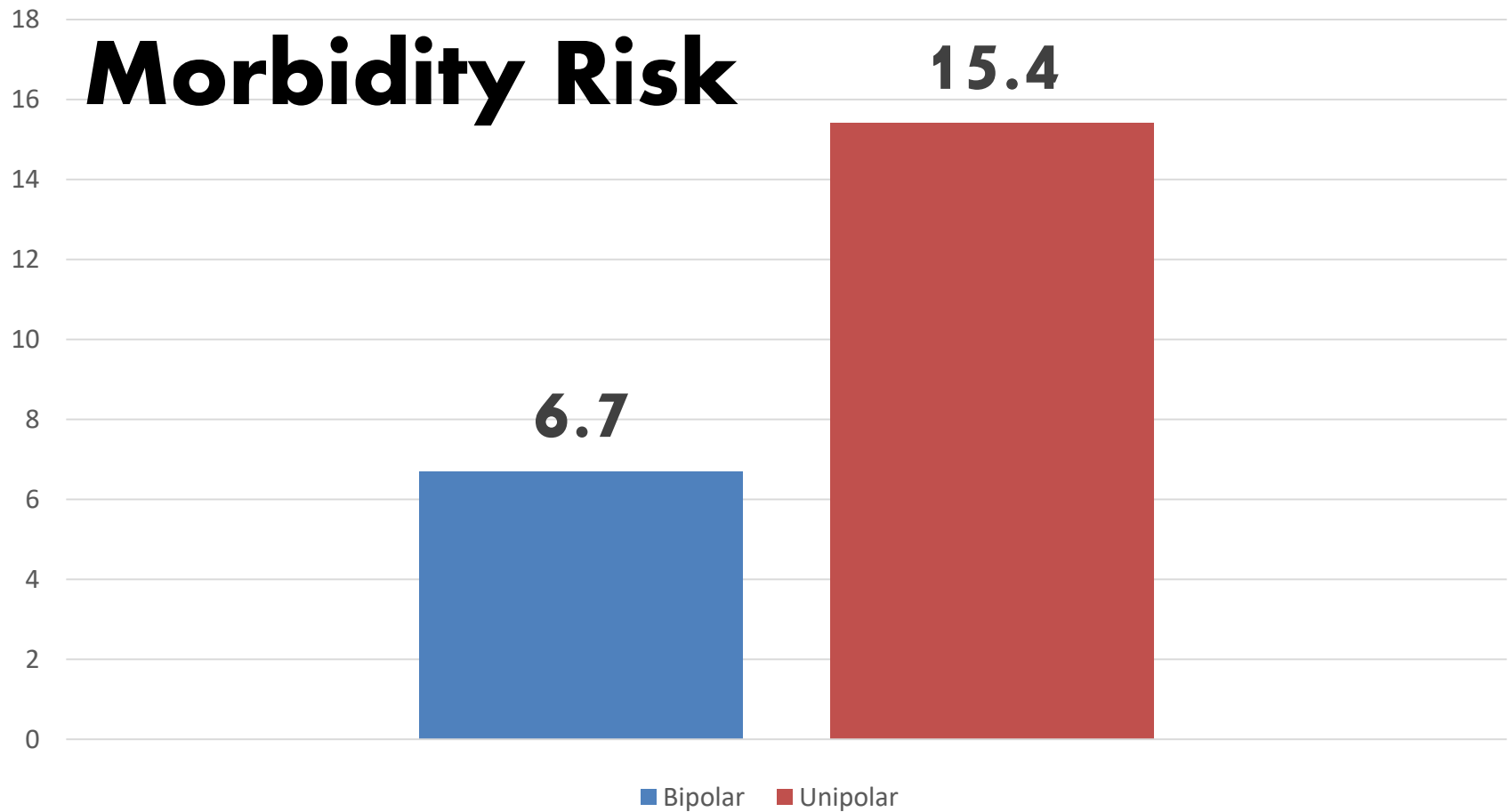
	First Degree Relatives			
	Bipolar		Unipolar	
Probands	MR	OR	MR	OR
Bipolar	6.7%	10.8*	15.4%	3.3*
Unipolar	2.2%	3.4*	18.7%	4.2*
Controls	0.7%	1	5.2%	1

MR = Morbid Risk;

OR = Odds Ratio (vs. controls) \*  $p < 0.001$

Adapted from Smoller and Finn  
(2003) Am J Med Genet 123C:48–58.

