Comorbidity and mortality in patients with psychotic disorders

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Universitetet i Oslo
Nydalen DPS
Mental and substance use disorders are the leading cause of years lived with disability (YLDs) worldwide

(Whiteford et al. 2013)
Outline

• Background

• Mortality in psychotic disorders

• Comorbidity in psychotic disorders

• How do we address this?
Psychosis

- Hallucinations
- Delusions
- Disturbance of thought
- Negative symptoms
Psychotic disorders

- Schizophrenia
  - Schizophreniform disorder
  - Delusional disorder
  - Schizoaffective disorder

- Bipolar disorder
- Depressive psychosis

- Other psychosis

Non affective psychosis

Affective psychosis
Hjertebank eller brystsmert?  
Få grundig hjerteundersøkelse hos spesialist med kort ventetid. 
Bestill time her

Psykisk syke lever 25 år kortere enn andre folk

Resten av befolkningen blir eldre og eldre. For psykiatriske pasienter er det stikk motsatt, viser studie fra nestor ved Sandviken sykehus.

Øyvind Lofdal Eidsvik


Han var tidlig i 60-årene da han ble innlagt på Sandviken sykehus med psykisk sykdom. Et par år etter ble han skrevet ut. Kort tid etter utskrivelsen
### Years of Life Lost (YLL) Schizophrenia

<table>
<thead>
<tr>
<th>Country</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sweden</td>
<td>15.0</td>
<td>12.0</td>
</tr>
<tr>
<td>Denmark</td>
<td>18.7</td>
<td>16.3</td>
</tr>
<tr>
<td>England</td>
<td>14.6</td>
<td>9.8</td>
</tr>
</tbody>
</table>

Source:
- (Crump et al. 2013)
- (Laursen et al. 2011)
- (Chang et al. 2011)
## Years of Life Lost (YLL)

### Bipolar disorder

<table>
<thead>
<tr>
<th>Country</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sweden</td>
<td>8.5</td>
<td>9.0</td>
</tr>
<tr>
<td>Denmark</td>
<td>13.6</td>
<td>12.1</td>
</tr>
<tr>
<td>England</td>
<td>10.1</td>
<td>11.2</td>
</tr>
</tbody>
</table>

Source:

- (Crump et al. 2013)
- (Laursen et al. 2011)
- (Chang et al. 2011)
### YLL to Cancer

<table>
<thead>
<tr>
<th>NORWAY 1997-2012</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer (average)</td>
<td>13.8</td>
</tr>
</tbody>
</table>

*(Brustugun et al. 2014)*

### YLL to Heart disease

<table>
<thead>
<tr>
<th>Sweden</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic heart disease</td>
<td>4.6</td>
</tr>
</tbody>
</table>

*(Steward et al 2010)*
What are the causes of the lost years?
Suicide

Vincent van Gogh (1853-1890)

Bryan Charnley (1949-1991)
Absolute suicide risk in Denmark

(Nordentoft et al. 2011)
What about Norway?

5.7% with a schizophrenia-like psychosis had committed suicide

(Melle et al. 2012, Early intervention in psychiatry)

45% with a Bipolar I or Bipolar II had attempted suicide

(Finseth et al. 2012)
Suicide in psychotic disorders affects the young - with the main risk in the first years of treatment

(Melle et al. 2012)
Psychotic disorder – only a brain disease?
Natural causes YLL
Schizophrenia

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<tbody>
<tr>
<td><strong>Sweden</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Lost years due to natural causes</strong></td>
<td>13.1</td>
<td>10.5</td>
</tr>
</tbody>
</table>

(Crump et al. 2013)
Natural causes YLL  
Bipolar disorder

<table>
<thead>
<tr>
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<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lost years due to natural causes</td>
<td>6.6</td>
<td>7.5</td>
</tr>
</tbody>
</table>

(Crump et al. 2013)
Schizophrenia
Increased risk dying from:

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>4.6</td>
<td>6.2</td>
</tr>
<tr>
<td>Influenza/pneumonia</td>
<td>7.7</td>
<td>6.8</td>
</tr>
<tr>
<td>COPD</td>
<td>9.1</td>
<td>5.4</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>3.0</td>
<td>3.7</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>2.7</td>
<td>2.6</td>
</tr>
</tbody>
</table>

