Schizophrenia is associated with adverse changes in cardiac structure independent of conventional cardio-metabolic risk factors: a cardiac MR imaging study

Dr Emanuele F Osimo
MRC London Institute of Medical Sciences
Imperial College London
People suffering from schizophrenia die younger than the general population

• **die 10-25 years younger** (Laursen, Munk-Olsen et al. 2012)

• Patients with schizophrenia have a **2-3 fold greater mortality** compared to the general population

• the **mortality gap** between patients with schizophrenia and the healthy population is not reducing (Saha, Chant et al. 2007), and may even be increasing (Olfson, Gerhard et al. 2015).
Mostly because of disease

- Natural causes (i.e. disease), unnatural causes (i.e. suicide) both increased

- Death from natural causes accounted for two-thirds (63%) of the excess mortality (Brown et al, 2000)

- Lose an additional 10-14.3 years of life from cardiovascular disease (CVD) alone, as compared to people in the general population (Laursen 2011, Westman, Eriksson et al. 2018)

- 40 million * 12 years = 480 million life years lost
What are the potential causes of additional mortality?

• An unhealthy adult lifestyle (sedentary lifestyle, smoking, diet)

• ↑ Prenatal and early life stressors

• Antipsychotic medication (next talk)
What are the potential causes of additional mortality?

- ↑ alleles favouring CVD, e.g. by increasing inflammation and schizophrenia

  - Inflammation and schizophrenia:
    - Schizophrenia (acute and chronic) is associated with higher levels of inflammatory markers (many reviews)
    - Inflammation is confirmed even in drug naïve, first episode of psychosis patients (Pillinger & Osimo et al. 2019)
    - Inflammation in childhood increases the risk of psychosis later on in life (Osimo et al. in press)
    - Mendelian randomization suggests causal relationship

- A pro-inflammatory state increases the risk of cardiovascular death (see for example Wang et al, 2017)
Our study: methods

*** patient selection!

matching for age (+/- 3 years), ethnicity, sex, and body surface area (BSA +/- 2, a parameter similar to BMI)
Our study: patient selection

**Exclusion** criteria for all participants were:
- age <18 or >65 years
- a **history of cardiometabolic disease**, pregnancy or breastfeeding
- history of significant or continuing substance abuse.
Our study: Magnetic Resonance Imaging

A) Structural and functional
B) Septal thickness
C) and D) native T1
Results
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Schizophrenia</th>
<th>Healthy Controls</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size</td>
<td>40</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>Male sex, %</td>
<td>77.5%</td>
<td>82.0%</td>
<td>p=0.61</td>
</tr>
<tr>
<td>Caucasian ethnicity, %</td>
<td>47.5%</td>
<td>53.9%</td>
<td>p=0.57</td>
</tr>
<tr>
<td>Age, years mean (SD)</td>
<td>39.80 (9.55)</td>
<td>38.92 (9.38)</td>
<td>p=0.68</td>
</tr>
<tr>
<td>Number of cigarettes smoked per day, median (IQR; min; max)</td>
<td>1 (4.25; 0; 35)</td>
<td>0 (0; 0; 10)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Activity score, median (IQR)</td>
<td>2 (0)</td>
<td>3 (1.5)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>BSA (m²), mean (SD)</td>
<td>2.05 (0.27)</td>
<td>1.95 (0.22)</td>
<td>p=0.07</td>
</tr>
<tr>
<td>Systolic BP (mmHg), mean (SD)</td>
<td>124.64 (11.11)</td>
<td>122.05 (12.45)</td>
<td>p=0.35</td>
</tr>
<tr>
<td>Diastolic BP (mmHg), mean (SD)</td>
<td>81.22 (9.50)</td>
<td>77.78 (9.58)</td>
<td>p=0.12</td>
</tr>
<tr>
<td>HbA1c (mmol/mol), mean (SD)*</td>
<td>36.28 (6.02)</td>
<td>33.90 (7.92)</td>
<td>p=0.31</td>
</tr>
<tr>
<td>Chlorpromazine Equivalent Dose (mg/day), Median (IQR)</td>
<td>377 (290)</td>
<td>0 (NA)</td>
<td>NA</td>
</tr>
<tr>
<td>Duration of treatment (years), Median (IQR)</td>
<td>12 (13)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Total PANSS score, Median (IQR)</td>
<td>62 (35.5)</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>
Left Ventricular Measurements in Patients with Schizophrenia and Healthy Controls.
Right Ventricular Measurements in Patients with Schizophrenia and Healthy Controls.
Other Measurements in Patients with Schizophrenia and Healthy Controls.
Cardiac remodelling