# First degree relatives of BP probands more likely to be unipolar

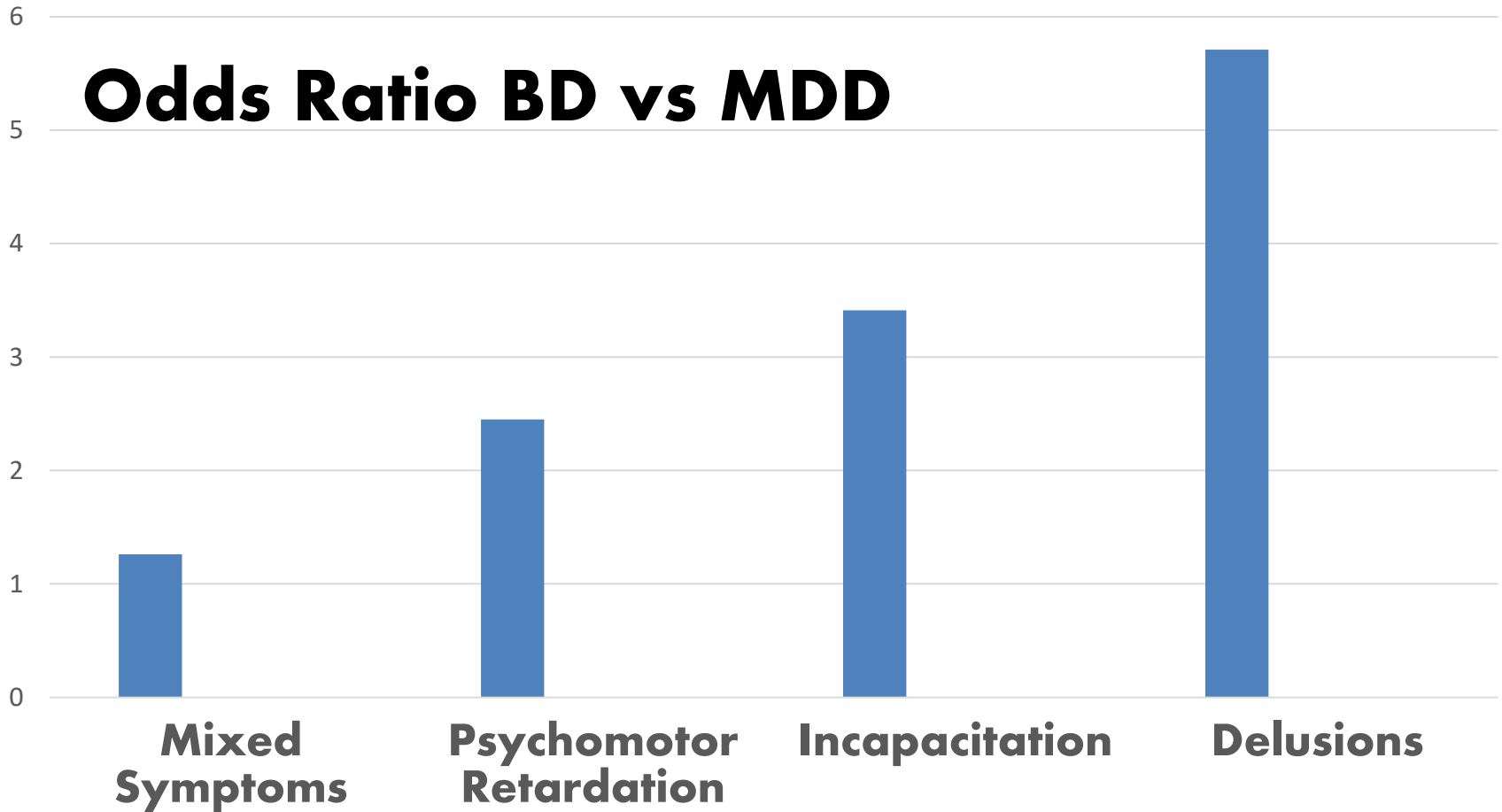


# Unipolar or Bipolar

---

## **Symptoms**

# Symptoms



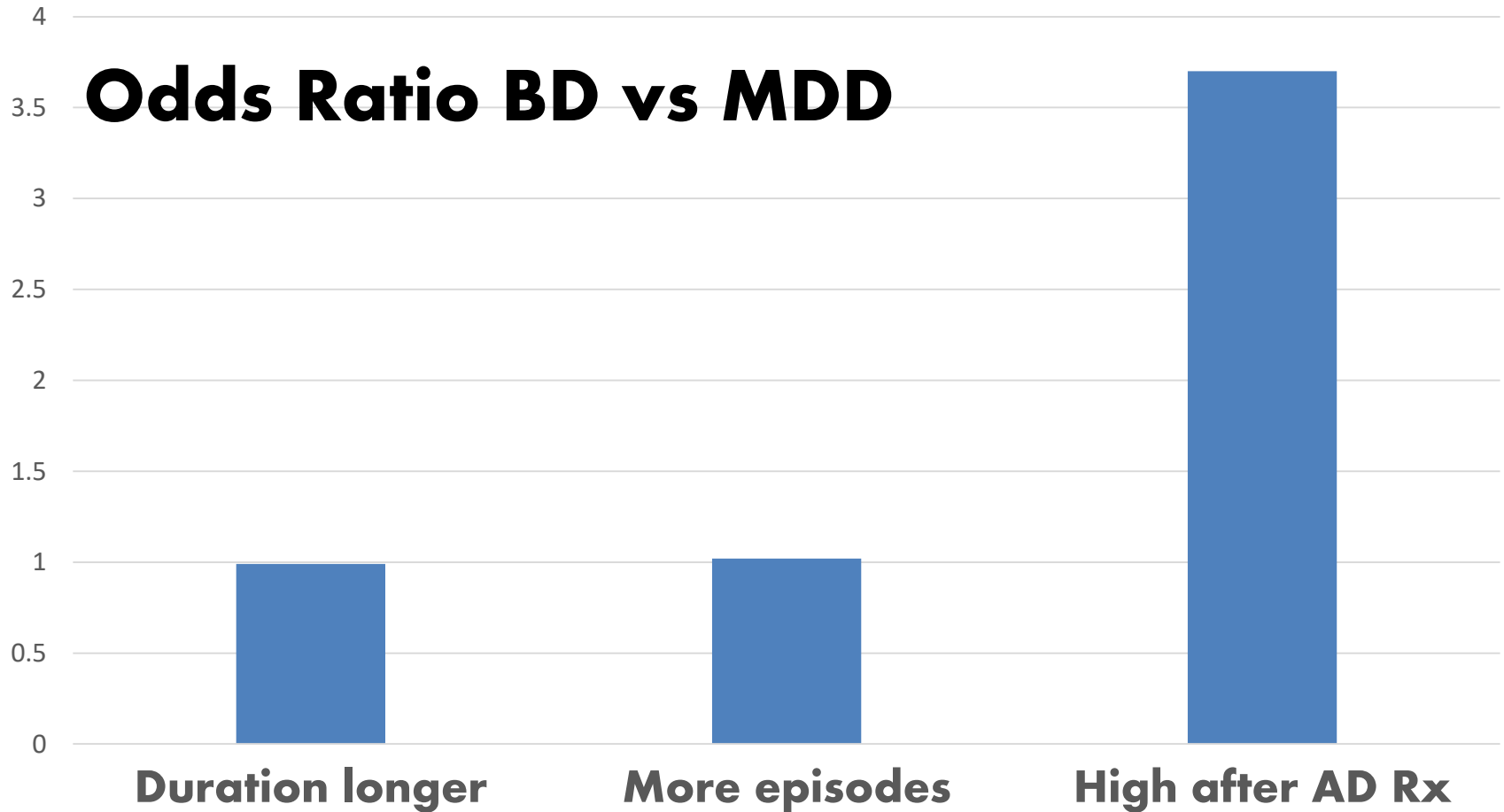
# Unipolar or Bipolar

---

**Course**



# Course





# **Early onset of depression before age 17-18 > risk of BPD**

Beesdo K, Hofler M, Leibenluft E, Lieb R, Bauer M, Pfennig A. Mood episodes and mood disorders: patterns of incidence and conversion in the first three decades of life. *Bipolar Disord* (2009) 11:637–49. doi: 10.1111/j.1399-5618.2009.00738.x

