



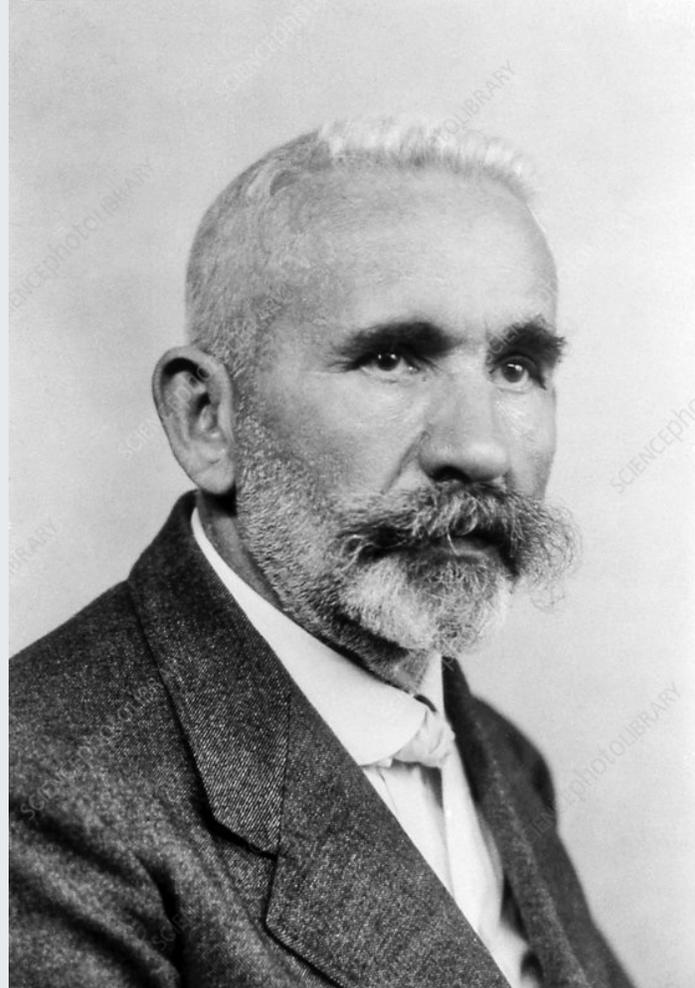
# Can polygenic risk scores explain differences in symptom dimensions in first-episode psychosis?

**Diego Quattrone & Evangelos Vassos**

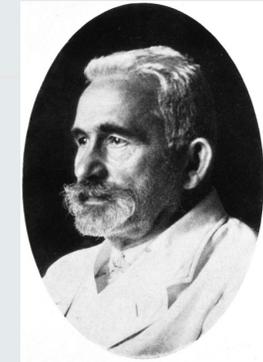
Social, Genetic, and Developmental Psychiatry Centre

Institute of Psychiatry, King's College London

# Why dimensions?



# Classification in Psychiatry



Emil Kraepelin (1856-1926)

## BETHLEM HOSPITAL PATIENT ADMISSION REGISTER, OCTOBER 1888

This record is available on Findmypast

REGISTER OF

NO.	NAME	RESIDENCE	DATE OF ADMISSION	BY WHOM REQUESTED	BY WHOM ADMITTED	REMARKS	BY WHOM RECEIVED	REMARKS
1	John J. ...	...	...	...	...	Dep.	...	...
2	William ...	...	...	...	...	P.P.	...	...
3	...	...	...	...	...	...	...	...
4	...	...	...	...	...	...	...	...

**1 SURETIES**  
Here you can find the names and addresses of friends or relatives who would vouchsafe for payment of a patient's fees, sometimes a deposit was left ("Dep.").

**2 SEX AND CLASS**  
This differentiates between paupers and private patients ("P. P.") — note that Bethlem stopped admitting paupers in 1857.

**3 BY WHOSE AUTHORITY SENT**  
This column provides the name/address of whoever requested admission; for county asylums, this would usually be a Poor Law Union official.

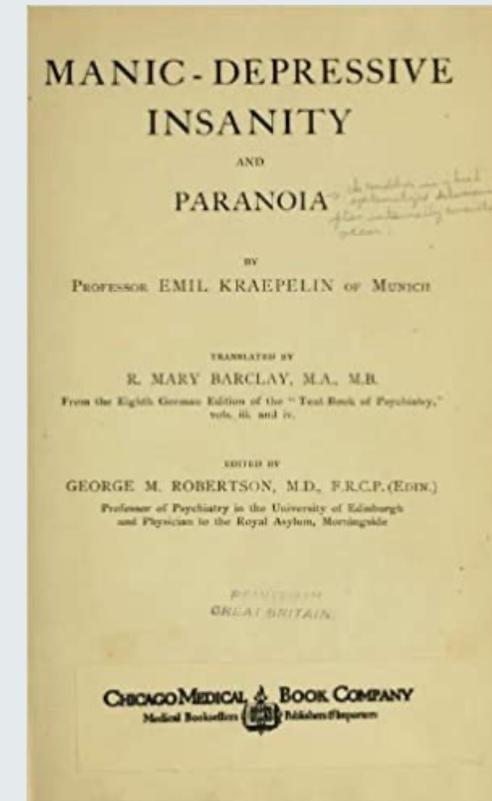
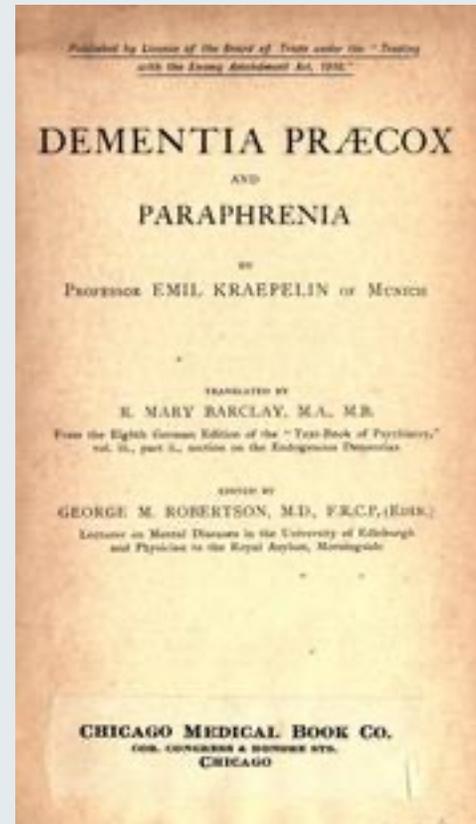
PATIENTS.

NO.	NAME	RESIDENCE	DATE OF ADMISSION	BY WHOM REQUESTED	BY WHOM ADMITTED	REMARKS	BY WHOM RECEIVED	REMARKS
1	...	...	...	...	...	...	...	...
2	...	...	...	...	...	...	...	...
3	...	...	...	...	...	...	...	...
4	...	...	...	...	...	...	...	...
5	...	...	...	...	...	...	...	...
6	...	...	...	...	...	...	...	...

**4 CONDITION OF LIFE, AND PREVIOUS OCCUPATION**  
The patient's occupation is given; other details may be provided such as "reduced circumstances".

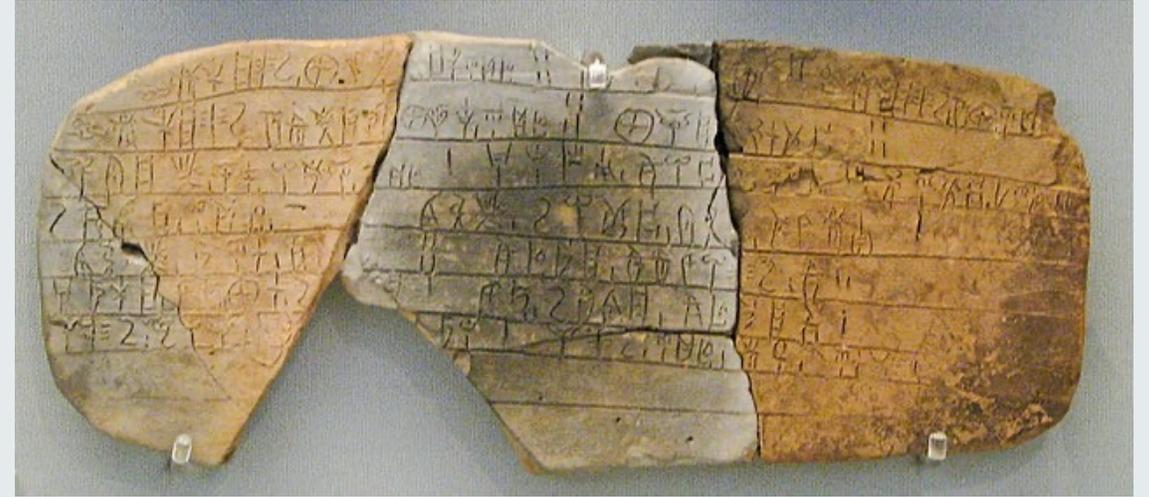
**5 DURATION OF EXISTING ATTACKS, AND NUMBER OF PREVIOUS ATTACKS**  
This reveals how long the patient was ill before their admission, and whether he or she had suffered from insanity before.

**6 SUPPOSED CAUSE OF INSANITY**  
This lists possible reasons given by the family for the patient's illness.



# Mycenaean Palace of Tiryns (1400 to 1200 BC)

## - Linear B script



This piece contains information on the distribution of bovine, pig and deer hides to shoe and saddle-makers. Linear B was the earliest Greek writing, dating from 1450 BC



# QUESTION

Are you happy with current diagnostic categories in psychiatry?