from Gjiesdal et al, 2011
Sensitivity analyses

- No change adjusting for smoking
- Little change adjusting for *smoking + activity levels* (end-systolic volumes no longer significant)

- No cardiac measure significantly correlated with total current chlorpromazine dose equivalents
- Concentricity in patients was above the reference range, other measures within reference ranges.
Interpretation: ↑ concentric cardiac remodelling

- The **strongest predictor of future CVD events** such as myocardial infarction, coronary insufficiency, heart failure, and stroke in healthy adults, with the **lowest CVD-free survival** over time, with a hazard ratio of 1.40 (Tsao et al 2015)

- A predictor of higher mortality **even in people with normal ejection fractions** (meaning normal cardiac function) (Milani, Lavie et al. 2006)

- Could therefore account for part of the increased CVD morbidity and mortality in schizophrenia
Myocardial native T1 relaxation time is prolonged in schizophrenia

Pillinger & Osimo et al. 2019
Meaning of native T1

- ↑ native T1 = diffuse myocardial fibrosis and/or subclinical myocardial inflammation

Diagram from Haaf et al, 2017
Summary of published studies

• Physically healthy subjects with chronic schizophrenia (no comorbidity)
• Well matched to controls (including age, sex, ethnicity and BMI)

• Found **concentric cardiac remodelling and ↑ nT1 (≈ fibrosis)**

despite:
• No differences in HbA1c or blood pressure (no pre-diabetes or hypertension) – which are the most common causes of concentric heart remodelling in the general population
• Not due to some lifestyle changes (smoking and ↓ activity levels)

**What is driving the changes?**
Potential molecular pathways
Potential molecular pathways

- ↑ sympathetic activation
- chronic pro-inflammatory state (CRP ↑)
- Metabolic abnormalities (hyperglycaemia, insulin resistance, hyperleptinaemia, HOMA IR ↑, ALP ↑, HbA1c ↑, Adiponectin ↓)
- ↑ endothelin-1
- ↑ TGF-beta
- ↑ blood pressure
- pressure overload (PWV ↑)
- ↑ renin-angiotensin2
- Cardiomyocyte (BNP ↑)
- PICP
- Cardiac remodeling
↑ insulin, glucose, HOMA insulin resistance, triglycerides, alkaline phosphatase and high-sensitivity CRP

unpublished data
Potential molecular pathways
Levels of select metabolites by diagnosis/treatment category

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>p-value</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endothelin1</td>
<td>0.01</td>
<td>66</td>
</tr>
<tr>
<td>TGF_Beta1</td>
<td>0.01</td>
<td>66</td>
</tr>
</tbody>
</table>

Diagnosis and treatment:
- **HC**
- unmedicated SCZ
- on clozapine/olanzapine/risperidone

p values are calculated on treatment categories, and adjusted with BH

unpublished data
In conclusion

- Concentric cardiac remodelling and ↑ nT1 (≈ fibrosis)

and biologically

- Activation of the dysmetabolic/inflammatory/endothelial pathway, potentially leading to ↑ cardiac fibrosis
- No evidence for the activation of the canonical ↑ blood pressure/overload pathway
- TGF-beta results are still mysterious
Thank you for your attention.