# Unipolar or Bipolar

---

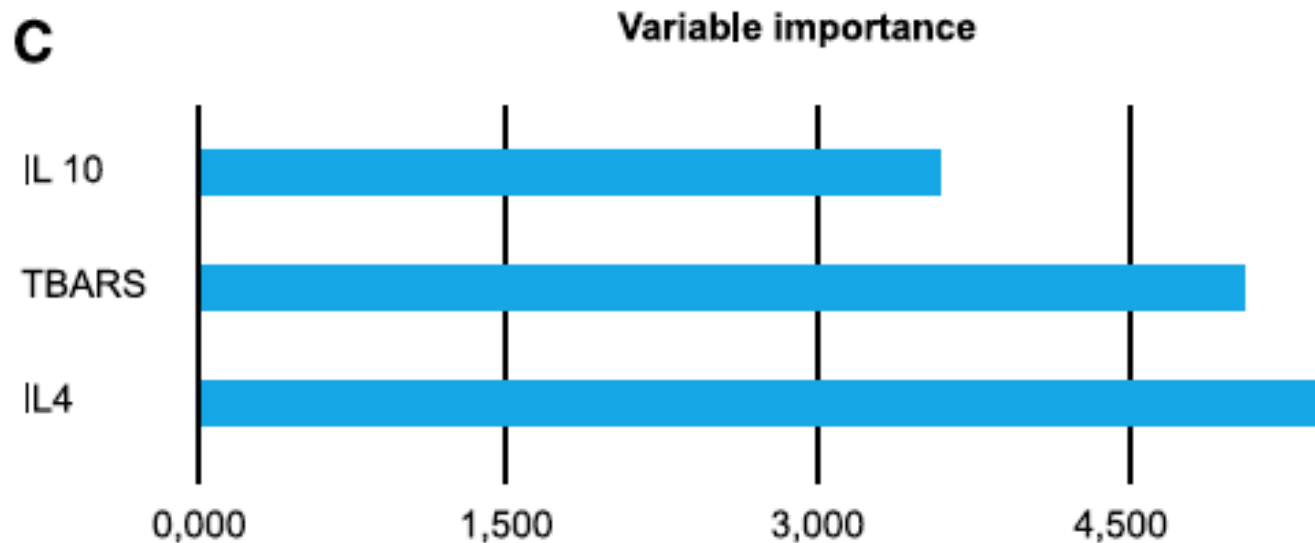
## **Biomarkers**

# Differential biomarker signatures in unipolar and bipolar depression: A machine learning approach

Australian & New Zealand Journal of Psychiatry  
2020, Vol. 54(4) 393–401  
DOI: 10.1177/0004867419888027

© The Royal Australian and  
New Zealand College of Psychiatrists 2019  
Article reuse guidelines:  
[sagepub.com/journals-permissions](https://sagepub.com/journals-permissions)  
[journals.sagepub.com/home/anp](https://journals.sagepub.com/home/anp)  
SAGE

Bianca Wollenhaupt-Aguiar<sup>1,2</sup> , Diego Librenza-Garcia<sup>1,2,3</sup>,  
Giovana Bristot<sup>2,4</sup>, Laura Przybylski<sup>5</sup>, Laura Stertz<sup>2,4</sup>,  
Renan Kubiachi Burque<sup>2</sup>, Keila Mendes Ceresér<sup>2,3</sup>,  
Lucas Spanemberg<sup>3,6,7,8</sup>, Marco Antônio Caldieraro<sup>3,6</sup>,  
Benicio N Frey<sup>1,9</sup>, Marcelo P Fleck<sup>3,6,10</sup>,  
Marcia Kauer-Sant'Anna<sup>2,3,4,10</sup>, Ives Cavalcante Passos<sup>2,3,10</sup>  
and Flavio Kapczinski<sup>1,2,3,10</sup>



Interleuken 10 and 4; thiobarituristic acid reactive substances

# Neuroimaging: Cortical Network Connectivity

## Functional connectomics of affective and psychotic pathology

Justin T. Baker<sup>a,b,1</sup>, Daniel G. Dillon<sup>b,c</sup>, Lauren M. Patrick<sup>d</sup>, Joshua L. Roffman<sup>b,e,f</sup>, Roscoe O. Brady Jr.<sup>a,b,g</sup>, Diego A. Pizzagalli<sup>b,c</sup>, Dost Öngür<sup>a,b</sup>, and Avram J. Holmes<sup>c,d,h,1</sup>

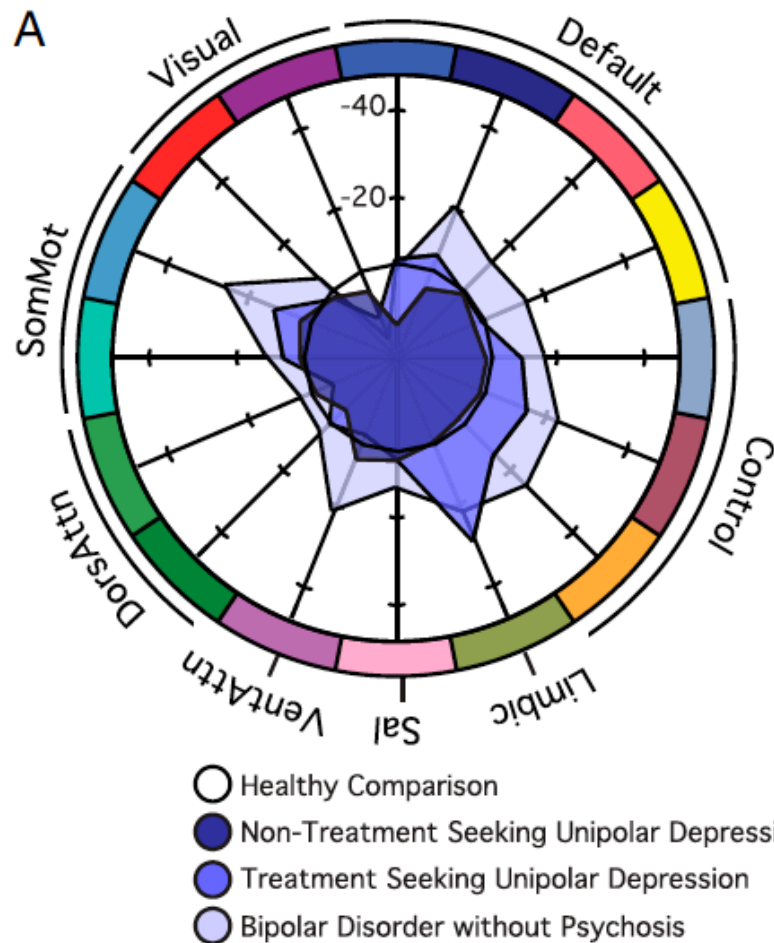
<sup>a</sup>Schizophrenia and Bipolar Disorder Program, McLean Hospital, Belmont, MA 02478; <sup>b</sup>Department of Psychiatry, Harvard Medical School, Boston, MA 02114; <sup>c</sup>Center for Depression, Anxiety and Stress Research, McLean Hospital, Belmont, MA 02478; <sup>d</sup>Department of Psychology, Yale University, New Haven, CT 06520; <sup>e</sup>Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Charlestown, MA 02129; <sup>f</sup>Department of Psychiatry, Massachusetts General Hospital, Boston, MA 02114; <sup>g</sup>Department of Psychiatry, Beth Israel Deaconess Medical Center, Boston, MA 02114; and <sup>h</sup>Department of Psychiatry, Yale University, New Haven, CT 06520

Edited by Marcus E. Raichle, Washington University in St. Louis, St. Louis, MO, and approved March 21, 2019 (received for review December 6, 2018)



PNAS 2019;116:9050-9059

## Affective Illness without Psychosis Percent Deviation from Health





**No clinically useful biomarker  
exists to differentiate bipolar  
from unipolar depression.**



**Will a first degree relative of someone who has bipolar disorder be more likely to have bipolar or unipolar depression?**

# Unipolar or Bipolar

---

## Genetics



# Polygenic risk scores (PRS)


- **Predictors of genetic susceptibility to diseases,**
- **Calculated for individuals**
- **Weighted counts of thousands of risk variants identified in genome-wide association studies**

JAMA Psychiatry. 2021;78(2):210-219. doi:10.1001/jamapsychiatry.2020.3042

## Original Article

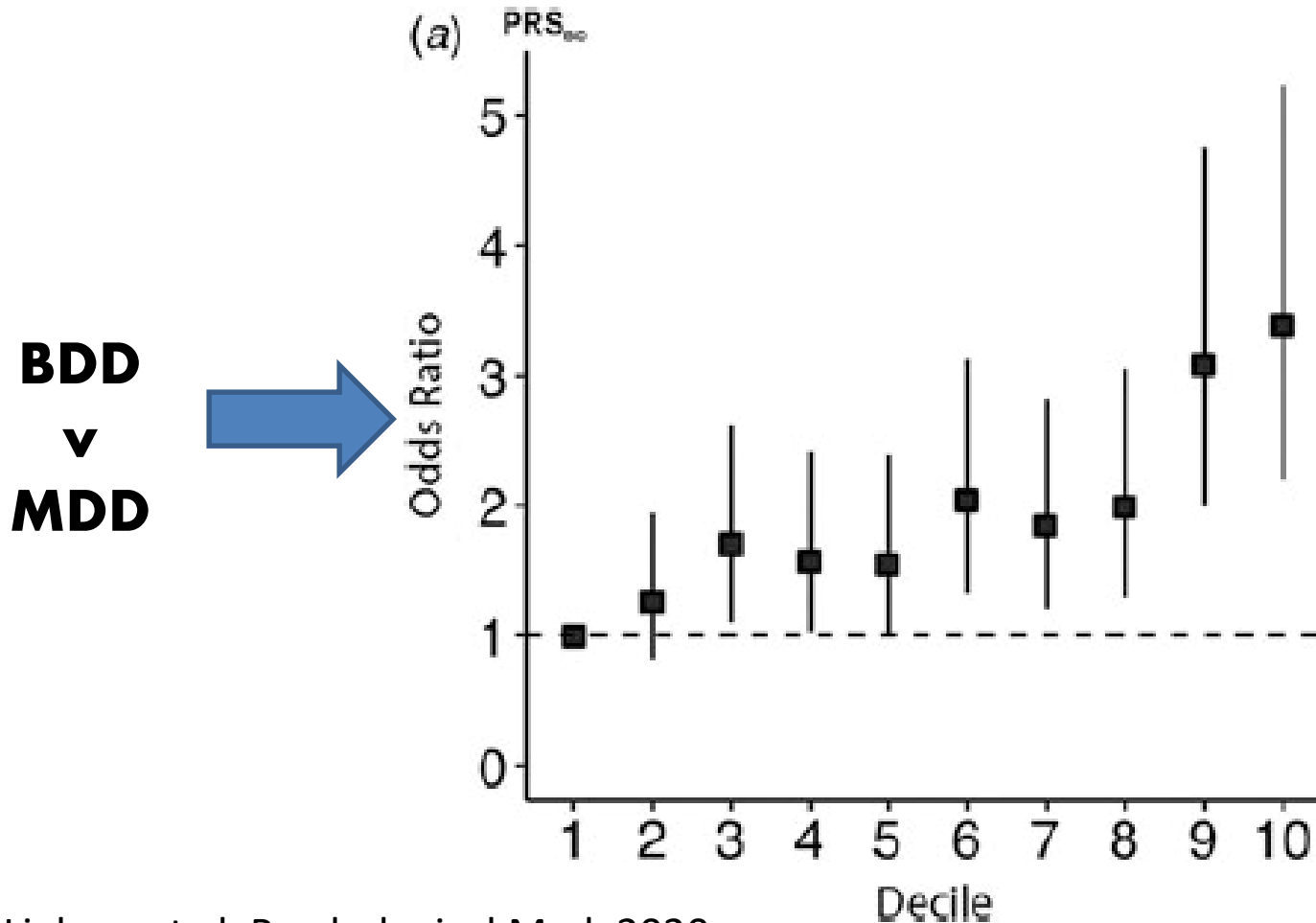
**Cite this article:** Liebers DT, Pirooznia M, Ganna A, Bipolar Genome Study (BiGS), Goes FS (2020). Discriminating bipolar depression from major depressive disorder with polygenic risk scores. *Psychological Medicine* 1–8. <https://doi.org/10.1017/S003329172000015X>

# Discriminating bipolar depression from major depressive disorder with polygenic risk scores

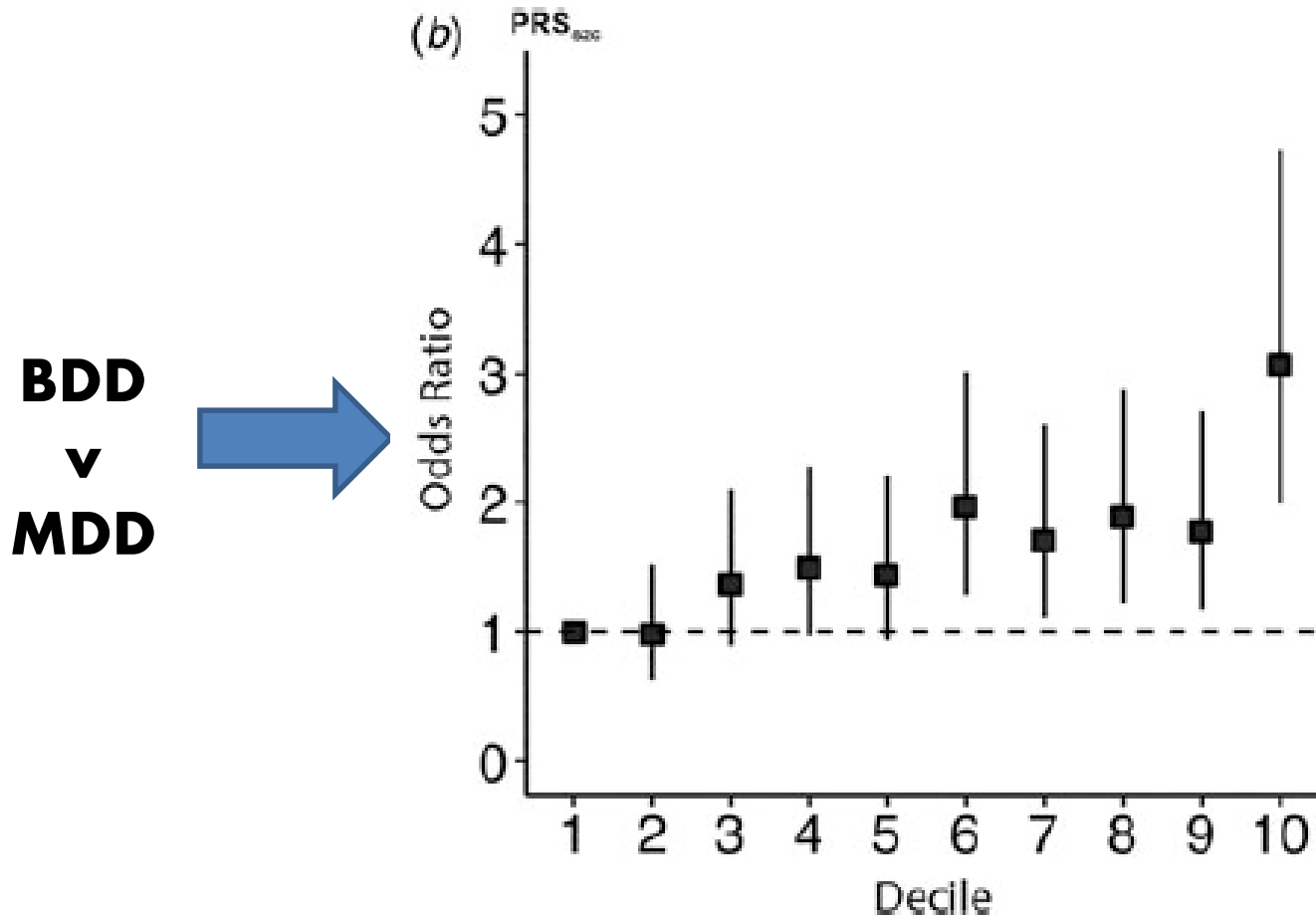
David T. Liebers<sup>1</sup>, Mehdi Pirooznia<sup>2</sup>, Andrea Ganna<sup>3,4,5,6</sup>, Bipolar Genome Study (BiGS) and Fernando S. Goes<sup>2</sup> 

