Prediction strategies in psychiatry: Genetic scores or environmental scales?

Dr Evangelos Vassos
King’s College London
SGDP centre

Twitter: @VangelisVassos
Would you order a 100€ genetic test for your patients today?
Typical psychiatric history

PRESENTING COMPLAINTS
• (in patient’s words)

HISTORY OF PRESENTING COMPLAINTS
• When problem start
• Event precede the problem
• How it developed (symptoms)
• Effects on patient’s condition or social situation
• Associated symptoms (psychic or physical)
• Effects on every day life
• Any help that he sought
• Screen for other problems (depression, anxiety, obsession, psychosis)
• Sleep, appetite

PAST PSYCHIATRIC HISTORY
• Nature of any illness
• Duration
• Hospital – outpatient treatment
• State of health between episodes
• Current psychotropic medication – side-effects

PAST MEDICAL HISTORY
• (Physical disorders, treatment, medication)

FAMILY HISTORY
• (Age, death, occupation, health, relation to the patient)
• Family psychiatric history

PERSONAL HISTORY
• Place of birth
• Childhood: (development, health, relation with others)
• School
• Occupation
• Sexual marital H.: (sexual orientation, history of abuse, gynaecological h.)
• Habits-Dependencies (alcohol, drugs, tobacco)
• Present social situation (housing and income, occupation and financial status, social relations, with whom they live, hobbies and social interests, Social support)

FORENSIC HISTORY

PERSONALITY (premorbid)
# Typical psychiatric history

## Presenting Complaints
- (in patient’s words)

## History of Presenting Complaints
- When problem start
- Event precede the problem
- How it developed (symptoms)
- Effects on patient’s condition or social situation
- Associated symptoms (psychic or physical)
- Effects on every day life
- Any help that he sought
- Screen for other problems (depression, anxiety, obsession, psychosis)
- Sleep, appetite

## Past Psychiatric History
- Nature of any illness
- Duration
- Hospital – outpatient treatment
- State of health between episodes
- Current psychotropic medication – side-effects

## Past Medical History
- (Physical disorders, treatment, medication)

## Family History
- (Age, death, occupation, health, relation to the patient)
- Family psychiatric history

## Personal History
- Place of birth
- Childhood: (development, health, relation with others)
- School
- Occupation
- Sexual marital H.: (sexual orientation, history of abuse, gynaecological h.)
- Habits-Dependencies (alcohol, drugs, tobacco)
- Present social situation (housing and income, occupation and financial status, social relations, with whom they live, hobbies and social interests, Social support)

## Forensic History

## Personality (premorbid)
Risk of developing schizophrenia in relatives of probands

Gottesman. Schizophrenia genesis,
## Family relative risk

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Method</th>
<th>N cases</th>
<th>Sibling RR</th>
<th>Offspring RR</th>
<th>Any 1st relat RR</th>
<th>Adjustments used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kendler 1993</td>
<td>Ireland</td>
<td></td>
<td>126</td>
<td>6.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortensen 1999</td>
<td>Denmark</td>
<td>Poisson regression</td>
<td>2669</td>
<td>9.04</td>
<td>fa:8.34</td>
<td>ma:11.3</td>
<td>age-sex, year, paternal ages</td>
</tr>
<tr>
<td>Pedersen 2001</td>
<td>Denmark</td>
<td>Poisson regression</td>
<td>10264</td>
<td>5.68</td>
<td>fa:5.39</td>
<td>ma:7.1</td>
<td>age, sex, year, age of parents, FH, season of birth</td>
</tr>
<tr>
<td>Byrne 2004</td>
<td>Denmark</td>
<td>Conditional logistic regression</td>
<td>7704</td>
<td>fa:4.61 ma:6.78</td>
<td>5.61</td>
<td>FH, death of relative, urbanicity</td>
<td></td>
</tr>
<tr>
<td>Li (males) 2007</td>
<td>Sweden</td>
<td>Poisson regression</td>
<td>9264</td>
<td>fa:5.97</td>
<td>ma:7.34</td>
<td>migration, income, employment, education, time</td>
<td></td>
</tr>
<tr>
<td>Li (females) 2007</td>
<td>Sweden</td>
<td>Poisson regression</td>
<td>5633</td>
<td>fa:5.45</td>
<td>ma:9.01</td>
<td>migration, income, employment, education, time</td>
<td></td>
</tr>
<tr>
<td>Li (both sexes) 2009</td>
<td>Sweden</td>
<td>Poisson regression</td>
<td>14885</td>
<td>7.34</td>
<td>fa:6.63</td>
<td>ma:8.97</td>
<td>migration, income, employment, education, time</td>
</tr>
<tr>
<td>Mortensen 2010</td>
<td>Denmark</td>
<td>Poisson regression</td>
<td>9324</td>
<td>7.53</td>
<td>fa:6.63</td>
<td>ma:8.97</td>
<td>age, age-sex, year</td>
</tr>
</tbody>
</table>

