Recent findings in Ultra High Risk (UHR) research

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and
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20 years of Ultra High Risk research - are we any closer to preventing schizophrenia?

• Depends on how you define prevention
• Depends on how you define schizophrenia
1990s
1973. Denmark joins the European Economic Community (EEC—an organization of states that lowered barriers to trade between them).


1979. Greenland, formerly part of Denmark, is granted home rule.

1985. Greenland leaves EEC over fears of EEC regulations' effects on its fishing industry.

1985. Denmark joins the European Union.

2000. Danes reject final stage of European Monetary Union (EMU) in a referendum.
Can we intervene before onset of psychosis?
Intervention in the prodromal phase

• Intervention in the prodromal phase may ameliorate, delay, or even prevent onset of fully-fledged disorder.
Idea of the UHR state

• Can we detect the prodrome of schizophrenia prospectively?
• If possible to identify the prodromal phase, can we intervene to ameliorate the onset of schizophrenia, delay onset or even prevent it?
I'm afraid there's not much I can do for you now. You should've come in sooner, before you got sick.
First episode of psychosis

sys
treatment
psychosis
DUP
prodrome

sys
time
The mental health intervention spectrum for mental disorders

- Prevention
  - Universal
  - Selective
- Indicated
- Case Identification
- Standard treatment for known disorders
- Compliance with long-term treatment (Goal: reduction in relapse and recurrence)
- After-care (including rehabilitation)
- Treatment
- Maintenance
Indicated prevention

‘…targeted to high-risk individuals with minimal but detectable signs or symptoms foreshadowing mental disorder … but who do not meet diagnostic levels at the current time’

– Mrazek and Haggerty, 1994
Prodromal symptoms

- Non-specific symptoms eg depressed mood, anxiety, sleep disturbance
- Subthreshold or attenuated psychotic symptoms
- Behavioural changes eg social withdrawal, deterioration in role functioning
• Subthreshold psychotic symptoms, distress and serious functional decline occur before frank psychosis

• Need for care ≠ threshold psychotic disorder
Threshold for diagnosis of psychosis
True Positive

Threshold for diagnosis of psychosis

prodrome

psychosis

time
False positive

Threshold for diagnosis of psychosis

resolving symptoms

sys

time
Threshold for diagnosis of psychosis

symptoms resolved with intervention

time
sys

prodrome

time
At Risk Mental State
At Risk Mental State (ARMS)

- A cluster of symptoms and signs that is associated with a high risk of onset of psychotic disorder in the near future
- Ultra High Risk (UHR) criteria are the operationalised criteria used to detect ARMS
Ultra High Risk criteria

• Age: adolescence to young adulthood: age range at highest risk for onset of a psychotic disorder
• Attenuated psychotic features, and/or
• BLIPS: Brief Limited Intermittent Psychotic Symptoms and/or
• Family history of psychotic disorder in a first degree relative PLUS evidence of deterioration - significant decline in functioning
Psychosis threshold

- Arbitrary line
Psychosis threshold

- Arbitrary line
- Full threshold positive psychotic symptoms
- For at least one week
- Several times per day
- Empirically defined
Setting

• PACE Clinic established
  □ Youth friendly and easily accessible health service
  □ “Personal Assessment and Crisis Evaluation”
Can we predict outcome?
N = 104
By 12 months 36 (34.6 %) subjects had developed psychosis

Yung et al 2004
<table>
<thead>
<tr>
<th>Service</th>
<th>Total pop</th>
<th>Follow up</th>
<th>Psychotic</th>
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<tbody>
<tr>
<td>PRIME Yale, 2002</td>
<td>13</td>
<td>1 year</td>
<td>7 (54%)</td>
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<tr>
<td>RAP New York, 2003</td>
<td>34</td>
<td>6 months</td>
<td>9 (34%)</td>
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<tr>
<td>PAS Newcastle NSW, 2004</td>
<td>74</td>
<td>26.3 mths</td>
<td>37 (50%)</td>
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<tr>
<td>EDIE Manchester</td>
<td>23</td>
<td>1 year</td>
<td>5 (22%)</td>
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<tr>
<td>FEPSY Basel, 2007</td>
<td>35</td>
<td>3 years</td>
<td>12 (34%)</td>
</tr>
<tr>
<td>NAPLS 8 NA sites, 2008</td>
<td>291</td>
<td>2.5 years</td>
<td>102 (35%)</td>
</tr>
<tr>
<td>EPOS 6 EU 2010</td>
<td>245</td>
<td>18 mths</td>
<td>19% but 20% for UHR</td>
</tr>
</tbody>
</table>
Reviews and meta-analyses