# The roots of DSM

**1920s: Operationalism**, a way to avoid metaphysical assumptions over the scientific progress (Bridgman, 1927)

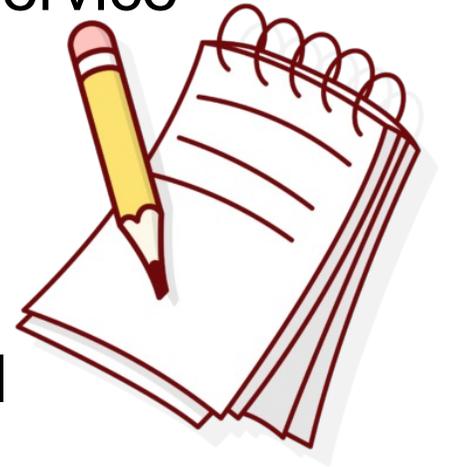
**1959:** Carl Hempel's lecture at the American Psychopathological Association

**1966-1971:** The US-UK diagnostic project

# Clinical case

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- Mr X is 37-year-old Cockney labourer presenting today to our service
- Normal developmental history
- Regular use of cannabis since adolescence
- Prodromal symptoms since his 20s with depressive symptoms, paranoia around colleagues, and progressive social withdrawal
- First episode of psychosis at age 21
- Florid psychotic symptoms, first rank symptoms
- Good response to antipsychotic medication



# Mr X presentation today

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- Taken to the place of safety (PoS) as wandering in the street, bizarre behaviour
- At the interview, he was euphoric and talkative
- He revealed an elaborate series of grandiose delusions, centred on the belief that he was “King David”
- UDS negative for common drugs
- **QUESTION** What diagnosis?



## Diagnostic Criteria of American and British Psychiatrists

*United Kingdom*  
R. E. Kendell, MD, MRCP, DPM }  
J. E. Cooper, MRCP, DPM } London  
A. J. Gourlay, MA }  
J. R. M. Copeland, MRCP, DPM }

*United States*  
L. Sharpe, MB, DPM }  
B. J. Gurland, MRCP, DPM } New York

PATIENT C.—This was a 37-year-old Cockney laborer who, like patient A, had both schizophrenic and affective symptoms. At the time of interview he was euphoric and talkative and revealed an elaborate series of grandiose delusions, centered on the belief that he was “King David,” but he was prone to marked fluctuations of mood and had had periods of deep depression in the past. Again, most raters in both countries regarded him as a schizophrenic but again a significant minority (20%) of the British raters regarded him as a manic depressive and a further 17% gave this as an alternative diagnosis (Table 3). By comparison, only 8% of the American raters even considered an affective illness as an alternative to schizophrenia.

# Are you more an American or more a British psychiatrist?

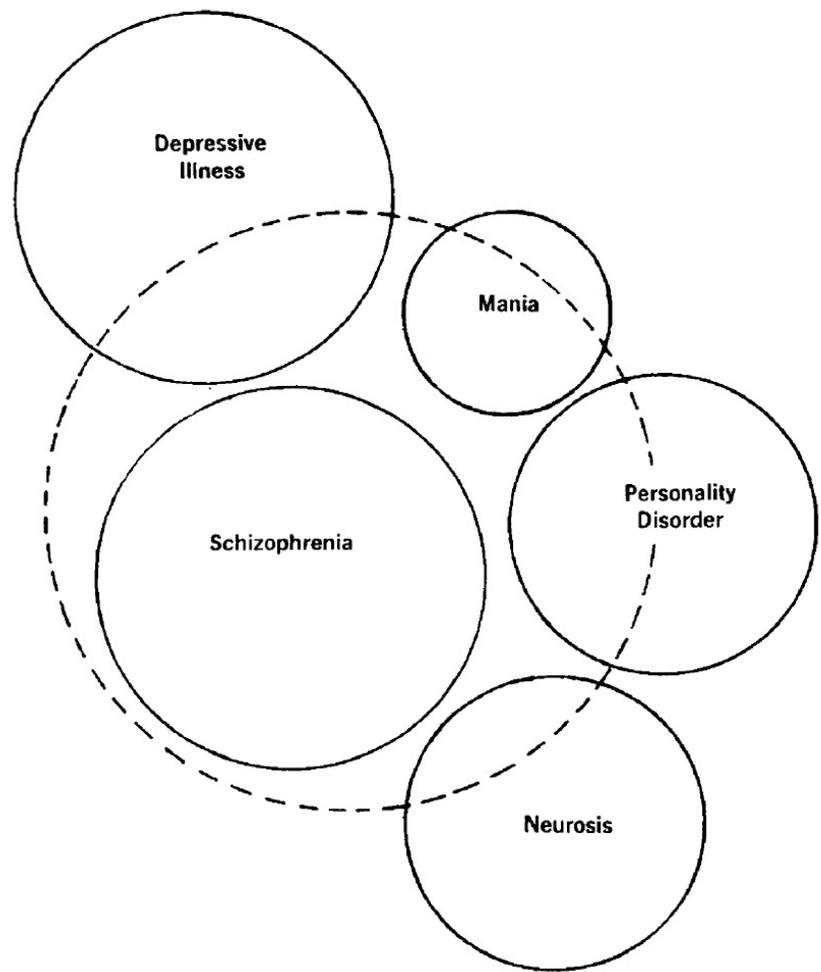
## Diagnostic Criteria of American and British Psychiatrists

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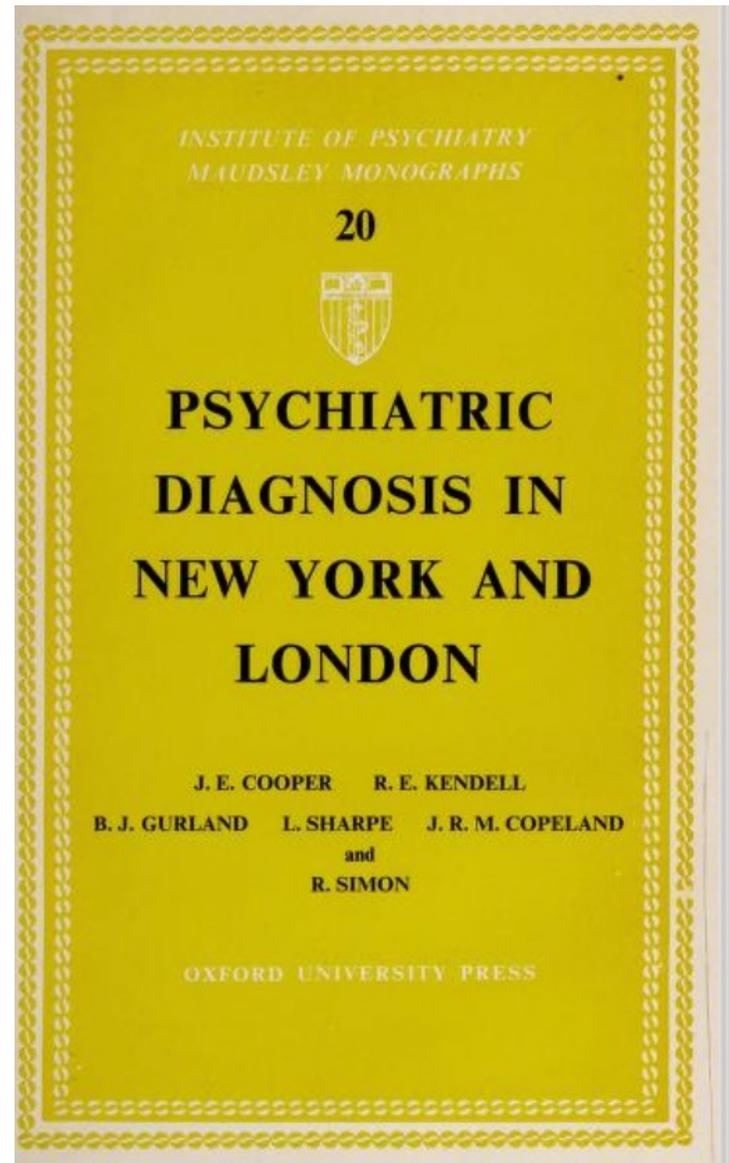
**Table 3.—Diagnoses Given to Patient C**

	American Psychiatrists (N = 39)	British Psychiatrists (N = 30)
<b>Schizophrenia</b>	37 (95%)	23 (77%)
Hebephrenic	0	1
Paranoid	32	15
Acute schizophrenic episode	1	3
Residual	1	0
Schizo-affective	2	3
Unspecified	1	1
<b>Manic Depressive Psychoses</b>	0	6 (20%)
Manic depressive, manic	0	2
Manic depressive, circular	0	4
<b>Other Diagnoses</b>	2	1
<b>Alternative Diagnosis of   Affective Psychosis</b>	3 (8%)	5 (17%)



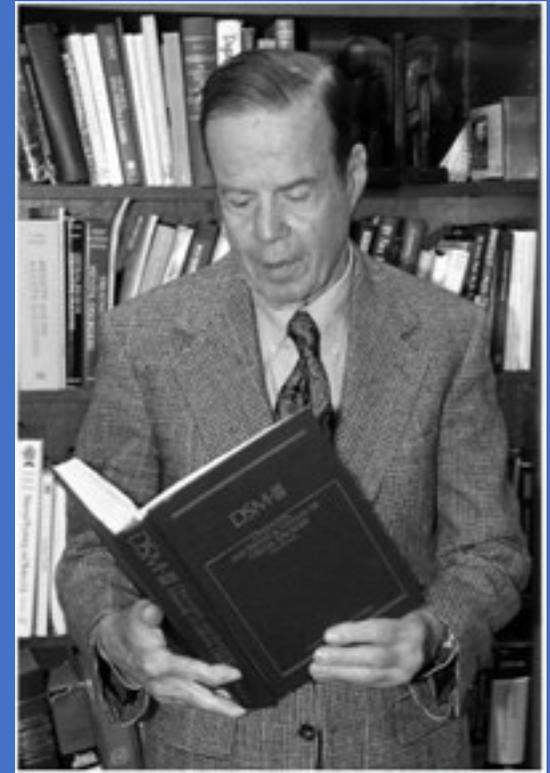
————— British Concepts  
 - - - - - American Concept of Schizophrenia

