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# **Coronary artery disease and schizophrenia:**

## **The interplay of heart and mind**

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This editorial makes reference to the following study:

Attar R, Valentin JB, Freeman P, Andell P, Aagaard J, Jensen SE. The Effect of  
Schizophrenia on Major Adverse Cardiac Events, Length of Hospital Stay and Prevalence of  
Somatic Comorbidities Following Acute Coronary Syndrome. Eur Heart J Qual Care Clin  
Outcomes 2018.

Mental health and cardiovascular disorders form two of the biggest expenditures in healthcare budgets in the Western world<sup>1</sup>. The interplay between the two is increasingly recognized in the academic literature, yet national and international guidelines tackling this directly are lacking. Schizophrenia is a particularly challenging mental health disorder which leaves its sufferers with a substantial degree of disability and higher rates of mortality. A number of meta-analyses have described a risk of death of up to three-fold compared to the general population<sup>2, 3</sup>. In fact, studies have described a shorter life expectancy for schizophrenia sufferers of approximately 15-25 years<sup>2, 4</sup>. This does not appear to be changing over time with studies showing similar rates between 1996 and 2006<sup>5</sup>. More recent studies from Nordic countries have shown similar trends in 2013<sup>2</sup>. Interestingly, the leading cause of death in this group is cardiovascular disease in both males and females<sup>4</sup>.

In the study published by Attar et al<sup>6</sup>, routinely collected data from nationwide registries were utilised to investigate the relationship between schizophrenia and acute coronary syndrome (ACS). The advantage of using this resource is to reflect what typically happens in our day-to-day clinical practice; also referred to in the literature as ‘real life’. They identified 726 patients with schizophrenia who experienced an ACS and matched them on a 1:2 basis for comorbidities and risk factors with ‘psychiatric healthy controls’ (PHC) with ACS. This serves to adjust, at least partially, for the higher inherent risks that patients with schizophrenia experience. The study revealed significantly higher major adverse cardiac events (MACE) in patients with schizophrenia, driven predominantly by mortality and stroke. This is consistent with previous studies that have shown an association between schizophrenia and poor outcomes in cardiovascular disease despite adjusting for baseline factors<sup>7</sup>.

The strengths of this study relate to the relatively large sample size which was used to examine this association. The use of ICD-10 codes allows for comprehensive documentation of cardiac risk factors and comorbidities, as well as statistical matching and adjusting for these. This reduces selection bias, which may accompany carefully selected clinical trial groups. Of course however, the study shares similar limitations with other registry studies, where unavailable or incomplete data entry limits its accuracy. Furthermore, despite matching for ICD-10 diagnoses, there may be other factors not recorded in the routinely collected data set that may confound the study, including life style factors such as smoking. In addition, analysis of large sets of data on the basis of ICD-10 diagnoses does not allow grading of the severity of such conditions, which may in turn influence outcomes. Finally, it is only possible to infer associations from these findings and not causation.

The prevalence of cardiovascular disease and its risk factors is high in patients with schizophrenia. This has been shown in a number of studies published in both psychiatric and cardiovascular journals. For instance, the prevalence of metabolic syndrome in patients with schizophrenia has been observed to be more than 40% in both males and females<sup>8</sup>. These rates are much higher (up to 4 fold) than the general population<sup>8</sup>. The components that make up this syndrome are hypertension, dyslipidaemia, obesity and fasting glycaemia – all of which have been shown to be individually elevated in this disease group above national averages. Furthermore, the prevalence of other risk factors such as diabetes mellitus is at least twice as high as in the general population<sup>8</sup>.

The literature has attributed the higher prevalence of cardiac risk factors to behavioural, socioeconomic and healthcare reasons<sup>4</sup>. These reasons are likely to interact and adversely affect each other, further complicating the picture. Behavioural risk factors include unhealthy

habits which are more prevalent in this patient group, such as tobacco smoking and substance abuse<sup>4</sup>. Patients with schizophrenia have also been shown to be more likely to lead a sedentary lifestyle compared to the general population by spending fewer leisurely hours on sports and more hours on sedentary activities<sup>9</sup>. Socioeconomic factors include poor education and poverty which in turn compound the behavioural risks. Healthcare factors have been implicated in both prevention of risk factors and treatment of acute coronary syndrome in patients with severe mental illness. For instance, documentation and treatment of cardiovascular risk factors has been shown to be poorly done for patients with schizophrenia<sup>10, 11</sup>. This could relate to patient factors in seeking health care, although patients with severe mental illness have been shown not to receive the same level of assessment for physical problems compared to those without mental illness<sup>11</sup>. Other healthcare factors include side effects from anti-psychotic medications which are recognized as contributors to the development of obesity, metabolic syndrome and possibly autonomic nervous system dysfunction<sup>4</sup>. To add insult to injury, patients suffering from schizophrenia who experience an ACS have been noted to receive suboptimal medical care and are half as likely to undergo coronary revascularisation compared to patients with no mental illness<sup>12, 13</sup>. This strongly highlights healthcare inequality when it comes to cardiac management and augments the problem by creating a 'health care paradox', where patients who need care the most, are less likely to receive it. This paradox could explain the observation of multiple studies, including the study by Attar et al, which showed that even after adjusting for ICD-10 baseline comorbidities and risk factors, outcomes of patients with schizophrenia remained poor<sup>7</sup>.

A number of studies have explored a biological basis for this observed association between schizophrenia and cardiovascular disease and risk factors<sup>14</sup>. The over-arching theme seems to

be related to systems inflammation where multiple pro-inflammatory cytokines are recognized to be altered in patients with schizophrenia. This state of immune dysregulation has been shown to be damaging to neuronal and microglial cells<sup>15</sup>, but also to form the basis for the development of insulin resistance, metabolic syndrome and other risk factors that are causative of atherosclerosis<sup>14</sup>. In addition to this, anti-psychotic medications have been implicated in pathological oxidative stress which is implicated in further compounding the dysregulated inflammatory response to tissue damage<sup>16</sup>.

The observations in the study by Attar et al<sup>6</sup> serve to strengthen the hypothesis of an interplay between schizophrenia and acute coronary syndrome. It highlights an exciting area of research where collaborative spirit between multiple disciplines (cardiology, epidemiology, neuropsychiatry and others) can be fostered to advance this area of research. Perhaps it is time for prospective cohort studies to be commissioned, where matching could take place in a more controlled fashion with rigorous follow up and measurement of co-morbid factors as well as biomarkers. Until then, both physicians and psychiatrists must weigh the increasing evidence that recognizes this interplay, and use their clinical judgement to tackle it. Specifically, efforts should be intensified to provide tailored education and management advice on diet, smoking cessation, weight management and physical activity. In addition, reviews of antipsychotic medications should take place on a regular basis in an attempt to choose the agent/dosage with the least possible physical side effects. Finally, the observation of reduced revascularisation rates in this patient group must be reviewed and tackled by tailoring revascularisation strategies, follow up and cardiac rehabilitation arrangements as well as intensifying efforts to manage risk factors by engaging with primary care services and keeping a closer eye on this high risk group<sup>13</sup>.

**Conflict of interest:** none declared.

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