• Combining sites, Ruhrmann et al (2003) calculated an average transition rate of 36.7% within 12 months
• Recent meta-analysis (Fusar-Poli 2012): 22% in 1 year, 29% in 2 years and 36% after 3 years
Proof of Concept

• Although transition rates not as high as initial study, still several hundred fold above rates of onset of psychotic disorder in the general population.

• UHR state identifies individuals at increased risk of psychotic disorder
How long is the risk period?

• Nelson et al, 2013. JAMA Psychiatry
# Kaplan-Meier estimated transition rates at various time points

<table>
<thead>
<tr>
<th>Time from entry</th>
<th>Estimated Transition rate (%)</th>
<th>95% confidence interval</th>
<th>Cumulative number of transitions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year</td>
<td>16.6</td>
<td>12.8 - 20.2</td>
<td>65</td>
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<tr>
<td>2 years</td>
<td>20.6</td>
<td>16.4 - 24.5</td>
<td>79</td>
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<td>3 years</td>
<td>24.7</td>
<td>20.2 - 29.0</td>
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<td>4 years</td>
<td>27.5</td>
<td>22.7 - 31.9</td>
<td>102</td>
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<tr>
<td>5 years</td>
<td>30.0</td>
<td>24.9 - 34.7</td>
<td>108</td>
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<tr>
<td>10 years</td>
<td>34.8</td>
<td>28.6 - 40.5</td>
<td>114</td>
</tr>
<tr>
<td>&gt; 10 years</td>
<td>34.8</td>
<td>28.6 - 40.5</td>
<td>114</td>
</tr>
</tbody>
</table>
Transition rate - Survival curve

Number of days from entry

Estimated transition rate

1y, 2y, 3y, 4y, 5y
• Highest risk is within the first 1-2 years of help-seeking

• About 73% of those developing a psychotic disorder fulfill criteria for schizophrenia.
Controversies 1

• Is it ethical to label these people?
• How to communicate increased risk?
• Important to address issues such as potential for decreasing risk, stigma
• Risk is not disorder
Do not go where the path may lead,
Go instead where there is no path and leave a trail

Ralph Waldo Emerson
(American Poet, 1803-1882)
Do not go where the path may lead,
Go instead where there is no path and leave a trial
Interventions in UHR individuals

- 3 trials have examined antipsychotics, either alone or in combination with Cognitive Therapy
- 5 studies of CBT
- 2 integrated therapy
- 1 PUFA
Reviews and meta-analyses

• Preti & Cella, 2010
• Receiving any of the focused treatment was associated with a lower risk of developing psychosis compared with no treatment or treatment as usual
• (Relative Risk = 0.36; 95%CI: 0.22–0.59).
• However long term follow up results show that treatment effects are not stable
Meta analyses
Hutton & Taylor (2013)

• 6 trials that have used CBT for UHR groups. They report that CBT was associated with reduced risk for transition to psychosis at 6, 12 and 18-24 months.
Stafford et al 2013

• Evidence of moderate quality showed an effect for cognitive behavioural therapy on reducing transition to psychosis at 12 months
• Early detection and intervention in people at ultra-high risk of developing psychosis can be successful to prevent or delay a first psychosis.
• Antipsychotic medication showed efficacy, but more trials are needed.
• Omega-3 fatty acid needs replication.
• CBT appears effective

• Antipsychotics: NNT 7
• Cognitive therapy: NNT 13
Controversies 2

Is it ethical to treat these people?