Arch Gen Psychiat/Vol 25, Aug 1971



# The roots of DSM

Spitzer and the development of the DSM-III



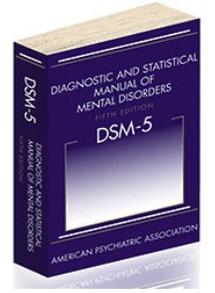
# The development of the DSM

In summary, the operationalised principles that guided the US-UK 'operationalised' task force required that:

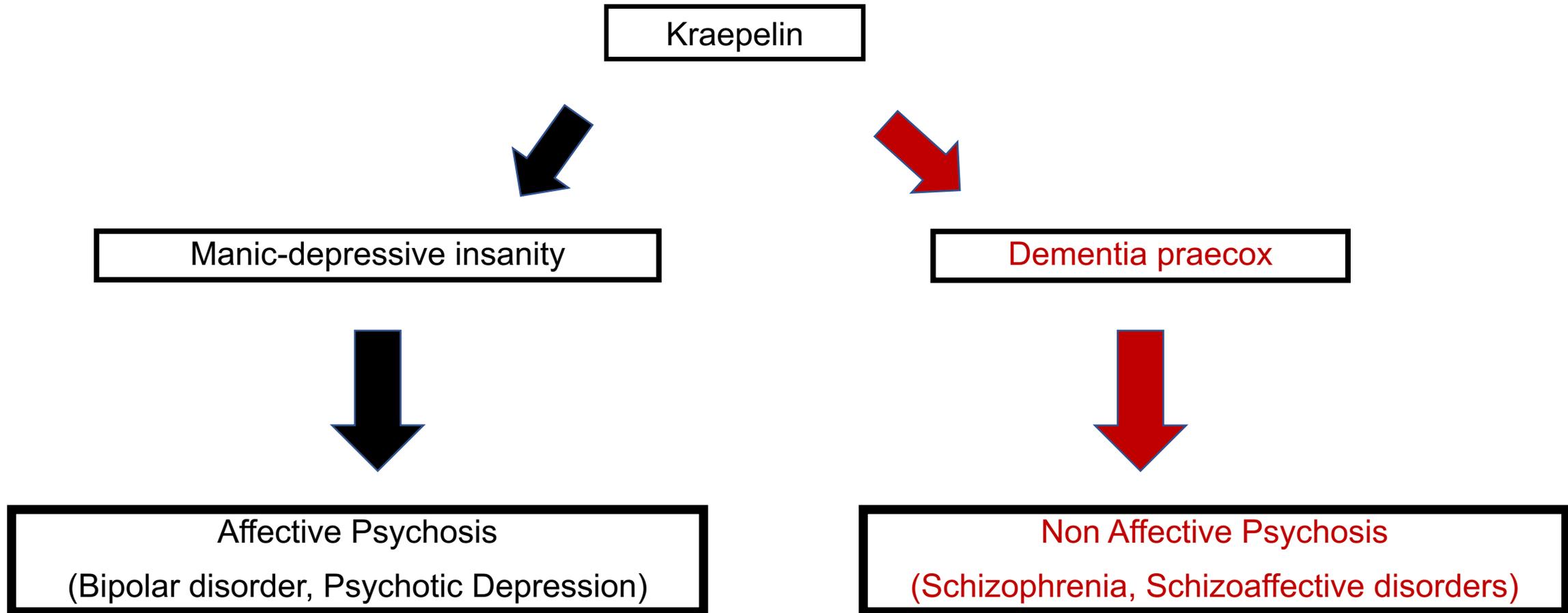
- 1) aetiology should be excluded as a classificatory principle since unknown;
- 2) phenomenology should be excluded as too complex;
- 3) diagnostic criteria should be based upon easily observable features;
- 4) diagnoses should reflect narrow, rather than broad, disorders;
- 5) diagnoses should be mutually exclusive



# The hot question in psychiatric nosology



Categorical diagnostic classification may not reflect clear biological entities



# Use of a Classification System

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- Communication: among clinicians, science and practice, doctor and patient
- Clinical: facilitate identification, treatment, and prevention of mental disorders
- Research: group individuals to test hypotheses. Context for providing causal understanding of phenomena and measure effects of treatment
- Education: organise psychopathology for teaching
- Information management: measure and cost mental health care services

## Some unforeseen consequences of operationalism: the decline of phenomenology

- ‘Reification’ of psychiatric disorders, due to the widespread acceptance of DSM (Stephen Hyman, 2010).
- *DSM led to the ‘death of phenomenology’ and dehumanised the practice of psychiatry* (Nancy Andreasen, 2007)



## Some unforeseen consequences of operationalism: the decline of phenomenology

*“...these [DSM-III] criteria may not be employed to the fullest advantage.[...] German phenomenological psychiatry, so influential elsewhere, never took root in North America. Consequently, even in the most research-oriented centres, the attempt to diagnose according to strictly defined conventions founders at times on an inability to elicit mental phenomena accurately”*

(Robin Murray, 1979)



# Transdiagnostic research

*“Schizophrenia is an idea whose very essence is **equivocal**, a nosological category without natural boundaries, a barren hypothesis.*

*Such a blurred concept is **'not a valid object of scientific enquiry'** ... It is a cloak for **ignorance** and exposes psychiatry to ridicule.*

*As a model of psychosis it is an **oversimplification**, which serves the interests of neither scientists nor patients.”*

I.F. Brockington 1992



# Dismantling of much of what we psychiatrists believed about schizophrenia

- First-rank symptoms are common in affective psychosis too
- There is no a schizophrenia gene
- Neurodegeneration in schizophrenia related to bad life habits, antipsychotics, etc., rather than the natural course of the disorder



ELSEVIER

Contents lists available at [ScienceDirect](#)

## Schizophrenia Research

journal homepage: [www.elsevier.com/locate/schres](http://www.elsevier.com/locate/schres)

### The Kraepelian concept of schizophrenia: Dying but not yet dead

Robin M. Murray<sup>\*</sup>, Diego Quattrone

*Institute of Psychiatry, Psychology, and Neuroscience, King's College, London SE5 8AF, United Kingdom of Great Britain and Northern Ireland*



Wall art  
East London

This finely preserved example of primitive art dates from the Post-Catatonic era and is thought to depict early man venturing towards the out-of-town hunting grounds. The artist responsible is known to have created a substantial body of work across the South East of England under the moniker Banksymus Maximus but little else is known about him. Most art of this type has unfortunately not survived. The majority is destroyed by zealous municipal officials who fail to recognise the artistic merit and historical value of daubing on walls.

PRB 17752.2-2.1

# Psychiatric Diagnosis

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“Our classification of mental disorders is no more than a collection of **fallible and limited constructs** that seek but **never find an elusive truth**. Nevertheless, this is our best current way of defining and communicating about mental disorders... It does its job reasonably well when it is applied properly and when its limitations are understood. One must strike a proper balance.”

Frances and Widiger; *Annu. Rev. Clin. Psychol.*, 2012



# Criticism of dimensions

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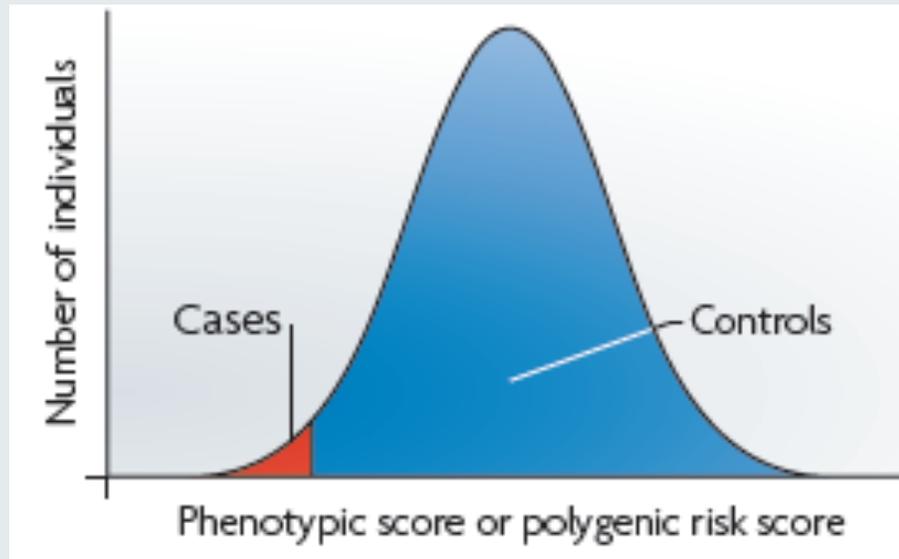
- Symptoms not stable over time
- Concept driven instruments reflect the underlying concepts
- Number of dimensions depends on the number of items used in the factor analysis
- Overrepresentation of specific groups of symptoms

QUESTION: What would be a good proof of the validity of dimensions?

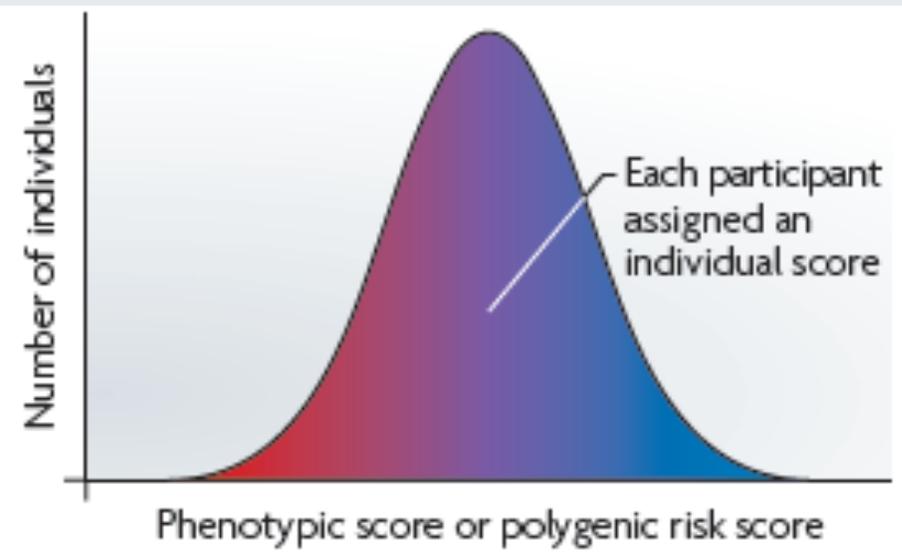
# A quantitative approach to common disorders

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Case - control



Quantitative measurement



Plomin et al. *Nature Review Genetics*, 2009

# Dimensional Approaches to Diagnosis

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- All persons are rated on pre-determined, quantitatively-based dimensions
- In dimensional approaches, there is no assumption of behavioural discontinuity – psychopathology is seen as falling on a continuum
- “more this or less that” not “either/or”

# Aims and hypotheses

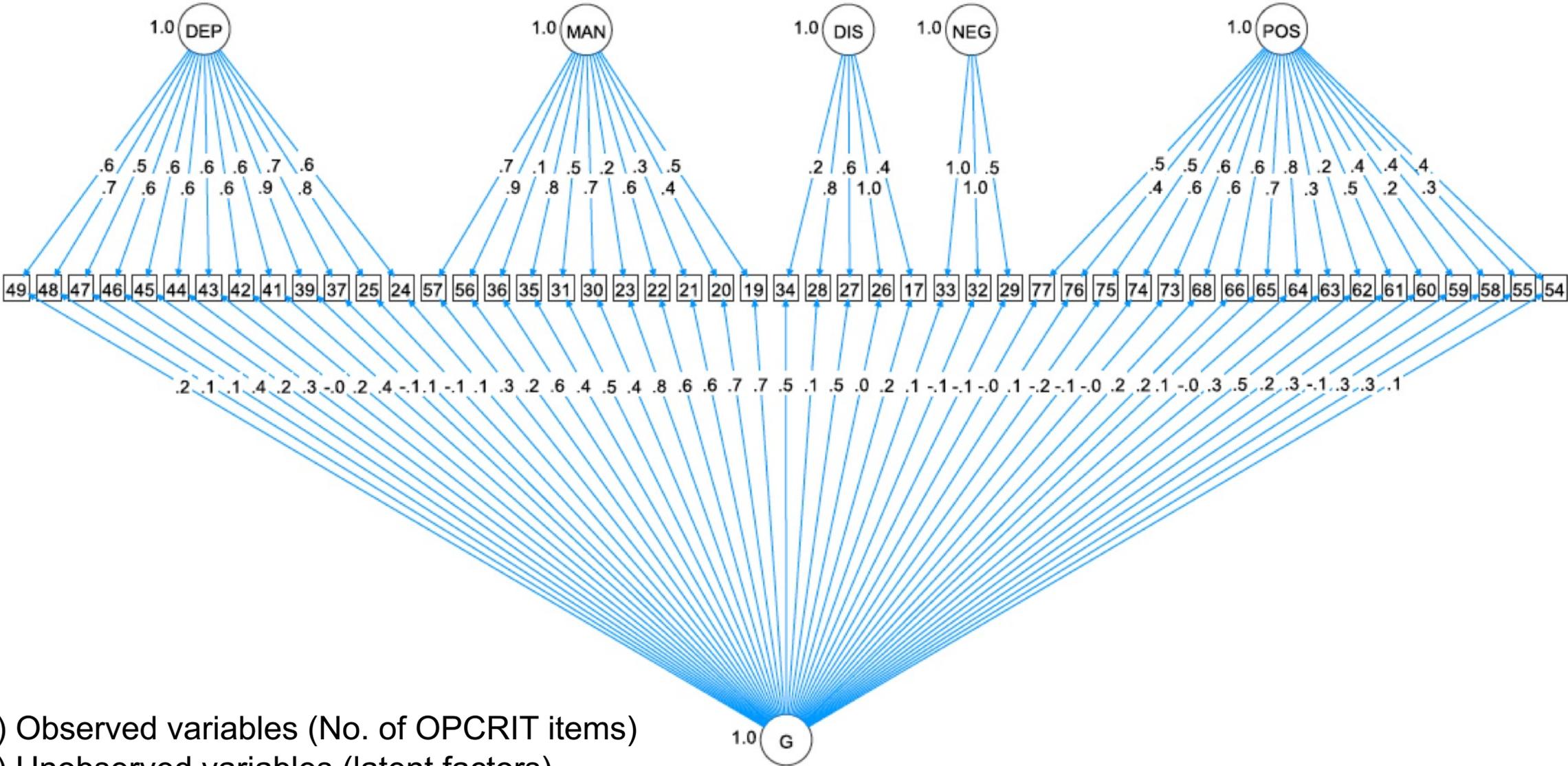
**Examine the dimensional structure of psychopathology in the**

**EUGEI study**

**Does a general factor of psychopathology encompass affective and**

**non-affective psychosis?**

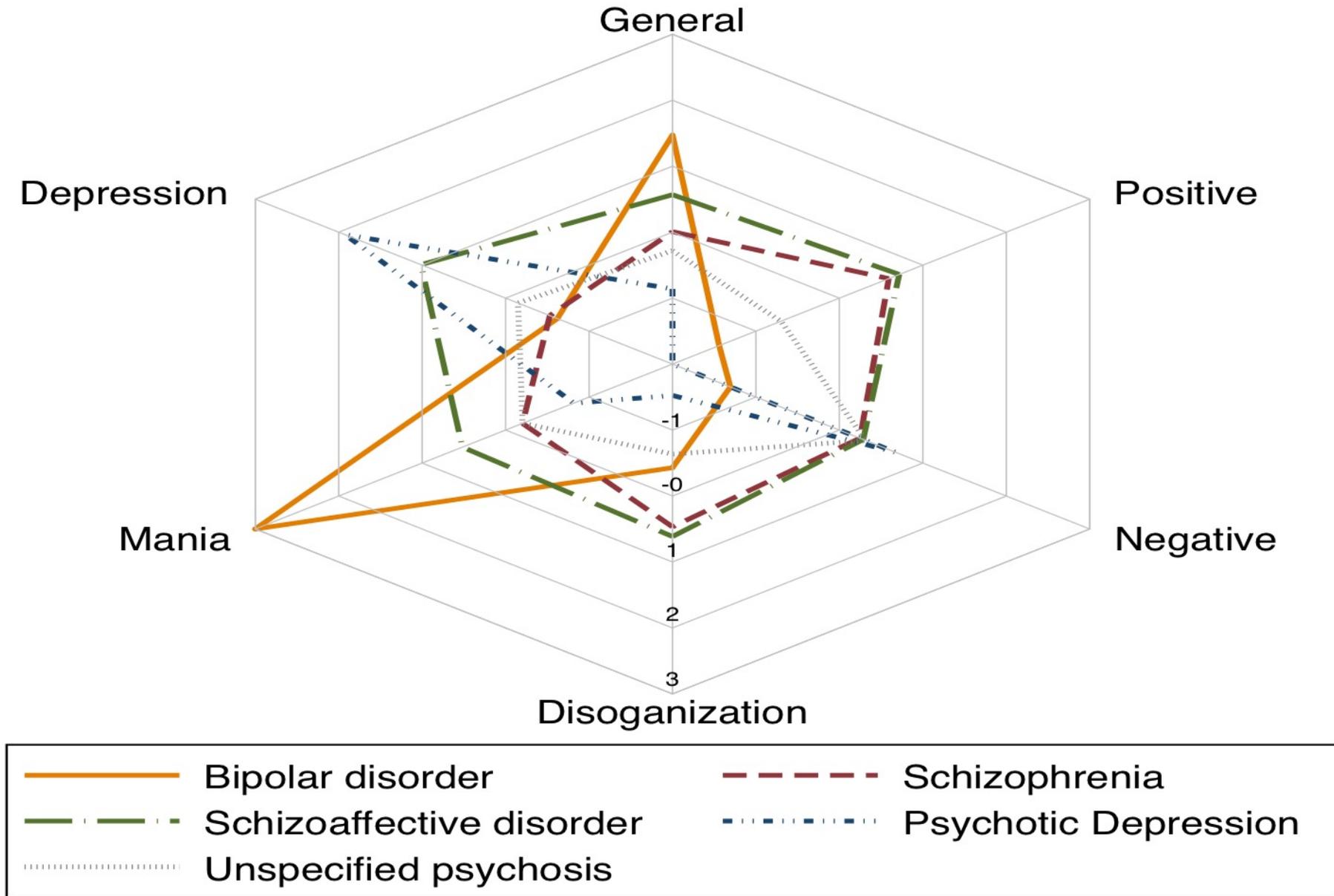
# Bi-factor conceptualization of psychosis



- (□) Observed variables (No. of OPCRIT items)
- (○) Unobserved variables (latent factors)
- (→) standardized item loading onto latent factors

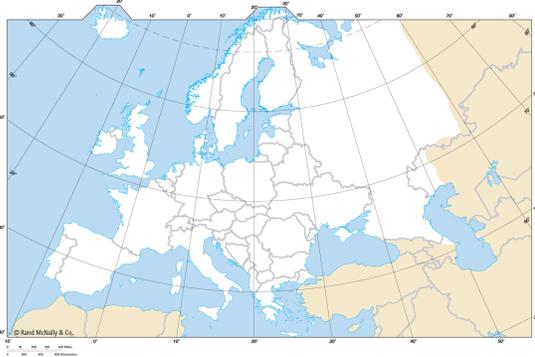
Quattrone D, Di Forti M, Gayer-Anderson C, et al. Transdiagnostic dimensions of psychopathology at first episode psychosis: findings from the multinational EU-GEI study. Psychological medicine. 2018;1-14.