Note: In Red adjusted values, in blue morbid risk estimates
Typical psychiatric history

PRESENTING COMPLAINTS
• (in patient’s words)

HISTORY OF PRESENTING COMPLAINTS
• When problem start
• Event precede the problem
• How it developed (symptoms)
• Effects on patient’s condition or social situation
• Associated symptoms (psychic or physical)
• Effects on every day life
• Any help that he sought
• Screen for other problems (depression, anxiety, obsession, psychosis)
• Sleep, appetite

PAST PSYCHIATRIC HISTORY
• Nature of any illness
• Duration
• Hospital – outpatient treatment
• State of health between episodes
• Current psychototropic medication – side-effects

PAST MEDICAL HISTORY
• (Physical disorders, treatment, medication)

FAMILY HISTORY
• (Age, death, occupation, health, relation to the patient)
• Family psychiatric history

PERSONAL HISTORY
• Place of birth
• Childhood: (development, health, relation with others)
• School
• Occupation
• Sexual marital H.: (sexual orientation, history of abuse, gynaecological h.)
• Habits-Dependencies (alcohol, drugs, tobacco)
• Present social situation (housing and income, occupation and financial status, social relations, with whom they live, hobbies and social interests, Social support)

FORENSIC HISTORY

PERSONALITY (premorbid)
Environmental risk factors for psychosis

- Low birth weight: 1.7
- Paternal age: 1.6
- Male sex: 1.4
- Childhood trauma: 2.8
- Cannabis: 1.5
- Urbanicity: 1.9
- Migration: 2.3

Odds Ratio
## Environmental Risk Score

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Study</th>
<th>N cases</th>
<th>Sub-categories</th>
<th>RR</th>
<th>ERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethnic minority</td>
<td>Bourque et al. 2011</td>
<td>38716</td>
<td>Native</td>
<td>1</td>
<td>-0.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Any origin*</td>
<td>2.3</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Black</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>White</td>
<td>1.8</td>
<td>2.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Other</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Urbanicity (at birth)</td>
<td>Vassos et al. 2012</td>
<td>47087</td>
<td>Low</td>
<td>1.156</td>
<td>-1.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Medium</td>
<td>1.546</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>High</td>
<td>2.067</td>
<td>1.5</td>
</tr>
<tr>
<td>Paternal age</td>
<td>Miller et al. 2011</td>
<td>16204</td>
<td>&lt;40</td>
<td>1.06</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>40-50</td>
<td>1.21</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&gt;50</td>
<td>1.66</td>
<td>2</td>
</tr>
<tr>
<td>Obstetric complications</td>
<td>Cannon et al. 2002</td>
<td>1294</td>
<td>Birth weight ≥2.5Kg</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Birth weight &lt;2.5Kg</td>
<td>1.67</td>
<td>2</td>
</tr>
<tr>
<td>Cannabis</td>
<td>Marconi et al. 2016</td>
<td>4036</td>
<td>No exposure</td>
<td>1</td>
<td>-1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Little to moderate</td>
<td>1.405</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>High exposure</td>
<td>2.775</td>
<td>3.5</td>
</tr>
<tr>
<td>Childhood Adversity</td>
<td>Varese et al. 2012</td>
<td>5698</td>
<td>No exposure</td>
<td>1</td>
<td>-1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Any exposure</td>
<td>2.78</td>
<td>3</td>
</tr>
</tbody>
</table>
Empirical distribution of ERS and corresponding RR in the general population
SNPs associated with schizophrenia (different levels of significance)

PGC, Nature, 2014
Polygenic risk score (PRS)

• A method of summarising the genetic effects of a large number of genetic variants (adding the individual effects to create a single score)

• It has been used to measure the “global” genetic predisposition to a disease or trait and to construct risk prediction models with much better predictive ability than single genes.
Polygenic traits are quantitative

Plomin et al. *Nat Review Genetics*, 2009
A POLYGENIC THEORY OF SCHIZOPHRENIA

By Irving I. Gottesman and James Shields

Department of Psychology, University of Minnesota, Minneapolis, and MRC Psychiatric Genetics Research Unit, London, England

Communicated by Theodosius Dobzhansky and read before the Academy April 26, 1967
Polygenic analysis:
Prediction based on thousands SNPs

Nagelkerke $R^2$

P-value threshold

Significance of test: $4^* < 0.001$, $5^* < 1.0 \times 10^{-04}$, $6^* < 1.0 \times 10^{-08}$, $7^* < 1.0 \times 10^{-12}$, $8^* < 1.0 \times 10^{-50}$, $9^* < 1.0 \times 10^{-100}$
An example of case-control prediction