• Help seeking, symptomatic
• Referred to PACE (or similar service) from another service eg GP, counseling service
• High rates of mood disorder, problems with living
Controversies 3

• Anti-psychotics for UHR?
• NAPLS study - UHR individuals prescribed anti-psychotics in an uncontrolled manner
• Reports also from Australia of this practice
• Recent study from South Korea - 82% of UHR people on antipsychotics
Anti-psychotics for UHR

• Why is this happening?
• General practitioners and psychiatrists may think they can tell that someone is about to become psychotic
Can they tell?

• Experienced PACE clinicians asked at the time of entry of a new patient into the PACE Clinic:

• “Do you think this person will become psychotic within one year?”
## Sensitivity & Specificity Analysis

<table>
<thead>
<tr>
<th>Will Develop Psychosis?</th>
<th>Transition to Psychosis</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NO</td>
<td>129</td>
</tr>
<tr>
<td></td>
<td>YES</td>
<td>27</td>
</tr>
<tr>
<td>Total</td>
<td>156 (92.9%)</td>
<td>12 (7.1%)</td>
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</table>
Implications

• Experienced clinicians cannot predict outcome on initial assessment
• Should sound a note of caution - doctors may be too hasty in prescribing anti-psychotics to UHR young people
Are antipsychotics ever justified for ARMS?

• see Clinical Guidelines
Current clinical guidelines for At Risk Individuals
UK
UK NICE guidelines
Psychosis and Schizophrenia in Adults 2014

• At risk or ‘ultra-high risk’ mental states:

• Any interventions used must benefit (and not harm) the majority of people (false positives) who do not develop psychosis
UK NICE guidelines
Psychosis and Schizophrenia in Adults 2014

• Do not offer antipsychotic medication to people considered to be at increased risk of developing psychosis
Australia
Australian Clinical Guidelines for Early Psychosis 2012

• Psychological and, where appropriate, pharmacological treatment of comorbidities should be used and consistent with guidelines on those comorbidities.

• CBT may reduce psychotic symptomatology and prevent or delay transition to psychosis.
Antipsychotic medication should NOT be considered as the first treatment option for UHR.
Australian Clinical Guidelines for Early Psychosis

• However, if rapid worsening of psychotic symptoms occurs together with significant deterioration in functioning related to these symptoms and elevated risk to self or others, a low-dose atypical antipsychotic may be considered, in conjunction with close monitoring and support.

• Note that this is not justified in the majority of such situations.
USA
In persons who meet the criteria for being prodromally symptomatic and at risk for psychosis in the near future, careful assessment and frequent monitoring are recommended until symptoms remit spontaneously, evolve into schizophrenia, or evolve into another diagnosable and treatable mental disorder.
• Antipsychotic medication treatment may also be helpful in some persons with prodromal symptoms
Canada
Patients who meet criteria for “ultra high-risk mental state” for psychosis should be offered monitoring for at least 1 to 2 years;

If clinically indicated, they may be offered supportive therapy and symptomatic treatment for emerging psychotic symptoms, depression, or anxiety
# Summary of guidelines

<table>
<thead>
<tr>
<th></th>
<th>Monitor</th>
<th>CBT</th>
<th>Supp</th>
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<td>✔️</td>
<td>✔️</td>
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</tbody>
</table>
Treatment of UHR state

• In RCTs: Antipsychotic medication, cognitive therapy and fish oil all seem to be of benefit in reducing current symptoms and preventing or delaying transition to psychosis
Treatment of UHR state

• Given the effectiveness of “benign” interventions, such as cognitive therapy and fish oil, antipsychotic medication is not recommended

• These “benign” treatments likely to be effective for mood disorder, general distress anyway ie treating “false positives”
ARMS in the NHS

• Assessment for ARMS now in the Access and Waiting Times Standard
• Implementation in April 2016
RTT Pathway

1. Referrer suspects first episode psychosis (FEP)

2. Urgent/emergency referral made flagged as suspected FEP

Central triage point?