Thanks to all collaborators: Mark Sweeney, Toby Pillinger, Stefan Brugger, Antonio de Marvao, Thomas Whitehurst, Ben Statton, Alaine Berry and many others!

and the supervisors: Prof **Oliver Howes** and Declan O’Regan

eosimo@ic.ac.uk

@eosimo
Previous studies investigating cardiac changes in schizophrenia

• Only few studies have previously directly investigated cardiac function in patients with schizophrenia (Unsal, Oran et al. 2013, Chow, Yeoh et al. 2014, Korkmaz, Korkmaz et al. 2016)

However, these studies:

• Not always identify and specify clear inclusion and exclusion criteria for participants (selection bias), such as co-morbidity
• Often showed enrolment bias
• Some had issues with the matching of controls (age, sex, ethnicity, body habitus, lifestyle…)
• Some had issues with the choice of measurement methods (USS is operator dependent)
• Some had power issues (sample size analysis before the study begins)
• None were blind in analysis
## CMR-Derived Cardiac Measurements in Patients with Schizophrenia and Matched Healthy Controls (BJP paper)

<table>
<thead>
<tr>
<th></th>
<th>Schizophrenia N=40</th>
<th>HCs N=39</th>
<th>Normal range of parameters in males &lt; 60 years (1)</th>
<th>Un-adjusted analysis</th>
<th>Adjusted for smoking (N of cigarettes)</th>
<th>Adjusted for activity levels</th>
<th>Adjusted for both smoking and activity levels</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LVEDVi (ml/m²)</strong></td>
<td>68.48 (10.95)</td>
<td>80.38 (17.40)</td>
<td>64, 100</td>
<td>-11.90, 0.0005</td>
<td>0.001</td>
<td>-0.82; -0.35; -1.29</td>
<td>-11.68, 0.001</td>
</tr>
<tr>
<td><strong>LVESVi (ml/m²)</strong></td>
<td>45.10 (7.38)</td>
<td>52.35 (9.49)</td>
<td>43, 67</td>
<td>-7.25, 0.0003</td>
<td>0.001</td>
<td>-0.85; -0.39; -1.32</td>
<td>-7.24, 0.001</td>
</tr>
<tr>
<td><strong>LVSVi (ml/m²)</strong></td>
<td>68.44 (12.61)</td>
<td>70.11 (17.23)</td>
<td>57, 91</td>
<td>-1.67, 0.62</td>
<td>0.75</td>
<td>-0.11; -0.34; -0.56</td>
<td>-2.5, 0.50</td>
</tr>
<tr>
<td><strong>LVMi (g/m²)</strong></td>
<td>80.88 (12.60)</td>
<td>96.21 (24.68)</td>
<td>63, 111</td>
<td>-15.32, 0.0008</td>
<td>0.002</td>
<td>-0.79; -0.32; -1.25</td>
<td>-14.79, 0.002</td>
</tr>
<tr>
<td><strong>RVEDVi (ml/m²)</strong></td>
<td>35.84 (8.80)</td>
<td>43.40 (9.65)</td>
<td>18, 46</td>
<td>-7.36, 0.01</td>
<td>0.02</td>
<td>-0.58; -0.12; -1.04</td>
<td>-7.10, 0.02</td>
</tr>
<tr>
<td><strong>RVESVi (ml/m²)</strong></td>
<td>45.01 (7.54)</td>
<td>53.10 (10.87)</td>
<td>39, 71</td>
<td>-8.09, 0.0002</td>
<td>0.001</td>
<td>-0.87; -0.40; -1.33</td>
<td>-7.79, 0.0008</td>
</tr>
<tr>
<td><strong>LV EF (%)</strong></td>
<td>66.08 (5.71)</td>
<td>65.85 (6.04)</td>
<td>57, 75</td>
<td>0.23, 0.86</td>
<td>0.94</td>
<td>0.04; -0.49; -0.40</td>
<td>-0.10, 0.94</td>
</tr>
<tr>
<td><strong>RV EF (%)</strong></td>
<td>55.90 (6.50)</td>
<td>55.95 (5.76)</td>
<td>50, 78</td>
<td>-0.05, 0.97</td>
<td>0.97</td>
<td>-0.01; -0.44; -0.46</td>
<td>-0.02, 0.99</td>
</tr>
<tr>
<td><strong>LV concentricity (g/ml)</strong></td>
<td>1.01 (0.17)</td>
<td>0.88 (0.17)</td>
<td>&lt;0.91</td>
<td>0.13, 0.002</td>
<td>0.003</td>
<td>0.73; 0.27; 1.19</td>
<td>0.10, 0.01</td>
</tr>
<tr>
<td><strong>Septal thickness (mm)</strong></td>
<td>10.49 (1.62)</td>
<td>8.79 (1.37)</td>
<td>&lt;15mm</td>
<td>1.71, 0.000003</td>
<td>0.00004</td>
<td>1.13; 0.65; 1.62</td>
<td>1.79, 0.000004</td>
</tr>
<tr>
<td><strong>PWV (m/s)</strong></td>
<td>4.75 (1.58)</td>
<td>4.52 (1.03)</td>
<td>N/A</td>
<td>0.23, 0.44</td>
<td>0.59</td>
<td>0.18; -0.62; -0.28</td>
<td>0.13, 0.68</td>
</tr>
</tbody>
</table>