- GAP: Case-control sample of first episode psychosis patients
- 712 individuals successfully genotyped and passed QC (447 cases, 265 controls)
- 340 Europeans (172 cases, 168 controls)
- 276 Africans (206 cases, 70 controls)
- Extension and replication using 2 samples:
  - 248 cases with chronic psychosis
  - 828 controls from African ancestry
Population structure
Testing polygenic scores in our samples

Vassos et al. *Biol Psychiatry*, 2017
Clinical use of current polygenic risk scores may exacerbate health disparities

Alicia R. Martin¹,²,³*, Masahiro Kanai¹,²,³,⁴, Yoichiro Kamatani⁵,⁶, Yukinori Okada⁶,⁷,⁸, Benjamin M. Neale¹,²,³ and Mark J. Daly¹,²,³,⁹
“We stress that the sensitivity and specificity of RPS do not support its use as a predictive test” (PGC, 2014)
Prediction of breast cancer risk based on profiling with common genetic variants

Mavaddat et al. *J Natl Cancer Inst*; 2015
10-year absolute risks of developing breast cancer by percentiles of the PRS
Genetic assessment of age-associated Alzheimer disease risk

Desikan et al. *PLOS Medicine*; 2017
Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations

Amit V. Khera1,2,3,4,5, Mark Chaffin4,5, Krishna G. Aragam1,2,3,4, Mary E. Haas4, Carolina Roselli4, Seung Hoan Choi4, Pradeep Natarajan1,2,3,4, Eric S. Lander4, Steven A. Lubitz2,3,4, Patrick T. Ellinor2,3,4 and Sekar Kathiresan1,2,3,4*
Odds Ratios of psychosis in Europeans ranked by PRS in deciles


Vassos et al. *Biol Psychiatry*, 2017
Where to go next?

Within clinical population:

- Severity of illness
- Symptom profile
- Course of illness
- Response to treatment
- Clarifying diagnosis
- Additive effect or interaction with other risk factors
- Specificity to illness
- Conversion of individuals with prodromal symptoms
Separating schizophrenia from other psychoses
Specificity to diagnosis in FEP and replication in chronic psychosis
• Physical abuse by the main mother and father figures
• Sexual abuse by any adult
• Separation from a parent for at least 6 months
• Death of a parent
• Taken into institutional care
• Number of family arrangements
Prediction of conversion to psychosis of individuals at high risk (prodromal)

• OASIS sample (N=103)
• Ultra high risk defined as:
  – attenuated psychotic symptoms
  – brief limited intermittent psychotic episode
  – a trait vulnerability plus a marked decline in psychosocial functioning
  – cognitive perceptive basic symptoms
Can we predict conversion to psychosis?

![Graph showing data comparing GAP and OASIS studies.](chart.png)
Gradient of phenotypic expression
Genetic liability to schizophrenia mapping to the psychosis continuum model
Can genetic profiling help with a clinical problem?

High quality care for all, now and for future generations

News

NHS England pledge to help patients with serious mental illness

© 20 January 2014 - 11:13

Patients with schizophrenia will on average die 14.6 years earlier, bipolar 10.1 and patients with schizoaffective disorder eight years earlier than the general population. They are dying of the same conditions as the general population but have the life expectancy of people living in the 1950s.

As the Department of Health launches its Mental Health Action Plan, NHS England is setting out how it will tackle a number of mental health issues. This includes the health inequalities between people with serious mental illness and the general population.

There are more than 40,000 deaths among people with serious mental illness which could be reduced if they receive the same healthcare checks and interventions as the general population.

Statistics show that patients with serious mental health conditions such as schizophrenia, bipolar disorder and other psychoses are dying earlier from conditions such as cardiovascular disease, cancer, lung disease and liver disease.

This is because the physical health risk factors of these conditions are not being managed as well in these patients who are missing out on vital health interventions.
Hypothesis

Polygenic risk profile scores for cardiometabolic risk factors (obesity, diabetes, dyslipidaemia, hypertension), identified through GWAS in the general population, can be used to determine cardiovascular risk in patients with schizophrenia.
Prediction of BMI change in FEP patients (GAP study) with prospective 1-year follow up (n=190)