<sup>1</sup>Harvard Medical School, Boston, MA 02115, USA; <sup>2</sup>Department of Psychiatry and Behavioral Sciences, Johns Hopkins Institute of Medicine, Baltimore, MD 21205, USA; <sup>3</sup>Analytic and Translational Genetics Unit, Massachusetts General Hospital, Boston, MA, USA; <sup>4</sup>Program in Medical and Population Genetics, Broad Institute of MIT and Harvard, Cambridge, MA, USA; <sup>5</sup>Stanley Center for Psychiatric Research, Broad Institute of MIT and Harvard, Cambridge, MA, USA and <sup>6</sup>Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

# Polygenic Risk Score for BD > Odds of BDD vs MDD



# Polygenic Risk Score for Schizophrenia > Odds of BDD vs MDD



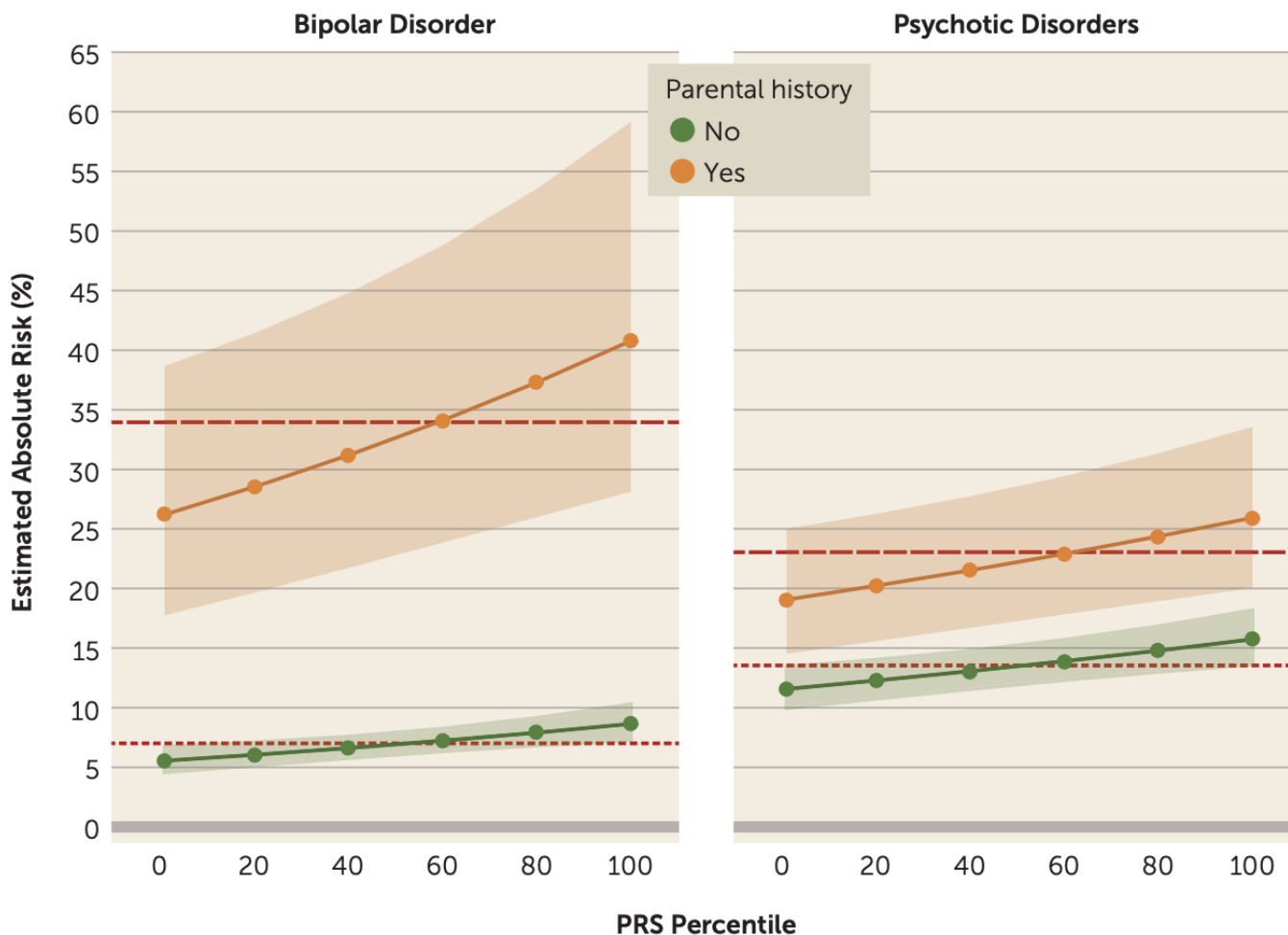
# Polygenic Risk and Progression to Bipolar or Psychotic Disorders Among Individuals Diagnosed With Unipolar Depression in Early Life