### Notes:
- BH-adjusted p value, Cohen’s d, 95% CI
- Normal range of parameters in males < 60 years (1)
66 participants with cardiac scan AND bloods (unpublished)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Chronic schizophrenia on cloz/olanz/risperidone</th>
<th>Untreated schizophrenia</th>
<th>Healthy Controls</th>
<th>Test statistic and p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size</td>
<td>26</td>
<td>8</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Male sex, N (%)</td>
<td>18 (69%)</td>
<td>5 (63%)</td>
<td>21 (66%)</td>
<td>$\chi^2 = 0.16; \text{d.f.} = 2; \ p=0.92$</td>
</tr>
<tr>
<td>White ethnicity, N (%)</td>
<td>11 (42%)</td>
<td>4 (50%)</td>
<td>19 (59%)</td>
<td>$\chi^2 = 1.7; \text{d.f.} = 2; \ p=0.43$</td>
</tr>
<tr>
<td>Age, years mean (SD)</td>
<td>39.88 (10.41)</td>
<td>28.38 (5.29)</td>
<td>35.41 (10.34)</td>
<td>$F = 4.5, \text{df} = 2, \ p = 0.02$</td>
</tr>
<tr>
<td>Number of cigarettes smoked per day, median (IQR; min; max)</td>
<td>5 (18)</td>
<td>1 (6)</td>
<td>0 (0)</td>
<td>Wilcoxon rank sum test p=0.0003</td>
</tr>
<tr>
<td>Activity score, median (IQR)</td>
<td>2 (0)</td>
<td>3 (1)</td>
<td>3 (1)</td>
<td>Wilcoxon rank sum test p=0.11</td>
</tr>
<tr>
<td>BSA (m$^2$), mean (SD)</td>
<td>2.02 (0.3)</td>
<td>1.91 (0.22)</td>
<td>1.95 (0.23)</td>
<td></td>
</tr>
<tr>
<td>Systolic BP (mmHg), mean (SD)</td>
<td>122.92 (10.95)</td>
<td>119.25 (9.85)</td>
<td>121.47 (12.35)</td>
<td>$F = 0.3, \text{df} =2, \ p = 0.72$</td>
</tr>
<tr>
<td>Diastolic BP (mmHg), mean (SD)</td>
<td>79.96 (8.62)</td>
<td>77.12 (8.58)</td>
<td>77.28 (7.26)</td>
<td>$F = 0.9, \text{df} =2, \ p = 0.42$</td>
</tr>
<tr>
<td>Chlorpromazine Equivalent Dose (mg/day), Median (IQR)</td>
<td>358.98 (221)</td>
<td>0</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Duration of treatment (years), Median (IQR)</td>
<td>12 (15)</td>
<td>0</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Total PANSS score, Median (IQR)</td>
<td>55 (29)</td>
<td>41 (14)</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>