# Symptom dimensions by diagnostic category

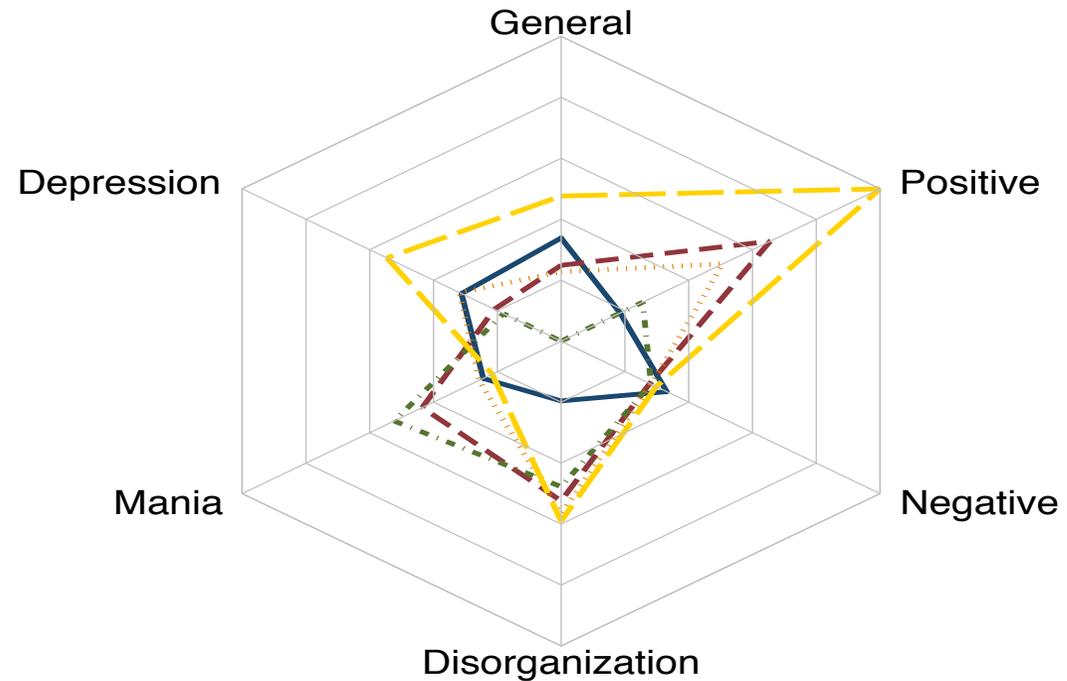


# Symptom dimensions

**EUGEI**



Quattrone et al, 2018, Psychological  
Medicine



# Aims and hypotheses

**Examine the dimensional structure of psychopathology in the EUGEI study**

**We expect that daily users of high-potency cannabis will present with more positive symptoms**

# Positive Dimension & Cannabis Use

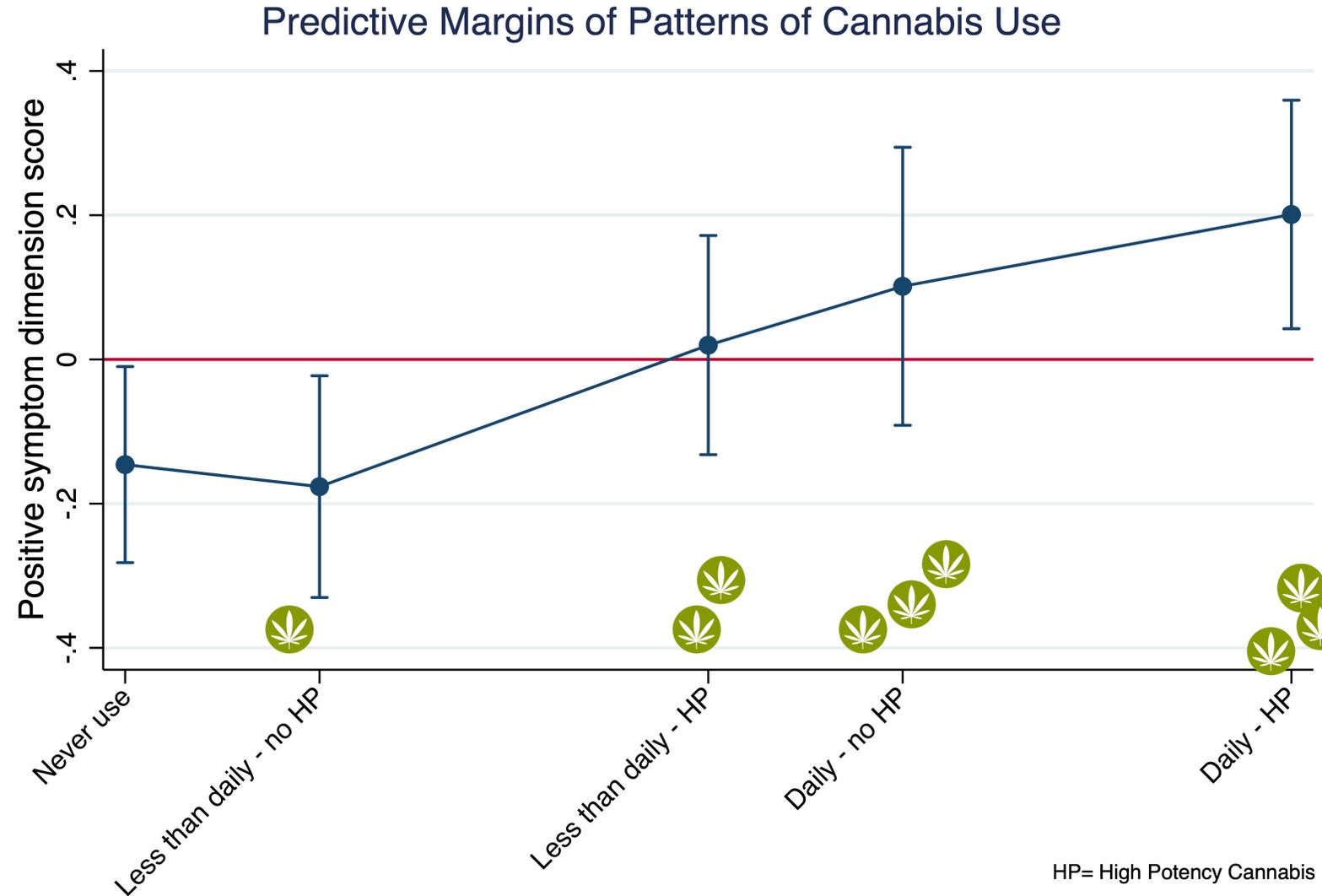
## Frequency

Less than everyday: 🌿

Everyday: 🌿🌿

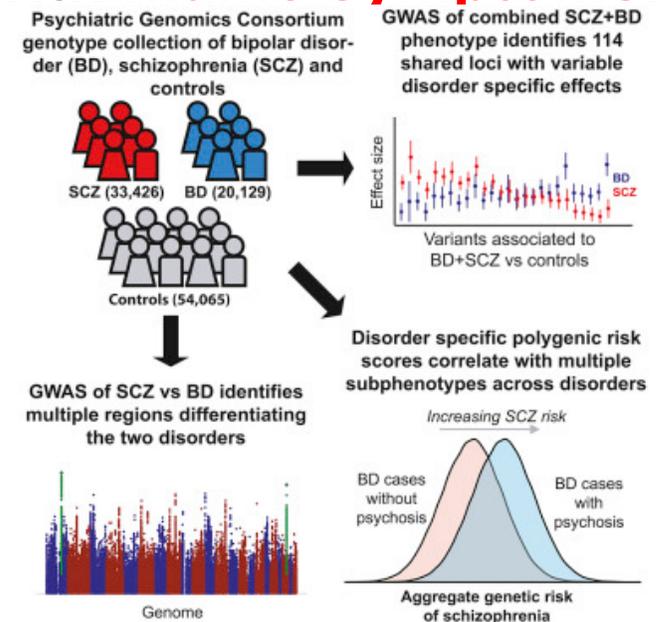
## Potency:

More than 10% THC: 🌿



# Aims and hypotheses

1. Examine effects of common genetic variants associated with Major Mental Disorders on general and specific psychosis dimensions
  - i. We expect that **schizophrenia PRS** would be associated with more **positive / negative symptoms**; **bipolar PRS** with **manic symptoms**.

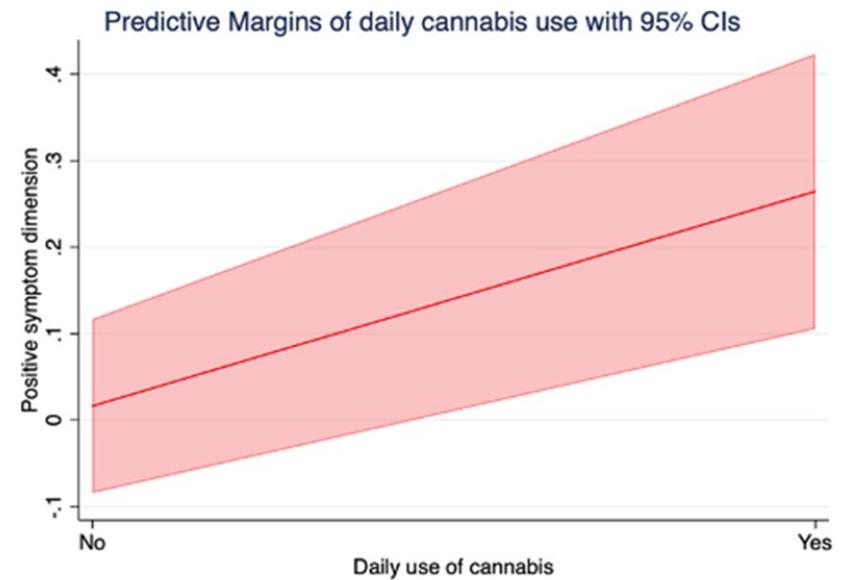
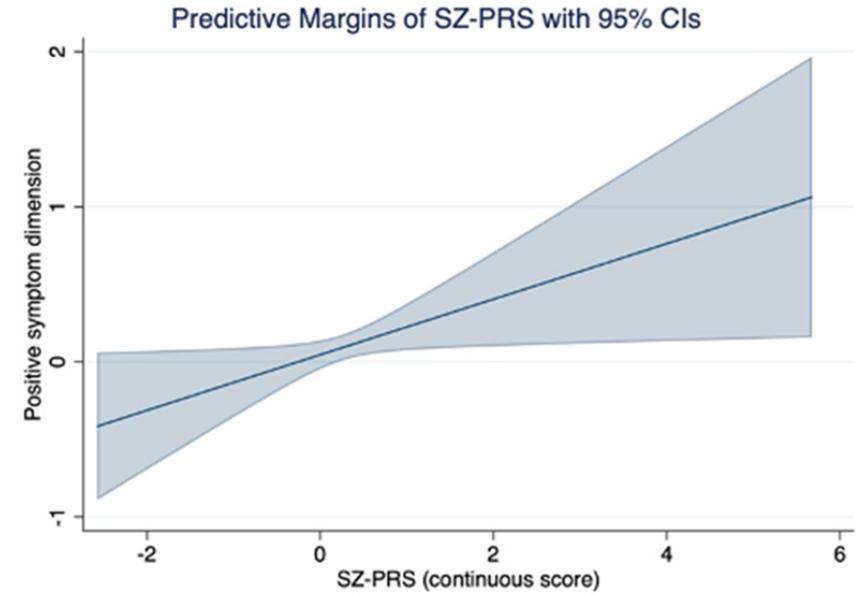
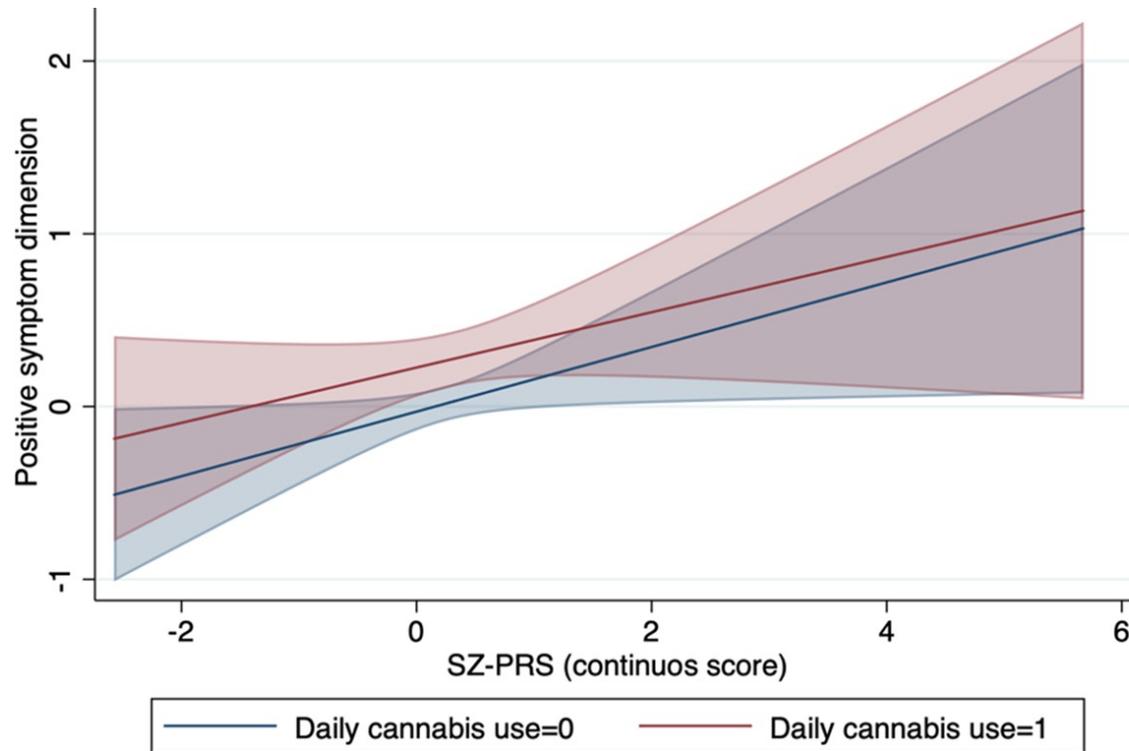


ARTICLE OPEN

Check for updates

# The continuity of effect of schizophrenia polygenic risk score and patterns of cannabis use on transdiagnostic symptom dimensions at first-episode psychosis: findings from the EU-GEI study

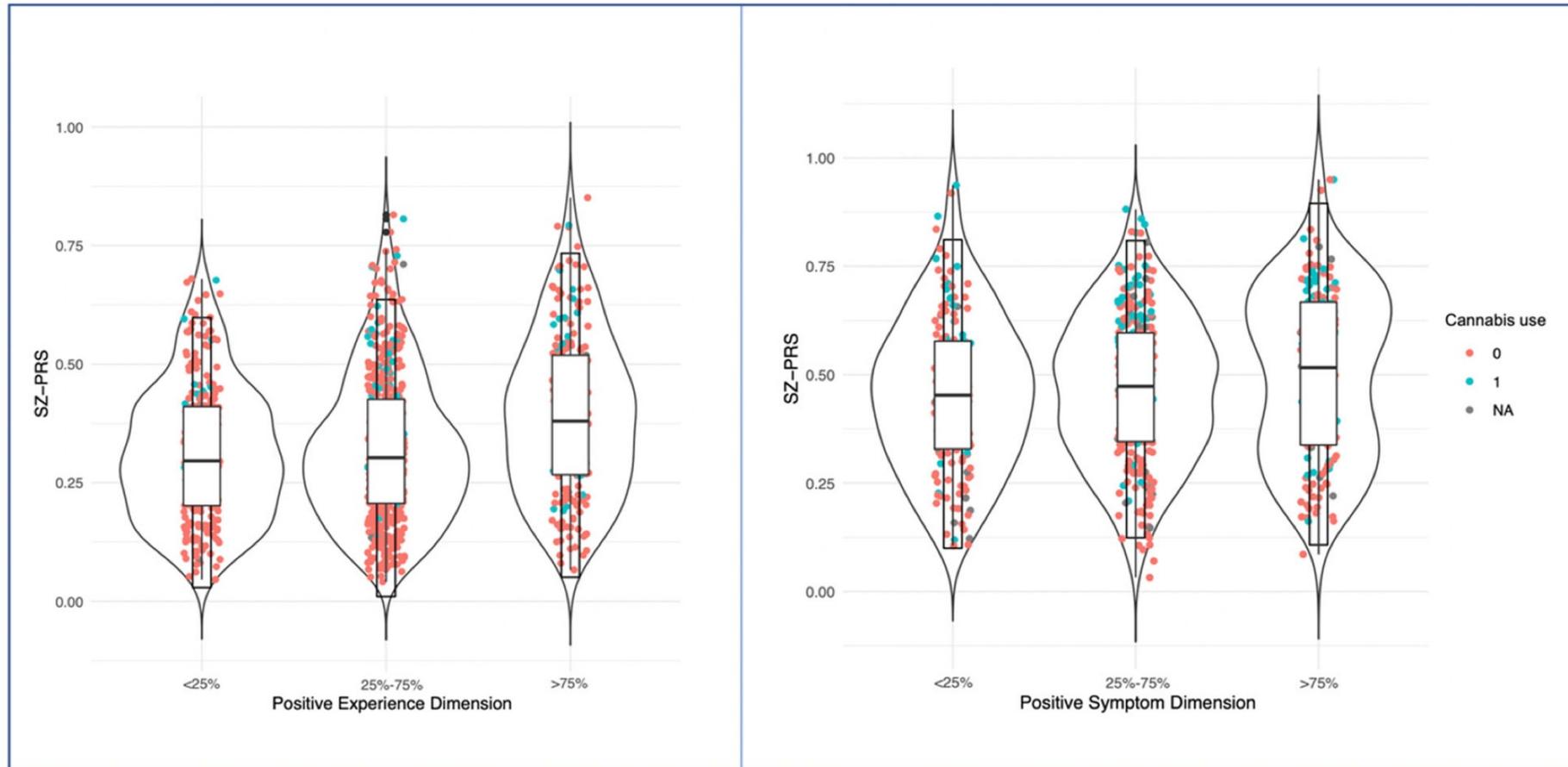
© The Author(s) 2021



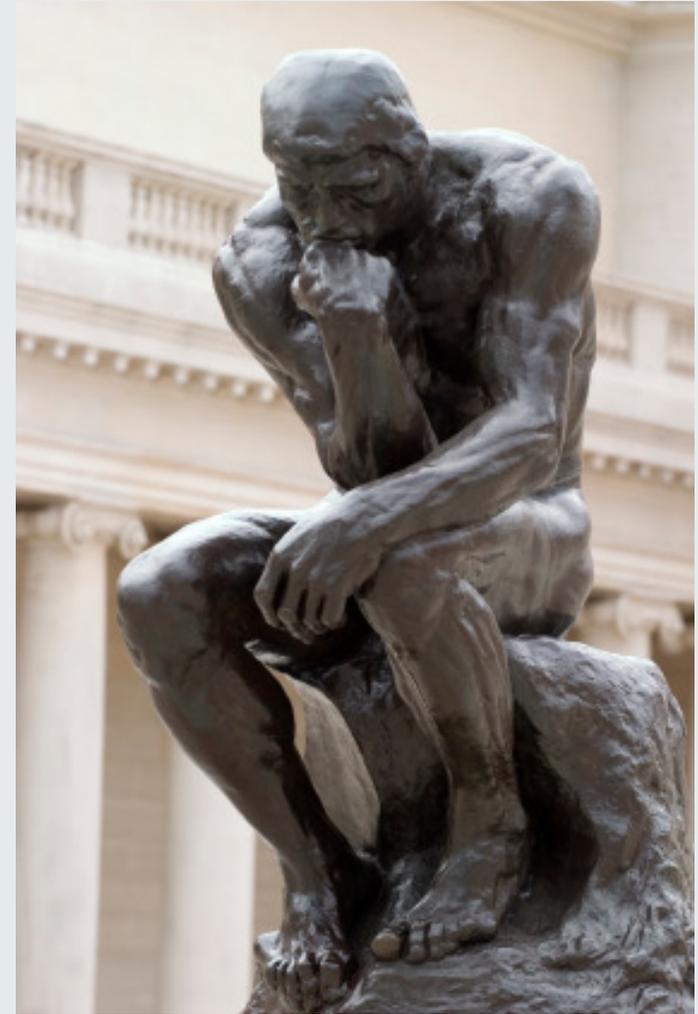
# Polygenic risk score for schizophrenia and positive symptoms

Controls

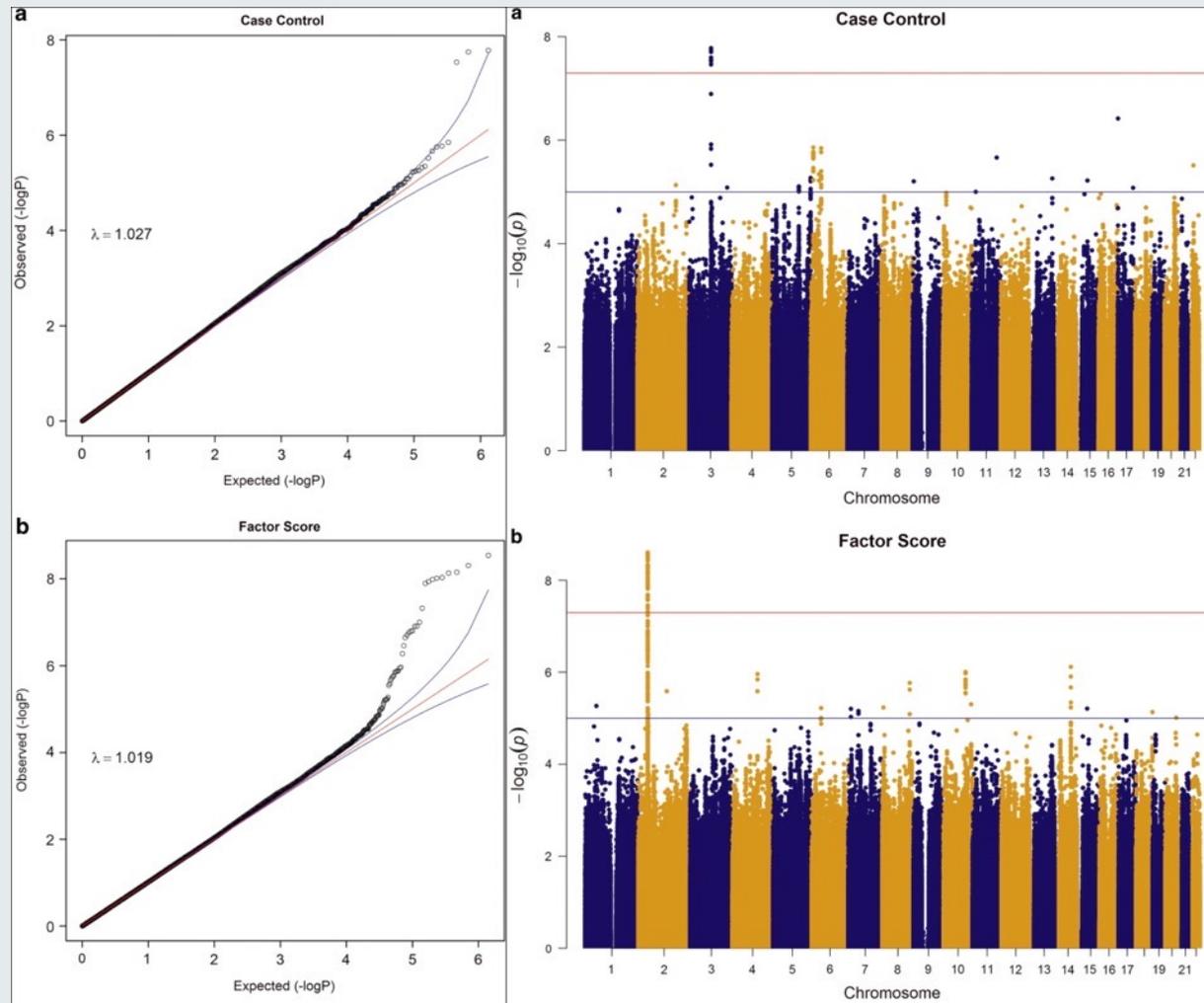
Cases



Yes but is the dimensional approach unequivocally supported by evidence?



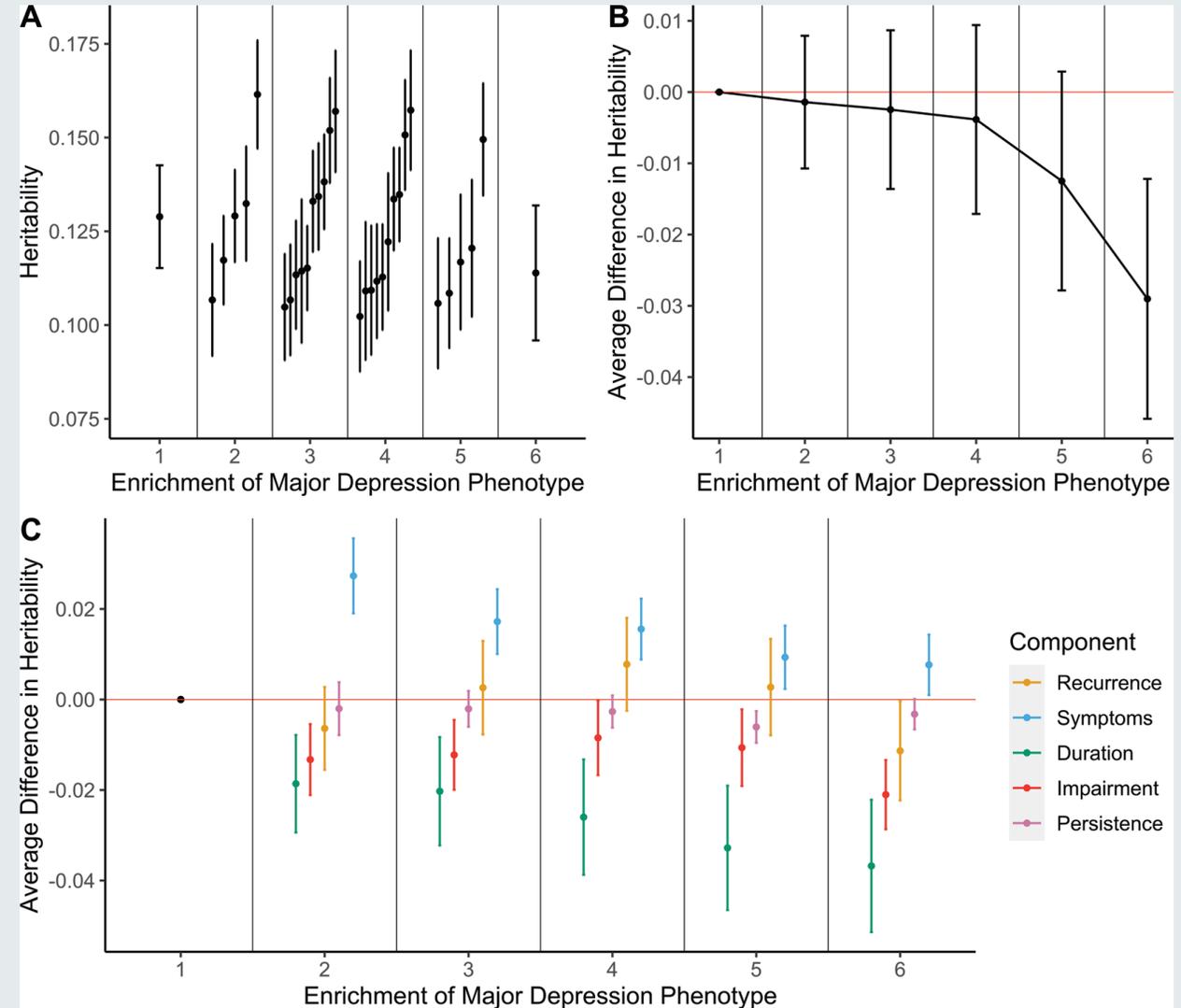
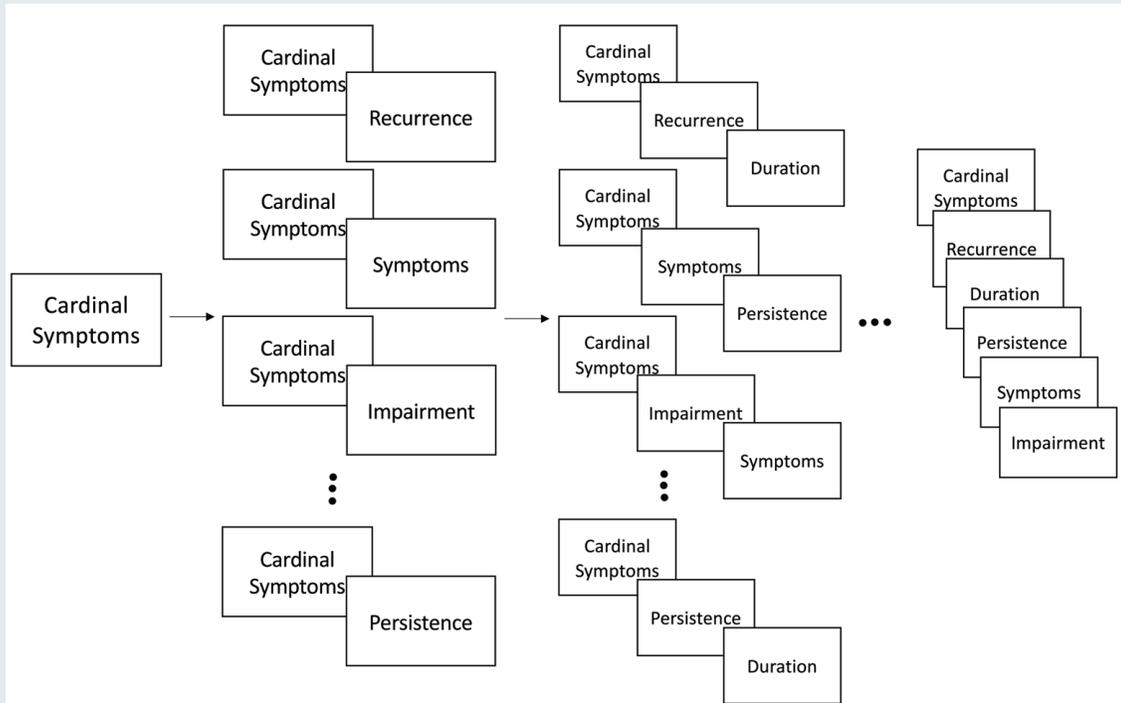
# GWAS of Anxiety (case-control and factor score)



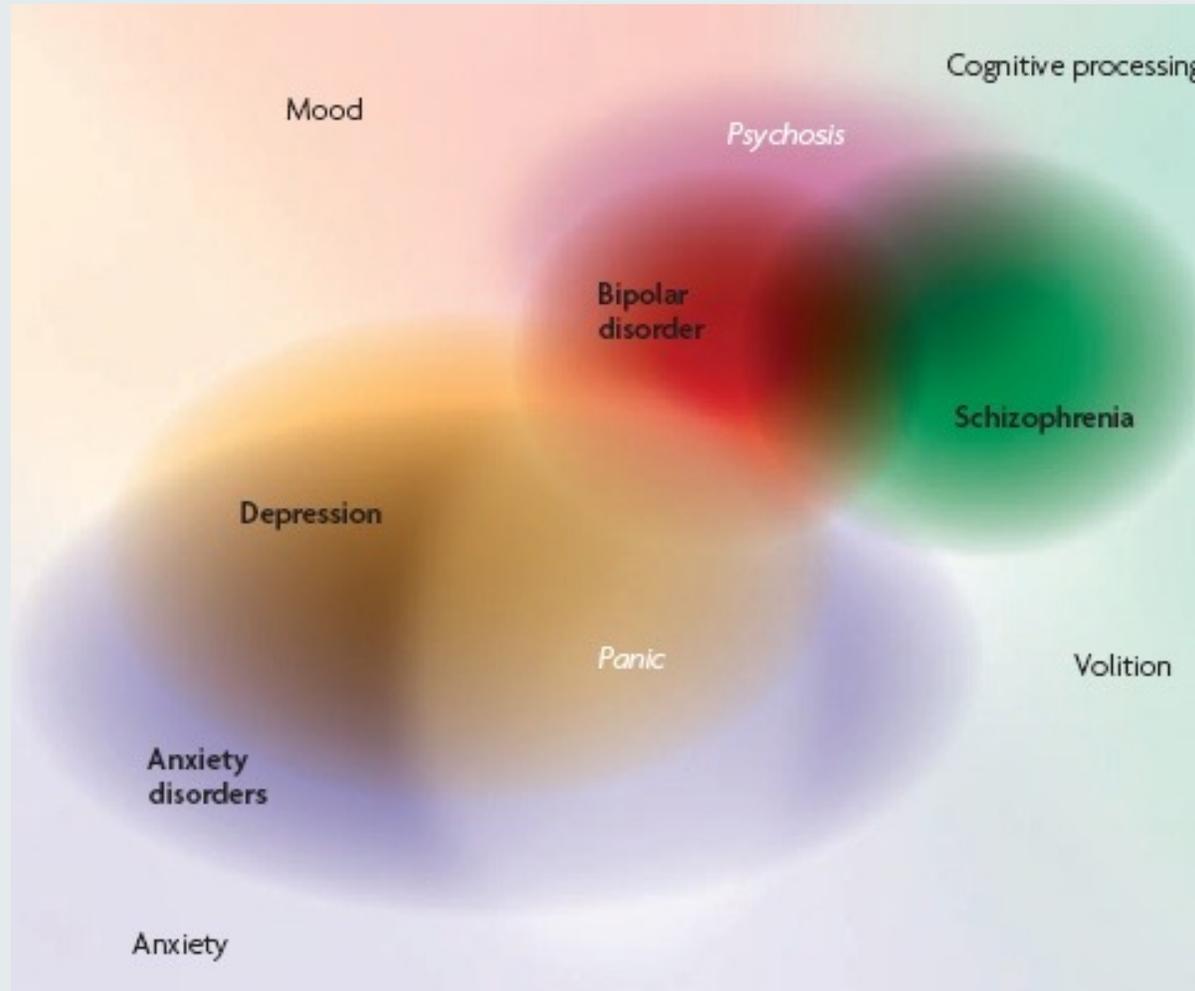
# Is phenotypic enrichment always good?



Jermy et al. *Mol Psychiatry*; 2021



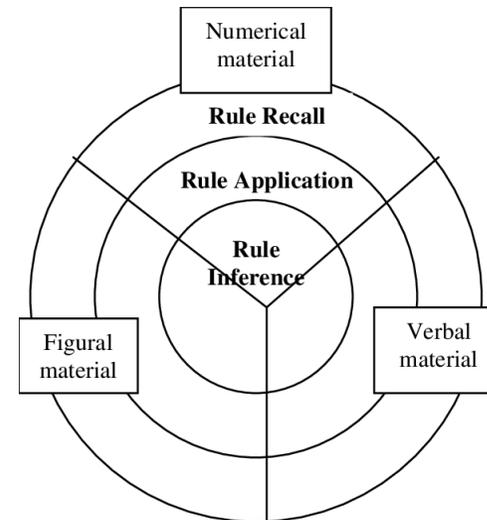
# Embrace complexity of Mental Disorders



Burmeister; *Nat Review Genetics*, 2008

# The idea of a general latent factor to unify psychopathology

- Successfully developed for conceptualizing intelligence (Guttman's intelligence radex, 1954)



- However, it implies arbitrary choices when we set boundaries (Turkmeier, 2008)

# The “reality” of clinical practice

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Despite the benefits of a dimensional approach to mental illness, clinicians are forced to make binary decisions:

- Treat or not
- Refer to other services
- Admit to hospital
- Assess capacity
- Assess accountability



Thank you to

All the **EUGEI** teams in Europe and Brasil, and all first episode psychosis patients and population controls, who kindly took part to the study





We want to hear your views on discussing **genetic** and **environmental** risk with patients!

**10 minute online survey**  
(including watching a short animated video)

Questions about you, your professional training, the disorder(s) you work with, perceptions of genetic and environmental risk, your interactions with patients, & your views on the video

Link to survey: [tiny.cc/PerPsych\\_MHPs](https://tiny.cc/PerPsych_MHPs)

Any questions? [perpsychstudy@kcl.ac.uk](mailto:perpsychstudy@kcl.ac.uk)  
[@perpsychstudy](https://twitter.com/perpsychstudy)