3a. Clock starts when central triage point receives referral

Onward referral to EIP service

3b. Clock starts when EIP service receives referral

Patient invited for EIP assessment
RTT Pathway

1. Patient invited for EIP assessment

2a. DNA or cancellation?
   Y → 3a. Active monitoring/watch and wait
   N → EIP assessment commences

2b. DNA or cancellation?
   Y → 3b. Active monitoring/watch and wait
   N → EIP assessment completed
• FEP – no
• Clock stops when:
  • Accepted into EI caseload
  • EI case manager allocated
  • Specialist ARMS assessment commenced
Controversies 4

• What are we trying to prevent?
• A first episode of psychosis?
• If we prevent a first episode of psychosis does this mean that schizophrenia is prevented?
• What do we mean by schizophrenia anyway?
What do we mean by schizophrenia?

• Syndrome
• Either current or a history of full blown positive psychotic symptoms
• Impaired social functioning
• Some negative symptoms
• Some cognitive impairment
positive
sys

Brief psychosis
“Schizotype”
Might never come to clinical attention

Psychosis threshold

Schizotaxia

UHR threshold

Social functioning

Scz

?
Social functioning

- "Scz" (Schizophrenia)
- "Schizotypy" (Brief psychosis, might never come to clinical attention)
- Positive Sys

Thresholds:
- Psychosis threshold
- UHR threshold

Social functioning

- Schizotaxia
Case 2: Stewart

- Symptoms
- Psychosis threshold
- UHR threshold

Timeline:
- 1997
- 1998
- 2008
Schizotaxia Revisited

Paul E. Meehl, PhD

A conjectured neural integrative defect (schizotaxia), due to a dominant schizogene completely penetrant for a parametric aberration in synaptic signal selectivity (hypokrisia), gives rise under ordinary social learning regimes to schizotypy, a personality showing ambivalence, aversive drift, dereism, autism, and cognitive slippage. Given unfavorable polygenic potentiators (e.g., introversion, hypohedonia, and anxiety) and adverse life experiences (e.g., childhood trauma or adult misfortune), around 10% develop schizophrenia. That schizophrenia is basically a neurologic disorder does not contradict whatever is known about its psychodynamics, nor preclude efficacy for psychotherapy or other psychosocial interventions. Research should concentrate on soft neurology and psychophysiology as indicators, being closer in the causal chain to the schizogene than psychometric, social, or high-level cognitive processes. Taxometric statistics are appropriate to testing a major locus model not simplistically formulated.

(Arch Gen Psychiatry. 1989;46:935-944)
Functioning as an outcome

- The majority of UHR patients do not develop psychotic disorder even up to 10 years post identification. Nonetheless, many remain symptomatic and disabled.
- It is important therefore to study psychosocial functioning as an outcome.
Review

What drives poor functioning in the at-risk mental state?
A systematic review

Jack Cotter a,*, Richard J. Drake a, Sandra Bucci b, Joseph Firth a, Dawn Edge a, b, Alison R. Yung a, c

a Institute of Brain, Behaviour and Mental Health, University of Manchester, United Kingdom
b School of Psychological Sciences, University of Manchester, United Kingdom
c Orygen Youth Health Research Centre, University of Melbourne, Australia
Associations with poor functioning - cross sectional studies

• Negative symptoms
• Disorganised symptoms
• Long duration of symptoms
• NOT positive symptoms
• NOT anxiety
• Mixed evidence for depressive symptoms
• Childhood trauma
• Neurocognitive and social cognitive deficits
Longitudinal predictors of poor social functioning

• Neurocognitive impairment (verbal memory, processing speed)
• Negative symptoms
• Disorganisation
• History of childhood trauma
• Transition to psychosis
Controversies 5:
Childhood trauma and psychotic disorder
Childhood maltreatment and transition to psychotic disorder independently predict long-term functioning in young people at ultra-high risk for psychosis

A. R. Yung¹*, J. Cotter¹, S. J. Wood², P. McGorry³, A. D. Thompson⁴, B. Nelson³ and A. Lin⁵
Mechanisms of the association between childhood maltreatment and poor functioning

- Is it because people with history of maltreatment are more likely to be depressed and anxious, and that these factors drive the association?
<table>
<thead>
<tr>
<th>Variables</th>
<th>Whole sample (n=217)</th>
<th></th>
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<th></th>
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</thead>
<tbody>
<tr>
<td>BPRS psychotic subscale at follow-up</td>
<td>-.250 (.265)</td>
<td>-.055</td>
<td>-.943</td>
<td>.347</td>
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<tr>
<td>SANS total at follow-up</td>
<td>-.721 (.075)</td>
<td>-.594</td>
<td>-9.563</td>
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<tr>
<td>HAM-A at follow-up</td>
<td>-.076 (.172)</td>
<td>-.039</td>
<td>-.441</td>
<td>.659</td>
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<tr>
<td>HAM-D at follow-up</td>
<td>-.012 (.170)</td>
<td>-.007</td>
<td>-.068</td>
<td>.946</td>
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<td>Baseline GAF score</td>
<td>.068 (.064)</td>
<td>.047</td>
<td>1.062</td>
<td>.289</td>
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<tr>
<td>CTQ total</td>
<td>-.216 (.038)</td>
<td>-.261</td>
<td>-5.648</td>
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<td>Variables</td>
<td>Non-transition group (n=166)</td>
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<tr>
<td>---------------------------------------</td>
<td>-------------------------------</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>B (SE)</td>
<td>β</td>
<td>t</td>
<td>p</td>
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<tr>
<td>BPRS psychotic subscale at follow-up</td>
<td>-0.342 (.385)</td>
<td>-0.057</td>
<td>-0.888</td>
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<td>SANS total at follow-up</td>
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<td>-0.524</td>
<td>-7.458</td>
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<td>HAM-A at follow-up</td>
<td>-0.212 (.186)</td>
<td>-0.110</td>
<td>-1.142</td>
<td>.255</td>
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<tr>
<td>HAM-D at follow-up</td>
<td>-0.095 (.205)</td>
<td>-0.051</td>
<td>-0.463</td>
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<td>Baseline GAF score</td>
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<td>0.033</td>
<td>0.613</td>
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<td>B (SE)</td>
<td>β</td>
<td>t</td>
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<td>BPRS psychotic subscale at follow-up</td>
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<td>SANS total at follow-up</td>
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<td>HAM-A at follow-up</td>
<td>.688 (.435)</td>
<td>.371</td>
<td>1.583</td>
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<td>HAM-D at follow-up</td>
<td>-.292 (.342)</td>
<td>-.192</td>
<td>-.852</td>
<td>.399</td>
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<td>Baseline GAF score</td>
<td>.037 (.155)</td>
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<td>.239</td>
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<td>CTQ total</td>
<td>-.350 (.077)</td>
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<td>-4.523</td>
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</tbody>
</table>
Possible mechanisms

• Biological

• Childhood trauma associated with reduced volume in
  – Hippocampus
  – Amygdala
  – Ventrolateral prefrontal cortex
  – Total grey matter
Possible mechanisms

• Biological
• Childhood trauma associated with increased stress sensitivity
• Decreased BDNF
• Increased markers of inflammation
Possible mechanisms

• Psychological
  – Insecure attachment
  – Paranoid world view
  – Low self-esteem
  – Behavioural hostility
  – Perceived discrimination

Difficulty making and maintaining relationships and employment
Possible mechanisms

• Social
• History of childhood maltreatment association with poor adherence and therapeutic alliance
Clinical implications – childhood trauma findings

• Assess history of childhood trauma
• Take difficulties in engagement into account
• Assess PTSD
• Consider treatments that have been successful in other trauma patients eg DBT, EMDR

• **Childhood trauma does not protect someone from developing psychotic disorder and is in fact associated with poor functional outcome in the UHR group**
• Association of “transition” to psychotic disorder and poor functioning at long term follow up
Method

• Poor functional outcome was defined by low scores on the Quality of Life Scale (QLS; Heinrichs, Hanlon and Carpenter, 1984) and the Social and Occupational Functioning Assessment Scale (SOFAS; Goldman et al., 1992) at follow-up assessment.
Method

Latent group analyses based on SOFAS and Quality of Life (QLS) scores at follow-up assessment.