<table>
<thead>
<tr>
<th>Status</th>
<th>N</th>
<th>Predictor</th>
<th>Outcome</th>
<th>R2</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>131</td>
<td>BMI PRS</td>
<td>Baseline BMI</td>
<td>0.025</td>
<td>0.065</td>
</tr>
<tr>
<td>Cases</td>
<td>55</td>
<td>BMI PRS</td>
<td>Baseline BMI</td>
<td>0.003</td>
<td>0.71</td>
</tr>
<tr>
<td>Cases</td>
<td>29</td>
<td>BMI PRS</td>
<td>F/u BMI</td>
<td>0.003</td>
<td>0.78</td>
</tr>
<tr>
<td>Cases</td>
<td>25</td>
<td>BMI PRS</td>
<td>BMI change</td>
<td>0.003</td>
<td>0.78</td>
</tr>
<tr>
<td>Controls</td>
<td>97</td>
<td>T2D PRS</td>
<td>HbA1c</td>
<td>0</td>
<td>0.87</td>
</tr>
<tr>
<td>Cases</td>
<td>95</td>
<td>T2D PRS</td>
<td>HbA1c</td>
<td>0.006</td>
<td>0.45</td>
</tr>
<tr>
<td>Cases</td>
<td>51</td>
<td>T2D PRS</td>
<td>Fast Glucose</td>
<td>0.06</td>
<td>0.088</td>
</tr>
</tbody>
</table>
## Prediction of BMI in FEP patients & controls in a multisite study (EU-GEI) (n=1100)

<table>
<thead>
<tr>
<th>Status</th>
<th>N</th>
<th>Predictor</th>
<th>Outcome</th>
<th>R2</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>434</td>
<td>BMI PRS</td>
<td>Baseline BMI</td>
<td>0.021</td>
<td>0.002</td>
</tr>
<tr>
<td>Controls</td>
<td>656</td>
<td>BMI PRS</td>
<td>Baseline BMI</td>
<td>0.078</td>
<td>3.34E-15</td>
</tr>
<tr>
<td>Cases</td>
<td>434</td>
<td>Height PRS</td>
<td>Baseline BMI</td>
<td>0</td>
<td>0.9</td>
</tr>
<tr>
<td>Controls</td>
<td>656</td>
<td>Height PRS</td>
<td>Baseline BMI</td>
<td>0.003</td>
<td>0.09</td>
</tr>
</tbody>
</table>

### Interaction test

| All       | 1091 | PRSxStatus  | Baseline BMI | 0.009 | 0.001       |
Polygenic Prediction of Weight and Obesity Trajectories from Birth to Adulthood

Graphical Abstract

Authors
Amit V. Khera, Mark Chaffin, Kaitlin H. Wade, ..., Nicholas J. Timpson, Lee M. Kaplan, Sekar Kathiresan

Correspondence
avkhera@mgh.harvard.edu (A.V.K.), skathiresan1@mgh.harvard.edu (S.K.)

In Brief
A genome-wide polygenic score quantifies inherited susceptibility to obesity, integrating information from 2.1 million common genetic variants to identify adults at risk of severe obesity.
Empirical distribution of schizophrenia risk in general population

Environmental score

Genetic score

[Graph showing the distribution of schizophrenia risk with bars for Environmental Risk Score (ERS) and a cumulative distribution function for risk ratio (RR).]
Would you order a 100€ genetic test for your patients today?
Challenges of translating PRS to clinic

• Paradigm-shift from rare-disorder genetics (yes/no of a high-risk variant) to the concept of genetic liability
• Education for clinicians and the public to increase understanding and genetic literacy
• The predictive ability of PRS in non-European populations is currently weak. => Need for GWAS in non-European samples
• Need to increase predictive power. => Larger samples or better phenotyping
# Acknowledgments

<table>
<thead>
<tr>
<th>GAP sample</th>
<th>OASIS sample</th>
<th>IMPACT sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>Robin Murray</td>
<td>Philip McGuire</td>
<td>Fiona Gaughran</td>
</tr>
<tr>
<td>Marta di Forti</td>
<td>Diana Prata</td>
<td>Robin Murray</td>
</tr>
<tr>
<td>GAP team</td>
<td>Lucia Valmaggia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>OASIS team</td>
<td>Genetic &amp; analysis team</td>
</tr>
<tr>
<td>EU-GEI sample</td>
<td>SELCoH sample</td>
<td>Amy Butler</td>
</tr>
<tr>
<td>Robin Murray</td>
<td>Matthew Hotopf</td>
<td>Gerome Breen</td>
</tr>
<tr>
<td>Marta di Forti</td>
<td>Vishal Bhavsar</td>
<td>Joni Coleman</td>
</tr>
<tr>
<td>Diego Quattrone</td>
<td></td>
<td>Cathryn Lewis</td>
</tr>
<tr>
<td>Shanice Tulloch</td>
<td></td>
<td>BRC Biomarkers &amp; Genomics team</td>
</tr>
<tr>
<td>EUGEI collaborators</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Sir Robin Murray and Staff of Maudsley Hospital, London, invite you to the
6th Maudsley Mediterranean Forum

Thank you for your attention

Palermo, 27-30 May 2019
www.mediterranean-maudsley-forum.co.uk