(Crump et al. 2013)
Bipolar disorder
Increased risk dying from:

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</tr>
</thead>
<tbody>
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<td>Diabetes</td>
<td>3.5</td>
<td>4.3</td>
</tr>
<tr>
<td>Influenza/pneumonia</td>
<td>4.9</td>
<td>3.5</td>
</tr>
<tr>
<td>COPD</td>
<td>3.2</td>
<td>3.6</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>2.3</td>
<td>2.2</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>1.4</td>
<td>1.2</td>
</tr>
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(Crump et al. 2013)
Ischemic heart disease

(Crump et al. 2013)
Metabolic syndrome, diabetes and cardiovascular disease

- Bipolar disorder: 61% increased 10-year risk of developing coronary heart disease
  - (Hua et al. 2011)

- Schizophrenia: 79%
  - (Birkenaes et al. 2006)

- Schizophrenia 46% had metabolic syndrome (MetS) at the age of 37
  - (Lee et al. 2012)

\(x^2\) the risk of metabolic syndrome in bipolar disorder and schizophrenia

- Bipolar disorder:
- Schizophrenia:
Østlandet 2003-2014

<table>
<thead>
<tr>
<th>Frisk kontroll 33 år</th>
<th>Psykosepasient 32 år</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BMI &gt;30</strong></td>
<td><strong>BMI &gt;30</strong></td>
</tr>
<tr>
<td>4%</td>
<td>20%</td>
</tr>
<tr>
<td><strong>Triglycerider&gt;2.6</strong></td>
<td><strong>Triglycerider&gt;2.6</strong></td>
</tr>
<tr>
<td>0.7%</td>
<td>8.4%</td>
</tr>
<tr>
<td><strong>HDL&lt;1</strong></td>
<td><strong>HDL&lt;1</strong></td>
</tr>
<tr>
<td>1%</td>
<td>4.5%</td>
</tr>
<tr>
<td><strong>Glukose&gt;6</strong></td>
<td><strong>Glukose&gt;6</strong></td>
</tr>
<tr>
<td>2%</td>
<td>6.8%</td>
</tr>
<tr>
<td><strong>Røyk</strong></td>
<td><strong>Røyk</strong></td>
</tr>
<tr>
<td>20%</td>
<td>53%</td>
</tr>
</tbody>
</table>

(Dieset et al. in progress)
Metabolic syndrome and antipsychotics

$x_2$ in patients treated with first generation antipsychotics

$x_5$ in patients treated with second generation antipsychotics

(De Hert et al. 2009)
My weight and blood sugar are going up on Zyprexa, Doc.

Good news! The same company makes diabetes treatments!
Antipsychotics save lives

Long term treatment with antipsychotics is associated with lower mortality compared to no antipsychotic use

(Tiihonen et al. 2009)
Increased Cardiometabolic Risk in Patients With First-Episode Schizophrenia Spectrum Disorders (mean age 23 yrs)

-RAISE-ETP Study

(Correll et al. 2014)
Cancers

(Crump et al. 2013)
COPD

(Crump et al. 2013)
Pulmonary diseases and cancer

Schizophrenia increased risk for pneumonia and COPD

(Copeland et al 2007)

No increased risk of getting cancer?
(Tabarés-Seisdedos et al. 2011)
(except perhaps breast cancer?)
How do we address this?
Lifestyle factors

- Poor physical activity
- Smoking
- Unhealthy diet
- Excessive alcohol intake

(Klilian et al. 2006)
Less aggressive cancer treatment

(Irwin et al. 2014)

Less aggressive diabetes treatment

(Desai et al. 2005)

Less aggressive use of statins and antihypertensiva

(Lahti et al. 2012)

Less use of invasive procedures in established cardiovascular disease

(Laursen et al. 2009)
Research

Our research topics:

- **Antipsychotic Medication**
  Define new targets to optimize the ratio of beneficial vs. adverse effects of antipsychotics.

- **Brain Imaging**
  Determine new brain imaging phenotypes linking genes and core clinical phenotypes.

- **Outcome Predictors**
  Using genetic and environmental factors to estimate illness course and outcome.

- **Genetics of Psychiatric Disorders**
  Identify rare genetic variants or expression variation to reveal "missing heritability".