2 group model had the best fit.

i.e. Defined 2 groups: “poor outcome” and “good outcome”
# Results

<table>
<thead>
<tr>
<th>Transition at follow up</th>
<th>Poor functioning at follow up</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td>32</td>
<td>41</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>34</td>
<td>161</td>
<td>195</td>
</tr>
<tr>
<td></td>
<td></td>
<td>66</td>
<td>202</td>
<td>268</td>
</tr>
</tbody>
</table>
Results

• Note:
• 41 individuals developed first episode psychosis but had good functioning at follow up
• 34 individuals did not develop first episode psychosis but had poor functioning at follow up
Results

• We can treat transition like a test and poor long term functional outcome as the gold standard definition of the disorder we are interested in.

• The question becomes, “How well does transition identify people with poor long-term functioning?” The usual methods of evaluating a test can be applied:
Results

• Odds Ratio of Transition predicting poor outcome = 4.04 (2.2, 7.6). Chi square p<0.0001
• Sensitivity = 0.485 [95% confidence interval (CI) 0.361–0.610].
• Specificity = 0.797 (95% CI 0.734–0.849).
• Positive predictive value = 0.438 (95% CI 0.324–0.559).
• Negative predictive value = 0.826 (95% CI 0.763–0.875).
Results

• Thus the likelihood of having poor outcome if a UHR individual “transitions” about 44%.

• = Most people who transition do not develop poor long-term outcome. (PPV)

<table>
<thead>
<tr>
<th>Poor functioning at follow up</th>
<th>Yes</th>
<th>No</th>
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<tbody>
<tr>
<td>Transiton at follow up</td>
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<td>161</td>
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<tr>
<td></td>
<td>66</td>
<td>202</td>
</tr>
</tbody>
</table>
Results

• Nearly half of those with poor long-term outcome have not experienced transition. (sensitivity)

<table>
<thead>
<tr>
<th>Poor functioning at follow up</th>
<th>Yes</th>
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</table>

66      202  268
Implications

• Good functioning in those who developed FEP:

• ? Early intervention, minimal duration of untreated psychosis?
“Transition” and good outcome

- Br J Psychiatry. 2015 June
- Duration of untreated psychosis and need for admission in patients who engage with mental health services in the prodromal phase.
- Valmaggia et al
- “Patients who develop psychosis after being engaged in the prodromal phase have a better short-term clinical outcome than patients who do not present until the first episode.”
Social functioning

Positive sys

Scz

Psychosis threshold

? schizotaxia

UHR threshold

Brief psychosis “Schizotype”
Might never come to clinical attention

Early intervention is effective in improving functional outcome
Implications

• Poor functioning in those who did not develop FEP

• ? Due to symptoms and syndromes such as depression?
<table>
<thead>
<tr>
<th>Variables</th>
<th>Non-transition group (n = 166)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$B$ (s.e.)</td>
</tr>
<tr>
<td>BPRS psychotic subscale at follow-up</td>
<td>$-0.342 (0.385)$</td>
</tr>
<tr>
<td>SANS total at follow-up</td>
<td>$-0.656 (0.088)$</td>
</tr>
<tr>
<td>HAMA at follow-up</td>
<td>$-0.212 (0.186)$</td>
</tr>
<tr>
<td>HAMD at follow-up</td>
<td>$-0.095 (0.205)$</td>
</tr>
<tr>
<td>Baseline GAF score</td>
<td>$0.042 (0.069)$</td>
</tr>
<tr>
<td>CTQ total</td>
<td>$-0.159 (0.044)$</td>
</tr>
</tbody>
</table>
Poor functioning in non-transitioned group

- Not due to depression or anxiety at follow up
- Associated with negative symptoms at follow up and childhood maltreatment
Social functioning

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Might never come to clinical attention

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schizotaxia

UHR threshold

Social functioning
Implications of transition status and functioning

• Are the people who have prolonged poor functioning, history of attenuated psychotic symptoms but have not developed FEP actually closer to the ‘schizophrenia’ concept than those who “transitioned” but have good functioning?

• Need to focus on predictors of poor functioning as well as transition
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- Any many more……….
The end - thanks!