Katherine L. Musliner, Ph.D., M.P.H., Morten D. Krebs, M.D., Clara Albiñana, M.Sc., Bjarni Vilhjalmsón, Ph.D., M.Sc., Esben Agerbo, Dr.Med.Sc., M.Sc., Peter P. Zandi, Ph.D., M.P.H., David M. Hougaard, Dr.Med.Sc., M.D., Merete Nordentoft, Dr.Med.Sc., M.D., Anders D. Børglum, Ph.D., M.D., Thomas Werge, Ph.D., M.Sc., Preben B. Mortensen, Dr.Med.Sc., M.D., Søren D. Østergaard, Ph.D., M.D.

Predictor	Diagnosis	HR (95% CI)
PRS-BD*	BD	1.11 (1.03-1.21)
Parental BD^	BD	5.02 (3.53-7.14)
PRS-SCZ*	Psychotic Disorder	1.10 (1.04-1.16)
Parental SCZ^	Psychotic Disorder	1.63 (1.30-2.06)
* per 1 SD increase; ^ adjusting for disorder PRS		

- N = 16,949 (iPsych); age 10-35 at first depression diagnosis
- Mean follow-up = 7 years
- Three PRS: SCZ, BD, MDD

# Parental History > Risk than PRS





**Parental history of bipolar  
disorder > impact on  
conversion of MDD to BD than  
polygenic risk score.**



**Write (at least) two things to  
differentiate bipolar from  
unipolar depression.**





# Rapid Mood Screener

Roger S. McIntyre, et al. (2021) The Rapid Mood Screener (RMS): a novel and pragmatic screener for bipolar I disorder, Current Medical Research and Opinion, 37:1, 135-144

# **Rapid Mood Screener**

---

- 1. Have there been at least 6 different periods of time (at least 2 weeks) when you felt deeply depressed?**

# Rapid Mood Screener

---

- 2. Did you have problems with depression before age 18?**

# Rapid Mood Screener

---

- 3. Have you ever had to stop or change your antidepressant because it made you highly irritable or hyper?**

# Rapid Mood Screener

---

**4. Have you ever had a period of at least 1 week during which you were more talkative than normal with thoughts racing in your head?**

# Rapid Mood Screener

---

**5. Have you ever had a period of at least 1 week during which you felt any of the following: unusually happy; unusually outgoing; or unusually energetic?**

# Rapid Mood Screener

---

**6. Have you ever had a period of at least 1 week during which you needed much less sleep than usual?**

# Rapid Mood Screener

**$\geq 4$  positive answers**

- Sensitivity .88**
- Specificity .80**
- Positive predictive value .80**
- Negative predictive value .88**



# Bipolar or Unipolar

---

**Demographics**

**Family history**

**Symptoms**

**Course**

**Biomarkers**

# Bipolar or Unipolar

---

**Genetics**

**Screening tools**