News

- **Review Article on Auditory Hallucinations**
  Jun 24, 2014

- **NORMENT Guest Researcher Among the Most Successful Norwegians Abroad**
  Apr 14, 2014

Publications

- **An open trial of group metacognitive therapy for depression in Norway**
  Aug 16, 2014 11:00 AM

- **The human amygdala encodes value and space during decision making**
  Aug 6, 2014 11:00 AM
Biological insights from 108 schizophrenia-associated genetic loci

Schizophrenia Working Group of the Psychiatric Genomics Consortium*
Original Article

Similar immune profile in bipolar disorder and schizophrenia: selective increase in soluble tumor necrosis factor receptor I and von Willebrand factor

Up-Regulation of NOTCH4 Gene Expression in Bipolar Disorder

Ingrid Diestet, M.D.
Srdjan Djurovic, M.D.
Martin Testi, M.D.
Sigrun Hope, M.D.
Morten Matingsdal, Ph.D.
Annika Michelsen, Ph.D.
Inge Jørn, Ph.D.
Tor Ketil Larsen, M.D., Ph.D.
Ingrid Agartz, M.D., Ph.D.
Ingrid Melle, M.D., Ph.D.
Jan Ivar Røssberg, M.D., Ph.D.

Pål Aukrust, M.D., Ph.D.
Ole A. Andreassen, M.D., Ph.D.
Thor Ueland, Ph.D.

Objective: Immunopathogenic mechanisms have been implicated in schizophrenia and bipolar disorder, and genome-wide association studies (GWAS) point to the major histocompatibility complex, a region that contains many immunologically related genes. One of the strongest candidate risk genes for schizophrenia and bipolar disorder is the NOTCH4 gene within the major histocompatibility complex. The authors investigated the expression of NOTCH4 in individuals with bipolar disorder and schizophrenia relative to healthy comparison subjects and identified relative expression quantitative trait loci in and around the NOTCH4 gene.

Method: The authors measured and compared NOTCH4 mRNA in whole-blood genomic DNA from 479 patients and 211 healthy comparison subjects and adjusted for a range of confounders. The authors also generated 20 single-nucleotide polymorphism (SNP) and investigated possible associations between expression quantitative trait loci and NOTCH4 expression.

Results: The authors found a strong association between NOTCH4 expression and bipolar disorder after adjusting for a range of confounders and multiple testing. In addition, seven 50% within the NOTCH4 gene region were associated with enhanced NOTCH4 mRNA levels. Three of these expression quantitative trait loci were independent (not in linkage disequilibrium).

Conclusions: These findings suggest that the association between NOTCH4 mRNA markers and bipolar disorder is related to altered function at the mRNA level, supporting the notion that NOTCH4 pathways are involved in the pathophysiology of bipolar disorder.

(Am J Psychiatry 2012; 169:1292-1300)

Cardiovascular risk factors during second generation antipsychotic treatment are associated with increased C-reactive protein

Ingrid Diestet, Sigrun Hope, Thor Ueland, Thomas Bjella, Ingrid Agartz, Ingrid Melle, Pål Aukrust, Jan Ivar Røssberg, Ole A. Andreassen

Association between altered brain morphology and elevated peripheral endothelial markers – Implications for psychotic disorders

Ingrid Diestet, Unn Kristin Haukvik, Ingrid Melle, Jan Ivar Røssberg, Thor Ueland, Sigrun Hope, Anders M. Dale, Srdjan Djurovic, Pål Aukrust, Ingrid Agartz, Ole A. Andreassen
Conjunctual Manhattan plot showing genetic overlap between several immune-mediated diseases and schizophrenia. Dieset et al. in prep
To identify shared genetic risk (pleiotropy) involving immune-mediated diseases, cardiovascular risk factors and psychotic disorders.

Determine the relationship between peripheral inflammatory activity and cardiovascular risk factors in patients with psychotic disorders.

To determine whether peripheral inflammatory markers together with polygenic risk score can predict a cardiovascular phenotype in patients with psychotic disorders.

Goals 2014-2017
WHO disability weight:

AIDS (with no treatment): 0.547

Terminal cancer: 0.519

Acute heart attack (day 1): 0.422

Schizophrenia psychosis: 0.756

Bipolar psychosis: 0.480

(Salomon et al. 2012)
Thank you all for your attention!

…and thank you: