Cardiac Dysfunction in People with Schizophrenia: Linking Clinical Outcome, the Heart, and the Brain

by

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Abstract

While cardiovascular disease remains the primary cause of mortality in people with schizophrenia, the link between cardiac dysfunction and clinical outcome remains poorly understood. The current study is an exploratory analysis, where a total of thirteen participants with schizophrenia were included to examine clinical outcome, cardiac structure and function, and brain volume of the anterior cingulate cortex (ACC) as measured by magnetic resonance imaging, where those participants achieving remission (N = 7) had better global functioning, with fewer positive and negative symptoms on PANSS and SNS. Cardiac function and structure did not differ between remitted and non-remitted groups; but, those not in remission had significantly less volume in the left ACC. As a whole sample, no significant relationships were found between ACC volume and clinical symptoms; however, inverse relationships between social withdrawal and left ventricular end diastolic volume (LVEDV), left ventricular end systolic volume (LVESV), left ventricle stroke volume (LVSV), left-ventricular concentricity (a ratio of left ventricular EDV/mass), and right ventricular end systolic volume (RVESV) were observed. Moreover, bilateral ACC volume was significantly correlated with higher LVEDV, LVSV, RVSV, and lower LV Concentricity, whereas only the left ACC was significantly related to higher RVEDV. Of note, all participants had significantly increased left ventricular concentricity compared to the general population. These results support that clinical outcome is indeed related to brain volume but may not be related to cardiac measures of function and structure in people with schizophrenia, but more research is required to verify these conclusions and to further explore the mechanisms of cardiac dysfunction.

Keywords: Schizophrenia, Magnetic Resonance Imaging, Clinical Outcome, Anterior Cingulate Cortex

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Prevalence of Schizophrenia, Diagnostic Criteria, & Economic Burden

Schizophrenia impacts approximately 1.13% of the global population and is one of the leading causes of disability among people aged 25 to 49 worldwide (Abbafati et al., 2020; Charlson et al., 2018). As per the Diagnostic and Statistical Manual of Mental Disorders, Version 5 (DSM-5, 2013), to be diagnosed with schizophrenia a person must present with two (or more) of the following symptoms: delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behaviour, affective flattening, alogia, anhedonia, asociality, or amotivation, for a significant portion of time during a 1-month period; symptoms must include at least one of delusions, hallucinations, or disorganized speech. The person must also show a significant reduction in level of daily functioning in various areas of life such as work/school, interpersonal relations, or self-care since the onset of symptoms. Finally, symptoms or reduced functioning cannot be attributable to the effects of a substance (e.g., drug of abuse, a medication) or any another medical condition.

The global economic burden of schizophrenia is estimated to be between $90 million to $102 billion USD (based upon a percentage of each country's GDP), where the greatest determinant of economic burden are the indirect healthcare costs (e.g., unemployment, underemployment, informal care, and premature mortality) and not the direct healthcare costs (e.g., doctor appointments, medication, etc.) (Chong et al., 2016; Jin & Mosweu, 2017). Of note, a recent systematic review found that healthcare and resource costs were directly related to the presence of more negative symptoms (Weber et al., 2022). In Canada, the economic burden for schizophrenia has been related to morbidity and multimorbidity (Goeree et al., 2005; Stewart et al., 2022). Of key importance, there has been a 99% increase over a ten-year period (from 2008 to 2017) in direct healthcare costs, largely driven by increased spending on younger people and

people with multiple somatic diagnoses with schizophrenia (Stewart et al., 2022). The research suggested increased pharmaceutical cost for young people with schizophrenia (aged 18-29) related most highly to increased spending; however, the percentage of people with schizophrenia living with 3 or more somatic diagnoses also rose from 33% to 47.3%. When stratified by age, increased spending for ages 18-69 rose over the ten-year period studied, driven by hospitalizations. It is important to note that hospitalizations in this study were not condition-specific and could have been for somatic illnesses as well as psychiatric. Finally, despite increased spending, the mortality rate in this study steadily rose each year from 1.8% to 2.3%.

Historical Overview of Schizophrenia Diagnosis and Symptoms

While Emil Kraepelin and Eugene Bleuler are credited with laying the foundation of the diagnostic criteria for schizophrenia through their early characterizations in the late 1800's and early 1900's, several others came before them. The documented history of schizophrenia began in 1810, when John Haslam and Philippe Pinel recorded the first cases of psychosis (Heinrichs, 2003). Bénédict Morel termed mental deterioration in early life as *démence précoce* in 1850, which was later used and translated into Latin by Heinrich Schule in 1886: dementia præcox (Adityanjee et al., 1999). In 1871, Ewald Hecker described *hebephrenia* (what would later become residual type schizophrenia) and Karl Ludwig Kahlbaum in 1874 described catatonia, the extreme disturbances in motor behaviours. Emil Kraepelin synthesized these disorders using the term dementia præcox in the 5th edition of his textbook in 1896. Eugen Bleuler then grouped the disorders under the term schizophrenia, a term of his own design to describe that the psychic functions of the mind experience a schism (Bleuler, 1911). An important note for Bleuler, compared with Kraepelin, included descriptions of many people who experienced intermittent remission.

Kraepelin wrote highly detailed accounts of the impacts of dementia præcox (Kraepelin, 1919). While full dementia did not occur in all cases, 'dementia' was the most applicable name to describe the severe deterioration of mental, cognitive, and emotional faculties. He noted that approximately 60% of patients had onset of symptoms before the age of 25 and noted "deficits" among the patients with many lacking affect (i.e., they presented with "flat affect"). In fact, he believed these "deficits" were the foundation for the psychopathological features of the disorder. Of note, the use of the term "patient" here is since most, if not all, people receiving care for a mental illness were institutionalised at the time. Similarly, Bleuler described the schizophrenias with primary symptoms (e.g., abnormality in volition, complete lack of emotional and affective expressions) and accessory symptoms (e.g., delusions, hallucinations) (Bleuler, 1915). He highlighted the primary symptoms were fundamental to schizophrenia. For both Kraepelin and Bleuler, the main symptoms of schizophrenia included deficits in motivation, flat affect, and ambivalence, which are now recognized as negative symptoms and still considered "core" to schizophrenia (Scharfetter, 2001; Stanculete, 2022). Today, these core symptoms are essential to both diagnosis and clinical outcome.

Understanding Outcome in Schizophrenia

Clinical outcome in schizophrenia refers to a person's psychopathological symptoms and can be measured in research by examining the number of hospitalizations (Verdoux et al., 2002), a response to antipsychotics (Joober et al., 2002), or a change in symptom severity – that can be measured as achieving remission or not (Leucht, 2014). In 2005, a consensus on the definition of remission in schizophrenia was outlined which created a standard measurement of clinical outcome for schizophrenia (Andreasen et al., 2005). To achieve remission, a person must obtain at a rating of mild or less on a standardized scale across eight core symptoms that must be

maintained for six months. The core symptoms include hallucinations, delusions, and unusual thought content (positive), concept disorganization and bizarre mannerisms (disorganized thoughts and behaviour) and blunted affect, social withdrawal, and lack of spontaneity (negative). Since 2005, the definition has been validated many times, with and without the time criterion (AlAqeel & Margolese, 2013) and even with a brief rating scale covering six symptoms (Østergaard et al., 2016).

Although there is a standardized definition of outcome, there is wide heterogeneity of outcome when looking at remission rates for schizophrenia – 17% to 86% (AlAqeel & Margolese, 2013; Carpiniello et al., 2022; Huxley et al., 2021; Lambert et al., 2010a). There are several reasons for this large variability that include differences in the care offered, variation in rating scales, differences in interview techniques from around the world, the inclusion of all people with psychosis, or even the varying number of episodes people with schizophrenia may experience. For example, the most recent review of outcome in schizophrenia by Huxley et al. (2021) found that 57.14% of people who experienced a single first-episode psychosis (FEP) achieved remission compared to 37.75% of people who experienced multiple-episode psychosis (MEP), and this is especially different compared to data from earlier in the 20th century where remission for both FEP and MEP was approximately 20% for both. Regardless, the remission definition from 2005 is considered the gold standard for measuring clinical outcome in schizophrenia.

Predicting Outcome

There are numerous documented predictors of outcome. For example, poorer outcomes have been related to a later onset of psychosis (Carbon & Correll, 2014b), worse insight into illness (Raucher-Chéné et al., 2022), poor medication adherence (Verdoux et al., 2000), and worse

cognitive functioning across all seven cognitive domains (social cognition, processing speed, reasoning and problem solving, working memory, attention/vigilance, visual learning/memory, verbal learning/memory) as proposed by the Measurement and Treatment Research to Improve Cognition in Schizophrenia consensus panel (MATRICS; Kern et al., 2004). Among the seven cognitive domains, verbal learning/memory is considered the strongest predictor of outcome (Fervaha et al., 2014). Historically, male gender was strongly related to a poor outcome. Carbon and Correll (2014b) discussed why this finding is controversial: most studies linking male gender to a poor outcome did not look beyond a one-year time frame and did not account for decreased help-seeking behaviours, increased substance use, and decreased medication and treatment adherence, all factors that have been related to the male gender.

Yet, of all the predictors, the most robust predictor of a poor outcome is negative symptom severity – from increased levels observed during a FEP to consistently high levels throughout care (Carpiniello et al., 2022; Foussias & Remington, 2010; Rammou et al., 2019). In fact, electronic health record data suggests that increased negative symptoms are related to clinical outcome where people with schizophrenia with more than two reported negative symptoms are more likely to have a longer length of stay when admitted to hospital, and greater chance of readmission compared to those with fewer negative symptoms (Patel et al., 2015). In fact, approximately 40% of people with schizophrenia are impacted by persistent and difficult to treat negative symptoms (Carbon & Correll, 2014a), that in turn, adversely impact outcome.

Negative Symptoms

Negative symptoms refer to behavioural or affective elements that are absent from an individual's normative experience and encompasses five key constructs: anhedonia, asociality, avolition/apathy, alogia, and blunted affect (Correll & Schooler, 2020). The negative symptoms

have also been presented as two domains: amotivation (including anhedonia, asociality, and avolition/apathy) and diminished expressivity (including alogia and blunted affect) (Correll & Schooler, 2020; Kirkpatrick et al., 2006; Messinger et al., 2011) where notably the domain of amotivation has the most severe impacts upon outcome, such that greater deficits in amotivation predict poorer outcome (Fervaha et al., 2014), and particularly avolition (Fervaha et al., 2014; Foussias & Remington, 2010; Martin et al., 2021). For purposes herein, the five separate symptoms will be referred to as defined by Andreasen et al (1984), where affect flattening is described as the inability to outwardly express, either verbally or otherwise, emotions during expected situations. Alogia is described as decreased content in conversation and is frequently referred to as 'poverty of speech.' Social withdrawal refers to the preference for solitary activities or simply the disinterest in social activities. Avolition is described as the lack of motivation or desire to engage in meaningful activities, to attempt or set goals. The last of the five core symptoms is anhedonia, described as the lack of enjoyment felt in pleasurable activities where one would normally find enjoyment. Negative symptoms are intrinsic to the diagnosis of schizophrenia and are considered core to the illness itself ("Diagnostic and Statistical Manual of Mental Disorders: DSM-5.," 2013), as they are known to appear during the prodromal stage of illness (i.e., before the onset of psychosis) and persist throughout the course of illness (an der Heiden et al., 2016).

Of note, negative symptoms can be classified as primary (idiopathic) or secondary (manifest in relation to clinically relevant positive, depressive, or extrapyramidal symptoms) (Buchanan, 2007). To distinguish between the two types, one must use a specialized scale, the Schedule for the Deficit Syndrome (SDS; Kirkpatrick et al., 1989), or apply a definition to data gathered across multiple scales to remove any factors that may be influencing the negative

symptoms. For the latter, an alternative concept - persistent negative symptoms – was created to explore primary negative symptoms. For this, negative symptoms needed to be present at moderate or higher ratings in the absence of positive symptoms (all rated mild or less), depressive symptoms (total score of 4 or less on the Calgary Depression Scale for Schizophrenia) (Addington et al., 1993), and extrapyramidal symptoms (i.e., not requiring anticholinergics); and all criteria maintained for at least 6 consecutive months.

Persistent negative symptoms can be found in FEP as well as MEP. The prevalence of persistent negative symptoms in FEP are between 15-27% (Buchanan, 2007; W. C. Chang et al., 2011; Hovington et al., 2012). In a recent review (Sauvé et al., 2019), negative symptoms were found to change in prevalence across the stages of psychosis, where prevalence of negative symptoms are lower during a FEP and increase as people age and enter MEP stage, especially for avolition (FEP = 28%; MEP = 73%), anhedonia (FEP = 26%; MEP = 57%), and asociality (FEP = 34%; MEP = 48%). So, as people with schizophrenia age, they may experience more severe negative symptoms and multimorbidity.

Understanding Morbidity and Mortality in Schizophrenia

Currently, people with schizophrenia have a lifespan shortened by approximately 11-13 years compared to the general population, where cardiovascular disease (CVD) is the leading cause of mortality (Gatov et al., 2017; Hennekens et al., 2005; Laursen et al., 2019; Rødevand et al., 2019; Yung et al., 2021). CVD includes arrhythmia, cardiomyopathy, coronary artery disease, heart attack, heart failure, and stroke (Everson-Rose & Lewis, 2005). It has been established that people with schizophrenia receive less equitable access to care compared to the general population (Crawford et al., 2014; Kisely et al., 2007; Mitchell & Lord, 2010; Osborn et al., 2011), where this suboptimal care often results in increased risk for psychiatric readmissions

where CVD risk factors have not been adequately monitored (Tan et al., 2022). Tan and colleagues (2022) found that psychiatric readmissions were 37% more likely for people with poor follow-up care for blood lipid levels and 32% more likely for people with poor follow-up care for hypertension. Furthermore, healthcare records revealed a lack of recognition of CVD despite documented evidence of multiple risk factors (Smith et al., 2013). In fact, people with schizophrenia are 53% more at-risk of a CVD than the general population, and among those diagnosed with a CVD, they were more likely to be older and have a lower socioeconomic status (Bresee et al., 2010; Fan et al., 2013). Moreover, those who were at higher risk of developing a CVD were more likely to have pre-existing CVD risk factors such as type II diabetes, regardless of sex (Bresee et al., 2010).

Brown (1999) found increased mortality due to natural causes for people with schizophrenia, with lifestyle-related factors as the most often examined risk factors for mortality. Chiu et al (2018) examined eight different CVD risk factors (smoking, hypertension, Type II diabetes, physical activity, diet, obesity, stress, and alcohol consumption) and found that almost 90% of people with schizophrenia had at least one risk-factor and almost 40% had three or more risk-factors, when compared to healthy controls where 82.3% had at least one risk-factor and 25% had three or more. These differences in number of risk-factors were significant. To research the differences in CVD risk-factors and assess their relationship with symptom severity, Storch Jakobsen et al. (2018) examined cardiorespiratory fitness, diet, waist circumference, BMI, blood pressure, HDL cholesterol, blood glucose and their relation to clinical symptoms. Using unstandardized linear regression modelling, they found relationships between negative symptoms and cardiorespiratory fitness, as well as with HDL cholesterol, suggesting that poorer fitness and lower HDL cholesterol related to worse negative symptoms. They also found positive

relationships between negative symptoms and waist circumference, as well as and blood glucose, suggesting greater waist circumference and higher blood glucose were related to worse negative symptoms. The results from Storch Jakobsen et al. (2018) give further evidence that CVD risk factors such as increased waist circumference, increased blood glucose, poor fitness and low HDL cholesterol related to increased negative symptoms – the greatest predictor of poor clinical outcome.

It is also likely that risk-factors for CVD may be present before the onset of psychosis. In fact, increased triglycerides, increased abdominal circumference, and decreased high-density lipoprotein (HDL) cholesterol have been observed in people with FEP (Barcones et al., 2018) as well as insulin resistance and high BMI in early childhood (Perry et al., 2021). Indeed, one of the highest risk-factors for CVD – metabolic syndrome – has been reported in 13.2% of people with FEP (Eckel et al., 2005; Garrido-Torres et al., 2021). To be diagnosed with metabolic syndrome, at least three of the following five symptoms must be present: (1) enlarged waist circumference (≥ 88cm in women; ≥ 102cm in men); (2) rising triglycerides (≥ 150 mg/dL) or be receiving drug treatment for rising triglycerides; (3) lower HDL cholesterol (< 50 mg/dL in women; < 40 mg/dL in men) or be receiving drug treatment for lower HDL cholesterol; (4) increased fasting blood glucose or HbA1c (≥ 100 mg/dL regardless of sex) or be receiving drug treatment for increased fasting blood glucose; and (5) hypertension (systolic pressure ≥ 130 mmHg or diastolic pressure ≥ 85 mmHg regardless of sex) or be receiving drug treatment for hypertension (Eckel et al., 2005). An FEP study explored metabolic syndrome in relation to symptom severity using the Positive and Negative Syndrome Scale (PANSS, Kay et al., 1987). The PANSS measures symptom severity on three separate symptom scales: positive symptoms, negative symptoms, and general psychopathology symptoms and a total of all three. The

positive and negative symptoms measured by the PANSS refer to the core diagnostic criteria related to schizophrenia: delusions, hallucinations, concept disorganization (positive symptoms) and blunted affect, social withdrawal, and lack of spontaneity (negative symptoms). General psychopathology, as measured by the PANSS, refers to bizarre mannerisms and bizarre thought content. Findings from this study suggested that waist circumference was positively related to general psychopathology ($r = .17$, $p < .001$) and total symptoms ($r = .16$, $p = .004$), and fasting glucose levels were positively related to negative symptoms ($r = .13$, $p = .03$), general psychopathology ($r = .19$, $p < .001$) and total symptoms ($r = .20$, $p < .001$) (Lang et al., 2021).

Early Accounts of Cardiac Abnormalities

Both Kraepelin and Bleuler noted cardiac abnormalities among their patients. Kraepelin observed variation in pulse rate that was not related to physical activity, and abnormal blushing and blanching of the face (Kraepelin, 1899). Bleuler noted that some patients experienced rapid weight gain after the onset of illness but further highlighted those experiencing weight gain during acute psychosis were more severely impacted in the long term (Bleuler, 1915). Like Kraepelin's cardiovascular observations, Bleuler also noted variable pulse rates but also noted that extremities could be either cold or hot to the touch despite stable body temperature, blood vessels were particularly fragile regardless of symptom severity, such that this population appeared to be more susceptible to increased bleeding from cuts and poorer wound healing.

More recent studies into heart function and structure using echocardiography have focused on evaluating left ventricular ejection fraction (LVEF) – the percentage of blood volume ejected from the left ventricle with each beat (Bogaert, 2011). LVEF has been the long-standing, most important measure of cardiac performance, such that decreased LVEF is one of the defining criteria for most forms of clinical heart failure (Lee et al., 2009). Unsal et al. (2013) found no

differences between people with schizophrenia and healthy controls among any cardiac variables when examining the heart using echocardiography. Chow et al. (2014) assessed ejection fraction in people with schizophrenia who were taking clozapine, people with schizophrenia who were taking any other antipsychotic, and healthy controls; results showed those who were taking clozapine had a significantly worse ejection fraction. Similarly, Curto et al. (2015) assessed left ventricular function using echocardiogram in people taking clozapine and then compared values after one month of treatment versus baseline. The authors found an 80% reduction in left ventricular end diastolic volume (LVEDV) and a 60% reduction in left ventricular end systolic volume (LVESV); a major limitation to this study was the small sample size of 15 participants. Finally, Korkmaz et al. (2016) used echocardiography to compare cardiac function in people with schizophrenia versus healthy controls in a sample of 40 age- and sex-matched participants. This study found that people with schizophrenia showed a significantly lower ejection fraction compared healthy controls. Considered as a group, with three of four studies finding similar results for ejection fraction, this body of literature indicates decreased left ventricular functioning in people with schizophrenia compared to the general population.

Investigating Cardiac Dysregulation with CMR

While echocardiography is appropriate for day-to-day patient assessment (Germain et al., 1992; Nosir et al., 1998), cardiac magnetic resonance (CMR) is now considered the gold standard of cardiac diagnostic assessment (Hundley et al., 2010). Despite CMR being a valuable tool for its superior diagnostic accuracy, only four research studies have been published examining the cardiac function and structure in people with schizophrenia (Andreou et al., 2020; Osimo et al., 2020, 2021; Pillinger et al., 2019). This small number of studies is largely due to reduced access

to CMR technology and that the research area is in fact in its infancy for psychosis, despite abnormalities being described more than 100 years ago.

The first study to use CMR to investigate cardiac function and structural integrity in people with schizophrenia was published by Pillinger and colleagues in 2019. This study explored the impacts of antipsychotic use on myocardial tissue and used an age, gender, ethnicity, and BMI matched design. People with schizophrenia were recruited from various community mental health services in London, UK and compared to healthy volunteers. All participants were required to have no history of diabetes mellitus, hypertension, or substance abuse including alcohol. Other variables of interest included blood pressure, a rating of weekly physical activity levels, smoking status, and blood glucose levels.

The final sample included 14 people with schizophrenia (aged 39.9 ± 13.1) and 17 healthy volunteers (37.9 ± 12.2) (Pillinger et al., 2019). There were no significant differences between the matched groups in smoking status, blood pressure, BMI, blood glucose levels, or weekly physical activity measures. People with schizophrenia were found to have a longer native myocardial T1 time. A longer T1 time is considered indicative of potential myocardial inflammation or fibrosis (Blissett et al., 2019; Burt et al., 2014; Puntmann et al., 2016). Of note, the observed myocardial inflammation was not related to antipsychotic dose, duration of antipsychotic treatment, mean arterial pressure, or blood glucose levels.

In terms of cardiac function, participants with schizophrenia had significantly reduced left and right ventricular end diastolic volume (LVEDV and RVEDV, respectively: the volume of blood in the ventricle after being filled) and significantly reduced left and right stroke volume (LVSV and RVSV, respectively: describes volume of blood pumped out of the ventricle during one cardiac cycle). In terms of structure, the participants with schizophrenia had significantly

lowered left ventricular mass (LVM: the weight of the left ventricle). No significant differences were found with left or right ejection fraction (LVEF and RVEF, respectively: the percentage of blood being pumped from the ventricle during one cardiac cycle) or left or right end systolic volume (LVESV and RVESV, respectively: the volume of blood remaining in the ventricle).

The implications of this study were substantial, not only as the first CMR publication in schizophrenia, but also as a departure from previous cardiac literature in schizophrenia where both left and right sides of the heart were assessed (Chow et al., 2014; Korkmaz et al., 2016; Unsal et al., 2013). Here, significant differences in stroke volume and end diastolic volumes on both the right and left sides, as well as decreased LVM, were observed in comparison to healthy volunteers (Pillinger et al., 2019). Also, unique to this study was the inclusion of several lifestyle and metabolic factors, which were found to be unrelated to cardiac function and structure. The researchers suggested these differences could be due to the careful selection of participants, but most importantly to the use of CMR techniques that provided more accurate measurements of volume. A potential limiting factor, however, was the small sample size but was considered within reason for the first published study using CMR in people with psychosis.

In 2020, Andreou et al. published the second research article using CMR to explore cardiac dysfunction in people with schizophrenia. The intent was to use CMR to explore LVEF in people with long-term antipsychotic use, which they defined as greater than ten years. They recruited 30 participants from an outpatient clinic in Uppsala, Sweden, aged 44 years (± 7.3) and compared them to an age, sex, and BMI matched sample of 30 healthy control participants. Like Pillinger at al. (2019), the authors had strict exclusionary criteria that included no history of CVD. Other variables of interest included: alcohol use, weekly physical activity, blood glucose, triglycerides, HDL cholesterol, low density lipoprotein (LDL) cholesterol, C-reactive protein

(CRP), smoking status, blood pressure, diet, family history of Type II diabetes, family history of CVD, resting heart rate, and corrected QT interval.

The results highlighted significantly higher blood glucose, CRP, resting HR, and longer corrected QT intervals in people with schizophrenia compared to healthy volunteers, with no effect from gender or medication (Andreou et al., 2020). However, the most significant finding was the impact of gender and antipsychotic type on LVEF; men who used antipsychotics had significantly lower LVEF compared to healthy volunteers. Even more striking, men who used clozapine had an even lower LVEF compared to men using other antipsychotics. This effect was not significant in women. LVEF was not related to any of the lifestyle or metabolic variables.

The overall significance of this study was that it implicated, with CMR, both effects of gender and the cardiotoxicity of long-term antipsychotic and clozapine usage on the heart. While many studies have demonstrated the potential cardiotoxic effects of second-generation antipsychotics by increasing CVD risk-factors (D'Errico et al., 2021; Howell et al., 2019; Pillinger et al., 2020; Stahl et al., 2009; Sweeney et al., 2020), none have made a connection to decreased cardiac function as verified by CMR.

This finding may potentially explain the lack of significant findings for the LVEF in previous studies as they did not fully account for gender and antipsychotic type (Chow et al., 2014; Korkmaz et al., 2016; Pillinger et al., 2019; Unsal et al., 2013). However, a significant limitation of this study was restricting the cardiac research variables to only LVEF and not using CMR technology to its full advantage and exploring the global cardiac functioning and structural parameters, such as ventricular volume or T1 relaxation time.

From the same research lab as Pillinger et al. (2019), in 2020, Osimo et al. investigated cardiac function and structure in people with schizophrenia using CMR., The final sample

included 40 age, sex, body surface area (BSA), and ethnicity-matched clinical participants and healthy volunteers; this group also excluded participants with CVD. In fact, the authors were largely interested in determining if concentric heart remodelling was occurring in people with schizophrenia. Thus, the structural heart variables of interest included (1) septal width, defined as the width of the septum between the left and right ventricles, and (2) left ventricular concentricity (LV Concentricity, the ratio of LVM to LVEDM). They also collected data on blood glucose levels, antipsychotic dose and treatment duration, physical activity levels, blood pressure, and smoking status. Of note, they also included a measure of symptom severity as per the Positive and Negative Syndrome Scale (PANSS, Kay et al., 1987). In terms of results, the only significant differences found among the lifestyle and metabolic variables were smoking status, where people with schizophrenia smoked more, and physical activity level, where people with schizophrenia were less physically active than healthy volunteers (Osimo et al., 2020). For functional cardiac variables, all measures for both ventricles except for left and right ejection fraction were significantly reduced compared to the healthy controls with moderate to large effect sizes: LVEDV and RVEDV, LVESV and RVESV, LVSV and RVSV. For structural variables, LV Concentricity and septal width were significantly increased compared to the healthy controls; however, LVM was not significantly different. None of the cardiac variables assessed were related to antipsychotic dose or duration. Moreover, post-hoc adjustments for smoking status and physical activity (i.e., included as covariates) had no effect on the results. Of note, symptom severity, as per PANSS total score, was not correlated to any cardiac variable; a median total score of 35.5 was reported that infers people experienced symptoms between mild and moderate level of severity (Leucht et al., 2005).

In 2021, Osimo et al. published a follow-up study to examine the potential mechanisms leading to concentric cardiac remodelling. They believed there were two potential mechanisms: a pathway created by chronic hypertension exerting stress on the myocardium or a pathway created by pro-inflammatory states in the body such as insulin resistance, increased CRP, or hyperlipidemia, that would lead to dysregulated myocyte activity upon the myocardium. For either proposed mechanism, the dysregulation was highly linked to increased adipose tissue due to obesity; therefore, they investigated whole-body fat via MRI. The final sample included 26 people with schizophrenia and 24 age, sex, ethnicity, and BSA-matched healthy controls. No participants had current or past CVD. Together with body fat, the measured cardiac variables included LVEDV, LVM, LV Concentricity, and native T1 time were measured. The study of native T1 mapping in CMR allows radiologists to characterize heart tissue without additional relaxation from gadolinium-based contrast media (Taylor et al., 2016). The authors also measured lifestyle and metabolic variables such as physical activity, smoking status, BSA and BMI, blood pressure, adipokines, liver function, HDL and LDL cholesterol, triglycerides, CRP, blood glucose, insulin levels, total PANSS score, and antipsychotic dose and duration. In terms of results, people with schizophrenia had decreased levels of adiponectin, increased CRP levels, decreased HDL levels, increased blood glucose levels, and increased triglycerides; more people with schizophrenia were active smokers of tobacco. The average PANSS total score for clinical participants was 55 suggesting symptoms of mild severity (Leucht et al., 2005).

The study reported significantly lower LVEDV and higher LV concentricity in people with schizophrenia compared to healthy controls. As well, the native T1 time was significantly longer. Differences in LVM were not significant. The Wilks' case-control test, to determine the hypertensive pathway for concentric cardiac remodelling, was non-significant; however, the test

for non-hypertensive pathway was significant, suggesting that while increased blood pressure leads to increased concentric cardiac remodelling for the control participants, increased blood pressure is not a likely mechanism of concentric cardiac remodelling for people with schizophrenia. Among the metabolic variables, only adiponectin levels were found to be negatively related to concentric cardiac remodelling. Finally, there were no differences in body fat content or distribution between people with schizophrenia and healthy controls, but that the adipose tissue itself was dysfunctional in the schizophrenia sample by decreased adiponectin secretion related to LV concentricity.

Bridging cardiac dysfunction with the brain and outcome

There is a knowledge gap in the use of CMR to measure cardiac dysfunction and its relation to outcome or symptom severity in people with schizophrenia; however, a great deal of work has explored the link between heart rate variability (HRV) and symptom severity. HRV refers to the fluctuations in the intervals between heart beats and has been implicated in autonomic control of the heart (Shaffer & Ginsberg, 2017); importantly, HRV is a risk factor for CVD (Thayer et al., 2010). Others have shown that people with schizophrenia have decreased HRV compared to the general population (J. S. Chang et al., 2009; Clamor et al., 2016; Liu et al., 2021; Montaquila et al., 2015; Quintana et al., 2016). Moreover, decreased HRV has been associated with greater likelihood of negative symptoms (J. S. Chang et al., 2015; Huang et al., 2020; J.-H. Kim et al., 2011; Toichi et al., 1999), positive symptoms (K.-J. Bär, 2015; J. S. Chang et al., 2015; J.-H. Kim et al., 2004), and general psychopathology symptoms (Benjamin et al., 2020; J. S. Chang et al., 2015) as rated on the PANSS.

There is one looming question: does the brain influence the heart or CVD-related factors? One region of interest is the anterior cingulate cortex (ACC). The ACC has a well-established

role in the autonomic control of the heart through both animal and human studies (Critchley et al., 2003; Devinsky et al., 1995a). The ACC is also an area of interest in schizophrenia research due to its role in cognitive processes, emotional appraisal, and interpretation of social cues (Devinsky et al., 1995a). However, it is also known that people with schizophrenia have functional and structural differences in the ACC: post-mortem studies of the ACC revealed volume differences related to decreased number of interneurons, which was unrelated to age and treatment duration (Baiano et al., 2007; Bersani et al., 2014; Bouras et al., 2001; Devinsky et al., 1995a). As well, neurochemical alterations suggest decreased Glutamate neurons as well as decreased GABA binding – a finding that suggests an imbalance in the excitatory/inhibitory chemistry of the ACC specific to schizophrenia (Concepcion et al., 2021).

Because emotional appraisal and regulation is a role of the ACC and negative emotions are a well-explored risk-factor for CVD, the ACC has been cited as a region of interest in cardiovascular studies (Kraynak et al., 2018). Decreased ACC volume, specifically in the dorsal region of the ACC, is related to increased repetitive negative thinking and pre-clinical risk for CVD such as the thickness of the carotid artery. Reduced volume in the ACC has been related to mood disorders and CVD (Drevets et al., 2008). Specifically in schizophrenia, the ACC volume was found to be reduced in relation to increased social withdrawal (Bersani et al., 2014); however, there is little research exploring the relationships between cardiac dysfunction, clinical outcome, and the ACC in schizophrenia.

In schizophrenia, functional connectivity between the ACC and the cerebellum has been positively correlated with heart rate variability which suggested that as heart rate variability is reduced, the functional connectivity between the ACC and the cerebellum is also decreased (Bengtsson et al., 2020); however, this result is only relational and not causal. Moreover, a

significant, negative correlation was found between antipsychotic type (olanzapine) and heart rate variability suggesting reduced heart rate variability with increased olanzapine dosage; again, this result is only relational and not causal. Although promising, this study only included 10 people with schizophrenia and 10 healthy controls. With HRV as a risk factor for cardiovascular disease (Thayer et al., 2010), it is key to explore the various relationships. With the exception of Bengtsson et al. (2020), there has been a dearth of research that has explored the ACC as a region of interest linking cardiac dysfunction and outcome in schizophrenia. Research involving the ACC in schizophrenia focused mostly on cognition and emotional processing (Bersani et al., 2014). Given that the ACC was implicated in cardiac autonomic control, and emerging evidence suggested relational links between the ACC and reduced HRV in schizophrenia, the ACC may be an excellent candidate for exploration for its role in cardiovascular health.

Summary of Findings and Knowledge Gaps

Imaging studies of the heart via CMR in schizophrenia have just begun to elucidate the functional and structural differences compared to healthy controls; the main findings included reduced bilateral end diastolic volumes and bilateral stroke volumes. Other, and more mixed evidence supports there were gender differences for ejection fraction, such that males who used clozapine showed the greatest reduction in ejection fraction (Andreou et al., 2020; Osimo et al., 2020, 2021; Pillinger et al., 2019). There was also evidence to suggest that structural changes occurred such that concentric cardiac remodelling was greater in people with schizophrenia (Osimo et al., 2020, 2021); there was mixed evidence to support changes in ventricular mass (Andreou et al., 2020; Osimo et al., 2020, 2021; Pillinger et al., 2019).

There is a clear knowledge gap in the exploration of outcome in relation with the heart – specifically cardiac function and structure, where no studies include the use of CMR. Some

findings highlight that reduced HRV in schizophrenia were related with more severe negative symptoms, the most robust marker of a poor outcome. There was also evidence linking those findings with the brain, namely the ACC. In short, reduced connectivity and activity were linked with reduced HRV (Bengtsson et al., 2020); however, those particular findings did not relate to outcome.

To date, no research exists linking measures of the heart via CMR, measures of the brain via MRI, and clinical outcome. This is imperative to understand the relationship between cardiac dysfunction and clinical outcome as it may lead to alternative care options aimed at the heart that could thus improve outcome, or inversely with care options aimed at outcome that subsequently improve cardiac dysfunction.

Objectives and Hypotheses

The objectives of this study were to:

1) assess cardiac function and structure in people with schizophrenia;
2) explore cardiac measures in relation with clinical outcome;
3) explore cardiac measures in relation with brain volume, namely left and right ACC.

The following hypotheses were considered:

1 a) All clinical participants will display significantly greater abnormalities in cardiac function and structure in comparison with the general population.

1 b) Clinical participants in remission will display fewer abnormalities in cardiac function and structure across all measured variables compared to those not in remission.

1 c) More severe levels of negative symptoms will relate to greater cardiac dysfunction, namely increased avolition will be positively related to increased cardiac dysfunction.

2 a) Clinical participants not in remission will have significantly lower grey matter volume in the ACC compared to those in remission.

2 b) For all clinical participants, lower grey matter volume in the ACC will be significantly related to cardiac dysfunction, namely lower bilateral ACC volume will relate with greater cardiac dysfunction.

Methods

Setting and Participants

This study took place at the Institute of Mental Health Research (IMHR), located in the Royal Ottawa Mental Health Centre, a tertiary care institute for mental health in Ottawa, Canada. The Royal provides mental health care to people over the age of 16 and has an active collaboration with clinical care and research.

Data for the current study were obtained from a larger longitudinal study that uses a clinically based research evaluation (CBRE) aimed at exploring outcome and recovery in people with psychosis. The CBRE research protocol involves the completion of questionnaires with key areas of interest including remission status, depression, anxiety and stress levels, sleep hygiene, insight into illness, overall functioning, substance use, and the recovery process. In addition, people can optionally participate in brain and cardiac magnetic resonance imaging (MRI) scans.

Inclusion criteria for all participants included being of any sex, aged 18 to 85 years (inclusive), and able to speak and read English or French. Additional criteria for clinical participants included having a primary diagnosis of schizophrenia-spectrum disorder (schizophrenia, schizophreniform or schizoaffective disorder) or a related psychotic disorder (delusional, brief psychotic, substance-induced psychosis, other specified or unspecified psychosis). Exclusion criteria for clinical participants were excluded if they were under active care of a psychiatrist or general practitioner in the region. Exclusion criteria for the non-clinical participants included having a history or current psychiatric and/or neurological disorder, having a first-degree relative with a diagnosis of schizophrenia or the related psychoses, and having had a substance or alcohol abuse/dependence in the last 6 months prior to screening. Finally, all participants aged 65 years or older were assessed for mild cognitive impairment (MCI) using the

Montreal Cognitive Assessment (Nasreddine et al., 2005) . A score of 26 or greater was required for participation. For MRI data collection, additional exclusion criteria for all participants include organic brain damage, a history of pervasive developmental disorder or epilepsy, or a specific contraindication for MRI (e.g., claustrophobia, non-removable metallic piercings, pacemaker, etc). Clinical participants had to be in a stable, but not necessarily asymptomatic state, in order to take part in the scan. This state was qualitatively assessed by the CBRE, with no specific cut-off values, with discretion to take part at the hands of the research assistant and MR technologist (on the day of the scan).

After a comprehensive description of the study was provided, written informed consent was obtained, where applicable as the CBRE is both in-person and virtual. For the MRI portion, verbal consent alone was not considered adequate, therefore all participants were required to sign an additional consent form. All participants were free to withdraw from research-based activities at any point without compromising current care. The research protocol was approved by the IMHR Research Ethics Board (REB# 2018055, see Appendix 1).

Description of Final Sample. Participants for these analyses were recruited between March 18, 2019, and March 9, 2020. 17 clinical participants elected to participate in a brain and heart MRI scan where one participant withdrew from the study and data from three participants were not usable (CMR image processing issues) leaving a final, clinical sample of 13 participants for image analyses. Four non-clinical participants also elected to participate in the brain and heart MRI scans; however, due to the restrictions imposed by the COVID pandemic, recruitment was halted. Due to the small number of non-clinical participants, statistical analyses were only performed on the 13 clinical participants with brain and heart scans.

Demographic Variables of Interest. Data were collected on age, sex, first language, education, employment, marital status, medication, medication dose, body surface area (BSA; Mosteller, 1987), smoking status, Level of Functioning as measured by the Global Assessment of Functioning (GAF; Hall, 1995) and Intelligence Quotient as measured by the Wechler Adult Intelligence Scale, Version IV (Wechsler, 1955).

Cardiac Magnetic Resonance Imaging

Scanning Procedures and Parameters. The cardiac magnetic resonance imaging exam (CMR) was completed using a 3T Siemens Biograph mMR scanner with both spine and body matrix receiver coils to acquire images in short axis oblique orientation. Full LV coverage was obtained by prescribing a stack of 8-13 SAO balanced steady state free precession cines with the following parameters: effective repetition time per segment (TR) = 40ms; time to echo (TE) = 1.22ms; field of view (FOV) = 400 x 320mm; 8mm slice thickness; 1.7 x 1.7pixel resolution; two-fold integrated parallel acquisition technique (iPAT).

Image Processing. Images were processed using commercially available clinical software (Circle CVI version 42.1; Calgary, Alberta), and by following international protocols for delineating endocardial and epicardial contours (Hundley et al., 2010; Schulz-Menger et al., 2013). The variables of Global Functioning Parameters (Bogaert et al., 2012) were assessed by the following definitions: left ventricular end diastolic volume (LVEDV) was defined as the volume of blood remaining in left ventricle before it contracts, measured in ml. Left ventricular end systolic volume (LVESV) was defined as the volume of blood remaining in the left ventricle after ejection, measured in ml. Left ventricular stroke volume (LVSV) was defined as the blood pumped by left ventricle in one contraction, measured in ml (LVEDV – LVESV = LVSV). Left ventricular mass (LVM) was defined as the weight of the myocardium at end of diastolic phase,

measured in g, determined by assessing the volume of the left ventricle and multiplying by the specific density of the myocardium (1.05g). Right ventricular end diastolic volume (RVEDV) was defined as the volume of blood remaining in right ventricle before it contracts, measured in ml. Right ventricular end systolic volume (RVESV) was defined as the volume of blood remaining in the right ventricle after ejection, measured in ml. Right ventricular stroke volume (RVSV) was defined as the blood pumped by right ventricle in one contraction, measured in ml (RVEDV – RVESV = RVSV). Left ventricular ejection fraction (LVEF) and right ventricular ejection fraction (RVEF) were defined as the amount of blood leaving the left or right ventricle with each contraction, expressed as a percentage, calculated as the SV/EDV x 100. LV Concentricity was defined as the ratio between LVM and LVEDV (Khouri et al., 2010).

During pre-processing, data collected from three participants were removed due to motion-degraded images from poor breath-holding. End diastolic and end systolic contours were used to perform LV measurements. Volume and mass measurements were indexed to Body Surface Area using the Mosteller formula: (BSA = √ (height (cm) x weight (kg)/3600)) (Mosteller, 1987). The indexed variables obtained were LVEDV, LVESV, LVSV, LVM, RVEDV, RVESV, and RVSV. LVEF and RVEF were also obtained but not indexed by BSA. Finally, LV concentricity was calculated, expressed as a ratio of the indexed LVM/LVEDV.

Magnetic Resonance Imaging of Brain

Scanning Procedures and Parameters. A structural T1-weighted, whole-brain MRI volume was obtained using the same scanner as for cardiac MRI, but with spine matrix coils activated to acquire images using multi-echo Magnetization Prepared Rapid Gradient Echo (MR-RAGE) with the following parameters: sagittal sections, where acquisition time (TA) = 5:48; inversion

time (TI) = 1100ms; TR = 2500ms; TE = 1.69, 3.55, 5.41, and 7.27ms; FOV = 256mm, matrix = 256x256pixels; 1mm resolution; 192 slices; two-fold iPAT.

Image Processing. Regional volumes were delineated using FreeSurfer (version 7.1, Charlestown, Massachusetts). All obtained volumes were presented in cubic millimetres.

Brain Regions of Interest. The primary region of interest was the anterior cingulate cortex (ACC). The following volumetric data was extracted: total left ACC and total right ACC.

Questionnaires

Positive and Negative Syndrome Scale. The Positive and Negative Syndrome Scale (PANSS, Kay et al., 1987) consists of 30, evaluator-rated items to assess three subdomains of symptoms in schizophrenia: positive, negative, and general psychopathology. It is adapted from Brief Psychiatric Rating Scale (Dingemans, 1990) and the Psychopathology Rating Schedule (Singh & Kay, 1975), and uses a seven point, Likert-type scale, with anchored definitions at each point. An example of an item (N3 – poor rapport) and its definitions is as follows: "Poor Rapport. Lack of interpersonal empathy, openness in conversation, and sense of closeness, interest, or involvement with the interviewer. This is evidenced by interpersonal distancing and reduced verbal and nonverbal communication… 1. Absent – definition does not apply. 2. Minimal – questionable pathology; may be at the upper extreme of normal limits. 3. Mild – conversation is characterized by stilted, strained, or artificial tone. It may lack emotional depth or tend to remain on an impersonal intellectual, plane… 7. Extreme – patient is totally uninvolved with interviewer. Patient appears to be completely indifferent and consistently avoids verbal and nonverbal communication during the interview."

Psychometric Properties. In the original rating of this scale, the psychometric properties were found to be high (Kay et al., 1987). The internal reliability was $\alpha = 0.73$ for the positive scale, α

= 0.83 for the negative scale, and α = 0.79 for the general psychopathology scale, with Pearson correlations for test-retest reliability: r = 0.80, $p < 0.01$ for the positive, r = 0.68, $p < 0.01$ for the negative, and r = 0.60, $p < 0.01$ for the general psychopathology scales. In terms of construct validity, there was a small, positive relationship between the positive and negative symptom scales (r = 0.27, $p < 0.01$). When evaluated for inter-rater reliability, there were significantly high Pearson coefficients: r = 0.83, $p < 0.0001$ for the positive, r = 0.85, $p < 0.0001$ for the negative, and r = 0.87, $p < 0.0001$ for the general psychopathology scales (Kay et al., 1988).

The current study used the PANSS-6 scale, downsized from the original, but included positive scale items (P1: delusions; P2: concept disorganization; P3: hallucinations) and negative scale items (N1: blunted affect; N4: social withdrawal; and N6: lack of spontaneity/flow in conversation). It has an internal consistency of α = .70 and correlates with the original PANSS-30 (r = .85, $p < .001$) (Lin et al., 2018).

Variables of Interest. Data were analysed in terms of total overall score, as well as the total score for positive symptoms (items P1, P2, P3) and negative symptoms (items N1, N4, and N6). Using the PANSS, the study will focus on remission status (remitted or non-remitted) as described by Andreasen et al., 2005; however, using an updated definition, those considered in remission will have a PANSS-6 total score of less than 14 (Østergaard et al., 2016).

Self-Evaluation of Negative Symptoms. The Self-Evaluation of Negative Symptoms (SNS, Dollfus et al., 2016) was created to provide a simplified way to gather data from patients regarding their experiences of negative symptoms across five domains: social withdrawal, decreased emotional range, alogia, avolition, and anhedonia. It is written in plain language with 20 items on a three-point Likert scale (0 – strongly disagree; 1 – somewhat agree; 2 – strongly agree). A minimum score is 0 and a maximum score is 40 and a higher score is indicative of

more negative symptoms. Examples of questions include: “I am not interested in going out with friends or family,” “People often say that I don’t talk too much,” and “It is difficult for people to know how I feel.”

Psychometric Properties. The internal consistency was $\alpha = 0.87$ across the 20 items and $\alpha = 0.78$ across the five symptom domains. The test-retest reliability was measured in intraclass coefficients (ICC) and was 0.942 (95% CI, 0.883 - 0.971). The current study used the SNS in its complete form.

Variables of Interest. Data were compiled by total score overall, as well as the total score for each subdomain: social withdrawal, decreased emotional range, avolition, alogia, and anhedonia. Those considered to have a pathological need have an overall total of 8 or more or a total of 5 or more on each subdomain (Dollfus et al., 2016).

Statistical Analyses

Descriptive and clinically based variables were analysed using independent t-tests with between-groups defined as remitted and non-remitted. Descriptive variables of a categorical or dichotomous nature were analysed using non-parametric tests, specifically Fisher’s Exact test, and Chi-square test. For the cardiac imaging variables, data for the whole sample were compared to population-based data (Bjerregaard, 1983; Kawel-Boehm et al., 2020; Marczak & Paprocki, 2001; Verbraecken et al., 2006). For this, sample data were first converted into z-scores using an online calculator (https://www.socscistatistics.com/tests/ztest/zscorecalculator.aspx) and then used to obtain p-values using a second online calculator (https://www.socscistatistics.com/pvalues/normaldistribution.aspx). Next, cardiac and brain imaging variables were compared between remitted and non-remitted subgroups using independent t-tests. A partial correlation analysis using Pearson’s r test, controlling for remission

status, was used to explore the relationship between brain volumes of the ACC and the obtained measures from the cardiac imaging protocol. Lastly, Spearman's Rho test was performed between cardiac variables and clinical symptoms and brain volume. All analyses were conducted using SPSS 28 (IBM Corp, NY, USA) and were two-tailed with a critical *p*-value of 0.05, except for comparisons involving the ACC volumetric differences were expected. As a study with a rather small sample size, the p-value was not adjusted for multiple comparisons.

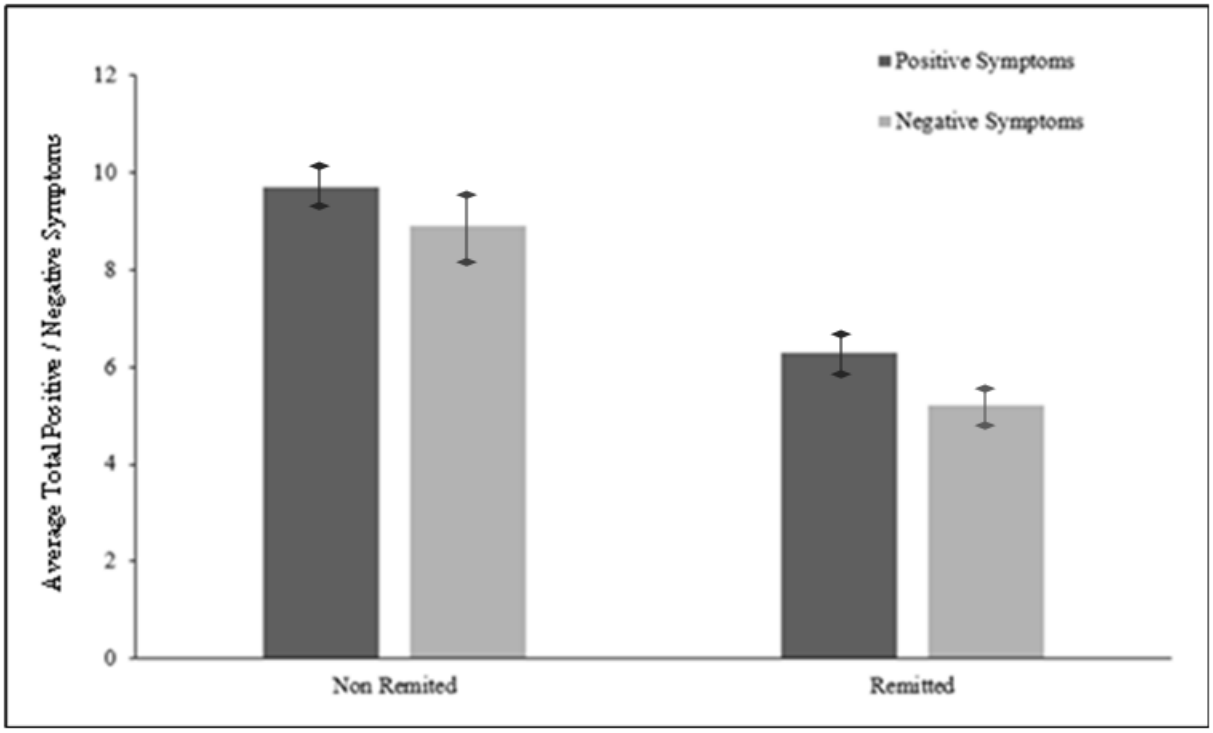
Results

Descriptive variables, outcome, and psychopathology

Among the 13 participants, 11 were male, all were single, two were daily smokers, and 10 were not working. Six participants were in a remitted state. The two subgroups did not differ in age, years of education, Full-Scale IQ, or antipsychotic dosage (Table 1). In relation to outcome, the whole sample average GAF score was well below the largely accepted cut-off of 70, with all participants scoring below 70. People in remission scored significantly higher on the GAF and displayed significantly lower positive and negative symptoms (Table 2, Figure 1). Regarding self-reported negative symptoms, the non-remitted group reported a significantly higher level for alogia with 5 of the 7 participants meeting the clinical threshold criteria for alogia (Table 2).

Figure 1

Difference in clinical symptoms between non-remitted and remitted participants



Note. Significant difference between non-remitted and remitted participants for positive symptoms at $p = .004$. Significant difference between non-remitted and remitted participants for negative symptoms at $p = .020$. Error bars indicate standard error of the mean.

Table 1

Descriptive Variables (data presented as mean (SD) / [n] (%))

Variable	Full Sample [n=13]	Non-Remitted [n=7]	Remitted [n=6]	Significance	p-value
Age, years	44.5 (10.2)	47.5 (10.3)	40.9 (9.6)	1.19[a]	0.259
Sex, male		[5] (71%)	[6] (100%)	2.026 (1)[b]	0.155
Marital status, single		[7]	[6]		
Smoker		[1] (14%)	[1] (17%)	0.20[b]	0.887
Full-Scale IQ (WASI)	98.5 (17.9)	94.6 (11.9)	103.0 (23.4)	-0.84[a]	0.420
Education, years	14.0 (2.4)	14.2 (2.5)	13.8 (2.4)	0.28[a]	0.785
Employment type				1.629[c]	1.000
Part time		[1]	[1]		
Unemployed / seeking		[1]	[2] (33%)		
Disability		[3] (43%)	[3] (50%)		
Volunteer		[1]	--		
Unknown		[1]	--		
Antipsychotic dosage, mg/day[d]	693 (379)	596 (331)	805 (430)	-0.99[a]	0.343
Primary antipsychotic				3.325[c]	1.000
Clozapine		[4] (57%)	[3] (50%)		
Olanzapine		[1]	[2] (33%)		
Aripiprazole		[1]	--		
Quetiapine		--	[1]		
Chlorpromazine		[1]	--		
Secondary antipsychotic				3.793[c]	1.000
Quetiapine		[1]	[1]		
Paliperidone		[1]	--		
Maintena		[1]	--		
Olanzapine		[1]	--		
Loxapine		--	[1]		
None		[3] (43%)	[4] (66%)		

Note: [a] Indicates t-tests performed on continuous variables. [b] Indicates Chi-square test performed on dichotomous / categorical variables. [c] Indicates Fisher-Freeman-Halton exact test performed on dichotomous/categorical variables. [d] Antipsychotic dosage presented in chlorpromazine equivalents.

Table 2

Psychopathology and Outcome (data presented as mean (SD) / [n] (%))

Variable of Interest	Non-Remitted [n=7]	Remitted [n=6]	Significance	p-value
GAF	43.7 (5.7)	56.0 (10.2)	-2.74[a]	**0.010**
PANSS				
Positive total	9.7 (1.9)	6.3 (1.9)	3.24[a]	**0.004**
Negative total	8.9 (3.6)	5.2 (1.5)	2.32[a]	**0.020**
SNS[c]				
Social withdrawal	2.9 (2.2) / [2] (29%)	1.5 (1.0) / [0]	6.561[b]	0.248
Diminished emotion	3.0 (1.4) / [1] (14%)	3.5 (1.5) / [2] (33%)	3.018[b]	0.811
Alogia	5.3 (1.4) / [5] (71%)	2.2 (2.0) / [1] (17%)	9.817[b]	**0.031**
Avolition	4.0 (2.2) / [3] (43%)	3.7 (2.0) / [3] (50%)	6.639[b]	0.423
Anhedonia	2.3 (2.1) / [1] (14%)	2.7 (2.0) / [1] (17%)	4.652[b]	0.685
Total	17.4 (5.5) / [7] (100%)	13.5 (6.5) / [5] (83%)	8.638[b]	0.364

Note. [a] Indicates t-tests performed on continuous variables. [b] Indicates Fisher-Freeman-Halton exact test performed on dichotomous/categorical variables. [c] A cut-off of 5 was used to express pathology for each subdomain; a cut-off of 7 was used to express pathology for Total. The number of people reaching this threshold is indicated.

Magnetic resonance imaging of the heart and brain

For the heart, LV concentricity was significantly larger compared to the general population (clinical participants = .90 ± .16 vs general population = .65 ± .10, p = .012); no other measures significantly differed on either the left or right side. Of note, BSA of participants was significantly larger compared to the general population (clinical participants = 2.2 ± .2 vs general population = 1.8 ± .2, p = .04) (Table 3). Of importance, there were no significant differences in any measure of the heart between the remitted and non-remitted participants (Table 4, Figure 2, Figure 3). However, for the brain, compared to remitted participants, the non-remitted participants displayed a smaller volume in the ACC that significantly differed on the left side and was trend-level on the right (Table 5).

Table 3

Cardiac Variables for Full Sample vs. Population

Variable	Sample Mean (SD)	Range	Population Mean (SD)[a]	z-score[b]	p-value[c]
LVEDV, ml/m²	67.2 (10.0)	46.4 – 80.9	77 (15)	-0.657	0.511
LVESV, ml/m²	25.2 (6.5)	13.9 – 34.5	29 (9)	-0.428	0.668
LVSV, ml/m²	42.0 (6.2)	32.5 – 55.2	48 (9)	-0.667	0.505
LVEF, %	62.9 (6.3)	54.2 – 72.9	63 (6)	-0.013	0.990
LVM, g/m²	59.4 (6.3)	46.9 – 71.4	56 (10)	0.343	0.732
LV Concentricity, g/ml	0.90 (0.16)	0.62 – 1.1	0.65 (0.10)	2.500	**0.012**
RVEDV, ml/m²	73.6 (17.2)	42.9 – 116.4	88 (17)	-0.849	0.396
RVESV, ml/m²	39.2 (11.6)	25.8 – 68.7	38 (11)	0.109	0.913
RVSV, ml/m²	34.4 (9.3)	17.1 – 47.7	52 (12)	-1.470	0.142
RVEF, %	46.7 (7.5)	38.7 – 61.2	57 (8)	-1.294	0.197
BSA, m^2	2.2 (0.2)	1.8 – 2.6	1.8 (0.2)[d]	2.050	**0.040**
HR (scan), beats/min	82.6 (14.2)	63 – 98	74 (18)[e]	0.478	0.632
HR (eval), beats/min	89.8 (13.4)	71 – 110	74 (18)[e]	0.878	0.380
BP systolic (eval), mmHg	129.7 (24.2)	90 – 173	123.5 (11.5)[f]	0.539	0.590
BP diastolic (eval), mmHg	91.2 (12.4)	69 – 112	74.0 (9.5)[f]	1.811	0.070

Note. LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVSV, left ventricular stroke volume; LVEF, left ventricular ejection fraction; LVM, left ventricular mass; RVEDV, right ventricular end-diastolic volume; RVESV, right ventricular end-systolic volume; RVSV, right ventricular stroke volume; RVEF, right ventricular ejection fraction; BSA, body surface area; HR, heart rate; BP, blood pressure.

[a] values from Kawel-Boehm et al. (2020).

[b] z-score calculated: (Sample Mean – Population Mean) / Population SD

[c] p-value derived from z-score; https://www.socscistatistics.com/pvalues/normaldistribution.aspx

[d] values from Verbraecken et al. (2006).

[e] values from Bjerregaard (1983).

[f] values from Marczak and Paprocki (2001).

Table 4

Cardiac Variables for Non-Remitted vs. Remitted Participants

Variable of Interest	Non-Remitted [n=7]	Remitted [n=6]	t-value	p-value
LVEDV, ml/m²	66.6 (12.1)	67.8 (8.2)	-0.21	0.834
LVESV, ml/m²	24.9 (8.6)	25.4 (3.5)	-0.13	0.898
LVSV, ml/m²	41.7 (4.3)	42.4 (8.4)	-0.21	0.838
LVEF, %	63.6 (7.0)	62.2 (6.0)	0.38	0.713
LVM, g	58.0 (8.1)	61.1 (3.1)	-0.87	0.401
LV Concentricity, g/ml	0.90 (0.19)	0.91 (0.10)	-0.19	0.852
RVEDV, ml/m²	70.8 (13.5)	76.7 (22.8)	-0.58	0.574
RVESV, ml/m²	37.5 (9.2)	41.2 (14.6)	-0.54	0.598
RVSV, ml/m²	33.3 (9.7)	35.6 (9.6)	-0.43	0.677
RVEF, %	46.7 (9.3)	46.7 (5.6)	0.002	0.998
BSA, m^2	2.1 (0.2)	2.3 (0.2)	-1.63	0.132
HR, beats/min	88.0 (13.2) [6]	91.7 (14.6)	-0.46	0.657
BP systolic, mmHg	114.3 (16.0) [6]	145.0 (21.7)	-2.79	**0.019**
BP diastolic, mmHg	86.2 (13.6) [6]	96.2 (9.5)	-1.47	0.171

Note. LVEDV, left ventricle end-diastolic volume; LVESV, left ventricular end-systolic volume; LVSV, left ventricular stroke volume; LVEF, left ventricular ejection fraction; LVM, left ventricular mass; RVEDV, right ventricular end-diastolic volume; RVESV, right ventricular end-systolic volume; RVSV, right ventricular stroke volume; RVEF, right ventricular ejection fraction; BSA, body surface area; HR, heart rate; BP, blood pressure.

Table 5

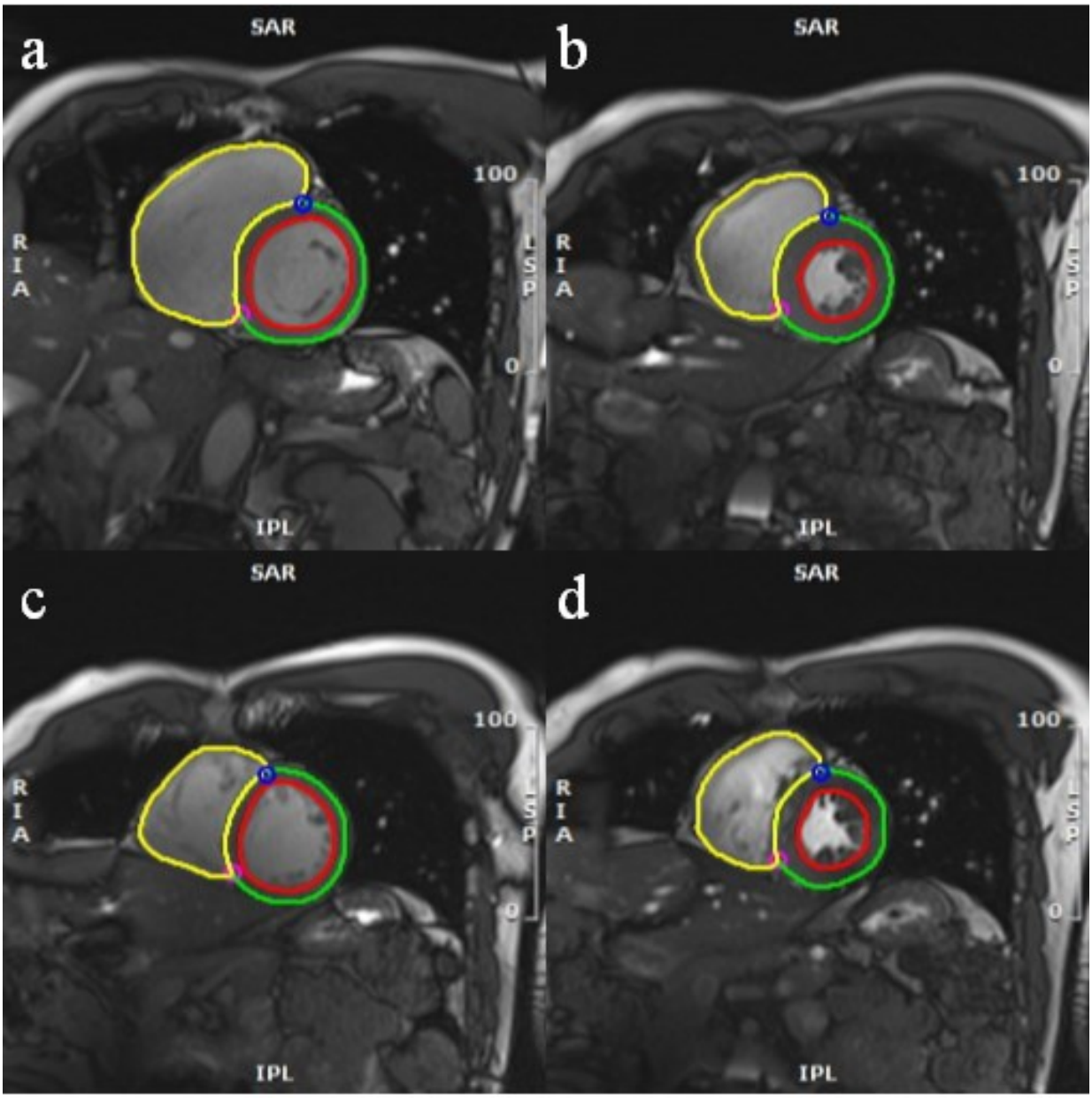
Anterior Cingulate Cortex Volume for Non-Remitted vs. Remitted Participants

Area of Interest	Non-Remitted [n=7]	Remitted [n=6]	t-value	p-value
Left	9815 (1004)	11044 (1191)	-2.02	**0.034**
Right	9021 (1622)	10440 (1533)	-1.61	0.068

Note. All volumes presented in mm^3.

Figure 2

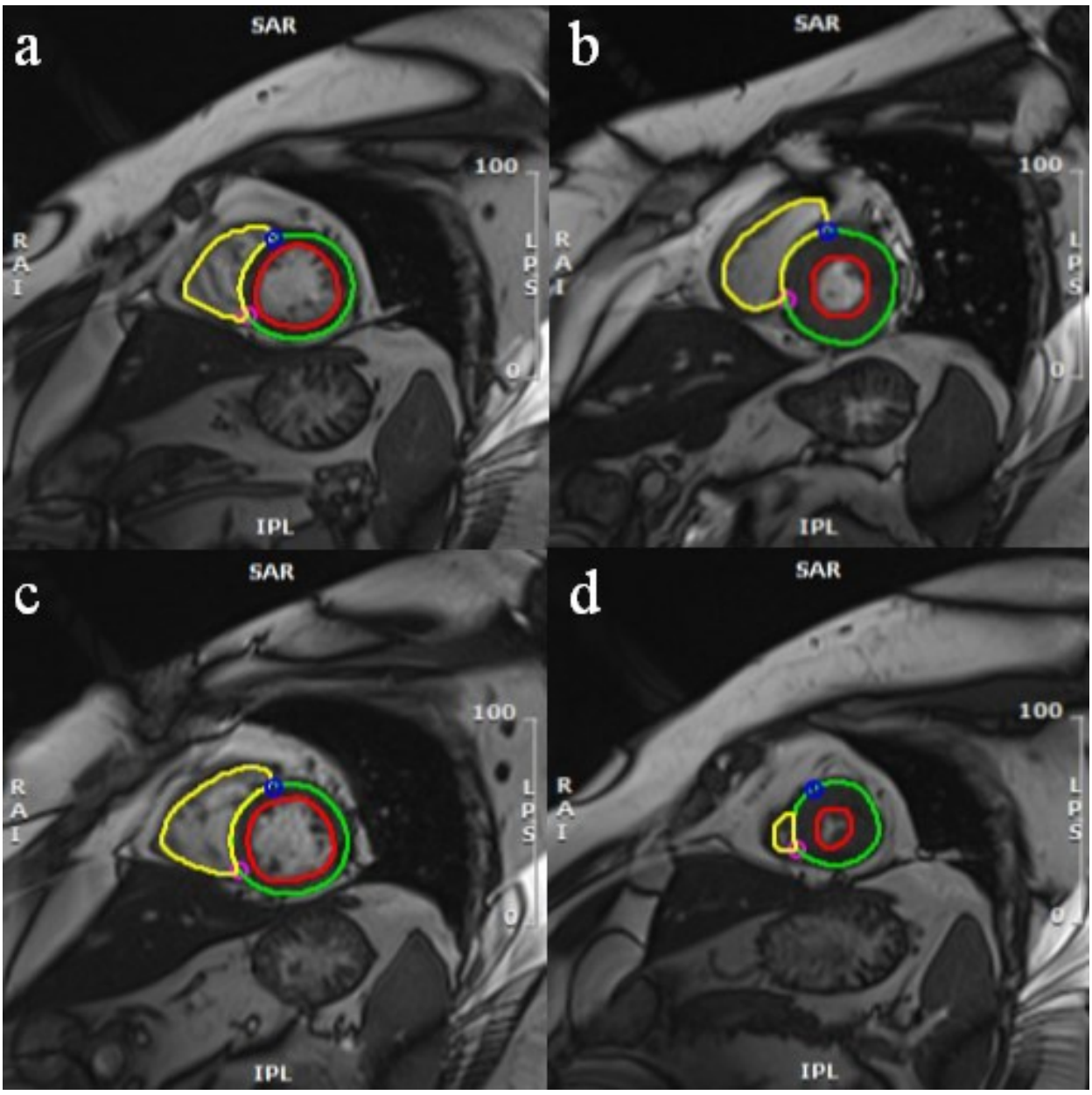
Left and right chamber assessment in remitted participant



Note. a: left ventricular diastolic phase; b: left ventricular systolic phase; c: right ventricular diastolic phase; d: right ventricular systolic phase. Participant cardiac functioning: LVEDV = 80.85 ml/m^2, LVESV = 25.71 ml/m^2, LVSV = 55.15 ml/m^2, LVEF = 68.21%, LVM 58.92 g/m^2, LV Concentricity 0.73 g/ml, RVEDV = 116.35 ml/m^2, RVESV = 68.70 ml/m^2, RVSV = 47.65 ml/m^2, RVEF 40.95%

Figure 3

Left and right chamber assessment of non-remitted participant



Note. a: left ventricular diastolic phase; b: left ventricular systolic phase; c: right ventricular diastolic phase; d: right ventricular systolic phase. Participant cardiac functioning: LVEDV = 46.38 ml/m^2, LVESV = 13.91 ml/m^2, LVSV = 32.47 ml/m^2, LVEF = 70.02%, LVM 51.92 g/m^2, LV Concentricity 1.12 g/ml, RVEDV = 42.90 ml/m^2, RVESV = 25.77 ml/m^2, RVSV = 17.13 ml/m^2, RVEF 39.93%

Relationship among outcome, heart, and brain

Using a Pearson's partial correlation, controlling for remission, the left hemisphere ACC volume significantly and positively correlated with both EDV (LV: $r_{partial}$ = .689, 95% CI [.106, .873], *p* = .013; RV: $r_{partial}$ = .618, 95% CI [.088,.869], *p* = .032); both SV (LV: $r_{partial}$ = .681, 95% CI [.094, .870], *p* = .015; RV: $r_{partial}$ = .635, 95% CI [.080, .867], *p* = .026); and negatively with LV Concentricity ($r_{partial}$ = -.676, 95% CI [-.843, -.007], *p* = .032) (Table 6). The right hemisphere ACC volume significantly and positively correlated with LVEDV ($r_{partial}$ = .728, 95% CI [.210, .896], *p* = .007) with RVEDV ($r_{partial}$ = .544, 95% CI [.009, .848], *p* = .050); both SV (LV: $r_{partial}$ = .813, 95% CI [.353, .923] *p* = .001; RV: $r_{partial}$ = 584, 95% CI [.038, .856], *p* = .046), and negatively with LV Concentricity ($r_{partial}$ = -.580, 95% CI [-.822, -.076], *p* = .048). There was also a positive, trend-level correlation between the right ACC and BSA ($r_{partial}$ = .530, 95% CI [-.030, .837], *p* = .063).

Significant relationships between aggregated clinical symptoms and cardiac variables, using Spearman's Rho correlation, included positive correlations between social withdrawal and LVEDV (rs[11] = .809, 95% CI [.451, .943], *p* < .001), LVESV (rs[11] = .695, 95% CI [.215, .904], *p* = .008), LVSV (rs[11] = .706, 95% CI [.236, .908], *p* = .007), and RVESV (rs[11] = .566, 95% CI [.004, .857], *p* = .044), and a positive, trend-level correlation between avolition and RVSV (rs[11] = .508, 95% CI [-.078, .833], *p* = .076). (Tables 7 and 8). A significant, negative correlation was found between social withdrawal and LV Concentricity (rs[11] = -.700, 95% CI [-.906, -.226], *p* = .008). Other clinical symptoms significantly correlating with cardiac variables included negative correlations between alogia and systolic blood pressure (rs[11] = -.679, 95% CI [-.905, -.153], *p* = .007) total negative symptoms (as measured by the SNS) and systolic blood pressure (rs[11] = -.576, 95% CI [-.869, .015], *p* = .050), and diminished expression and diastolic

blood pressure (rs[11] = -.587, 95% CI [-.873, -.001], p = .045). A negative, trend-level correlation between total positive symptoms (as measured by PANSS) and heart rate (rs[11] = -.545, 95% CI [-.857,.062], p = .067), and a negative, trend-level correlation between diminished emotion expression and BSA (rs[11] = -.548, 95% CI [-.849, .022], p = .052) were also found. In terms of the ACC, the left ACC was significantly and positively related to LVEDV (rs[11] = .560, 95% CI [-.005, .854], p = .046), and a positive, trend-level correlation between the right ACC and LVEDV (rs[11] = .500, 95% CI [-.089, .830] p = .082) was found (Table 7). Negative, trend-level correlations were found between the bilateral ACC and LV Concentricity (left: rs[11] = -0.527, 95% CI [-.841, .051], p = .064; and right rs[11] = -.500, 95% CI [-.830, .089], p = .082) (Table 8). Positive, trend-level correlations were found between the bilateral ACC and RVSV (left ACC: rs[11] = .516, 95% CI p = .071; and right ACC: rs[11] = .511, 95% CI p = .074). There were no significant or trend-level correlations between brain volume and aggregated clinical symptoms.

Table 6

Partial Pearson's r Correlation between Cardiac Variables and ACC

	Left ACC	95% CI	Right ACC	95% CI
LVEDV, ml/m²	**0.689***	**[.106, .873]**	**0.728***	**[.210, .896]**
LVESV, ml/m²	0.414	[-.223, .767]	0.349	[-.269, .746]
LVSV, ml/m²	**0.681***	**[.094, .870]**	**0.813****	**[.353, .923]**
LVEF, %	-0.069	[-.628, .463]	0.059	[-.546, .553]
LVM, g/m²	-0.133	[-.628, .463]	0.098	[-.535, .567]
LV Concentricity, g/ml	**-0.676***	**[-.843, -.007]**	**-0.580***	**[-.822, -.076]**
RVEDV, ml/m²	**0.618***	**[.088, .869]**	0.544	[.009, .848]
RVESV, ml/m²	0.436	[-.132, .803]	0.364	[-.201, .776]
RVSV, ml/m²	**0.635***	**[.080, .867]**	**0.584***	**[.038, .856]**
RVEF, %	0.281	[-.359, .698]	0.312	[.320, .720]
BSA, m^2	0.372	[-.225, .766]	0.530	[-.030, .837]
HR, beats/min	-0.293	[-.694, .423]	-0.385	[-.786, .240]
BP systolic, mmHg	-0.198	[-.434, .686]	0.064	[-.434, .686]
BP diastolic, mmHg	-0.093	[-.481, .654]	-0.009	[-.454, .673]

Note. Partial Pearson correlation controlled for remission. LVEDV, left ventricle end-diastolic volume; LVESV, left ventricular end-systolic volume; LVSV, left ventricular stroke volume; LVEF, left ventricular ejection fraction; LVM, left ventricular mass; RVEDV, right ventricular end-diastolic volume; RVESV, right ventricular end-systolic volume; RVSV, right ventricular stroke volume; RVEF, right ventricular ejection fraction; BSA, body surface area; HR, heart rate; BP, blood pressure.

* significant at p-value < 0.05 (two-tailed).

** significant at p-value < 0.01 (two-tailed).

Table 7

Spearman's Rho Correlations between cardiac variables of the left ventricle, clinical symptoms, and brain volume (with 95% confidence intervals)

	LVEDV	LVESV	LVSV	LVEF	LVM	LV Conc	HR
PANSS							
PANSS POS	0.381, [.199, -.232]	0.395, [-.217, .784]	0.325, [-.292, .751]	-0.270, [-.723, .346]	-0.342, [-.759, .274]	-0.362, [-.769, .254]	-0.545, [-.857,.062]
PANSS NEG	0.249, [.413, -.366]	0.243, [-.371, .709]	0.386, [-.228, .780]	-0.078, [-.615, .508]	0.112, [-.482, .635]	-0.318, [-.748, .299]	0.028, [-.568, .605]
PANSS TOT	0.235, [.439, -.379]	0.288, [-.329, .733]	0.271, [-.345, .724]	-0.138, [-.651, .461]	-0.124, [-.643, .472]	-0.246, [.417, -.711]	-0.248, [-.729, .397]
SNS							
SNS SW	**0.809******, [.451, .943]**	**0.695*****, [.215, .904]**	**0.706******, [.236, .908]**	-0.432, [-.801, .173]	0.033, [-.540, .586]	**-0.700******, [-.906, -.226]**	-0.454, [-.822, .181]
SNS DE	0.39, [-.536, .590]	-0.205, [-.689, .406]	0.129, [-.469, .646]	0.263, [-.353, .720]	0.000, [-.564, .564]	0.039, [-.536, .590]	0.320, [-.329, .763]
SNS ALO	0.148, [-.454, .657]	0.195, [-.414, .683]	0.192, [-.417, .682]	-0.075, [-.613, .510]	-0.059, [-.602, .522]	-0.181, [-.676, .426]	0.066, [-.542, .628]
SNS AVO	0.149, [-.453, .657]	0.253, [-.363, .714]	0.073, [-.512, .611]	-0.227, [-.701, .386]	-0.339, [-.758, .277]	-0.351, [-.763, .265]	-0.196, [-.702, .441]
SNS ANH	0.271, [-.345, .724]	0.361, [-.254, .768]	0.131, [-.467, .647]	-0.422, [-.796, .185]	0.087, [-.501, .620]	-0.283, [-.730, .334]	-0.038, [-.611, .561]
SNS TOT	0.418, [-.190, .795]	0.368, [-.246, .772]	0.360, [-.255, .768]	-0.230, [-.703, .383]	-0.047, [-.595, .531]	-0.404, [-.788, .206]	-0.141, [-.672, .486]
ACC							
Left	**0.560*****, [-.005, .854]**	0.302, [-.315, .740]	0.522, [-.059, .839]	-0.170, [-.670, .435	0.121, [-.475, .641]	-0.527, [-.841, .051]	-0.004, [-.589, 584]
Right	0.500, [-.089, .830]	0.236, [-.378, .706]	0.511, [-.074,.834]	-0.049, [-.596, .529]	0.115, [-.479, .638]	-0.500, [-.830, .089]	-0.189, [-.699, .447]

Note. LVEDV, left ventricle end-diastolic volume, measured in ml/m^2; LVESV, left ventricular end-systolic volume, measured in ml/m^2; LVSV, left ventricular stroke volume, measured in ml/m^2; LVEF, left ventricular ejection fraction, measured in percentage; LVM, left ventricular mass, measured in g/m^2; LV Conc, left ventricular concentricity, measured in g/ml; HR, heart rate, measured in beats/min; PANSS Pos, Positive and Negative Syndrome Scale – Positive Symptoms Only; PANSS Neg, Positive and Negative Syndrome Scale – Negative Symptoms Only; PANSS Tot, Positive and Negative Syndrome Scale – Total Symptoms; SNS SW, Self-Evaluation of Negative Symptoms – Social Withdrawal; SNS DE, Self-Evaluation of Negative Symptoms – Diminished Expression; SNS ALO, Self-Evaluation of Negative Symptoms – Alogia; SNS AVO, Self-Evaluation of Negative Symptoms – Avolition; SNS ANH, Self-Evaluation of Negative Symptoms – Anhedonia; SNS Tot, Self-Evaluation of Negative Symptoms – Total Symptoms; ACC, anterior cingulate cortex

** indicates correlation is significant at the .001 level (two tailed).

* indicates correlation is significant at the .05 level (two tailed).

Table 8

Spearman's Rho Correlations between cardiac variables of the right ventricle, clinical symptoms, and brain volume (with 95% confidence intervals)

	RVEDV	RVESV	RVSV	RVEF	BSA	BP (Systolic)	BP (Diastolic)
PANSS							
PANSS POS	0.189, [-.419, .680]	0.256, [-.360,.716]	-0.253, [-.715, .362]	-0.423, [-.797, .185]	-0.455, [-.811, .146]	-0.404, [-.801, .238]	-0.470, [-.828, .161]
PANSS NEG	-0.142, [-.654, .458]	-0.117, [-.639, .478]	-0.064, [-.606, .518]	0.031, [-.542, .584]	0.042, [-.534, .592]	-0.261, [-.735, .384]	-0.124, [-.663, .499]
PANSS TOT	-0.055, [-.600, .525]	-0.036, [-.588, .539]	-0.249, [-.713, .366]	-0.268, [-.723, .348]	-0.238, [-.707, .376]	-0.452, [-.821, .184]	-0.303, [-.755, .345]
SNS							
SNS SW	0.477, [-.118, .820]	**0.566*, [.004, .857]**	0.109, [-.485, .634]	-0.237, [-.706, .377]	-0.263, [-.720, .353]	-0.429, [-.812, .211]	-0.473, [-.830, .157]
SNS DE	0.003, [-.562, .566]	0.224, [-.389, .699]	-0.191, [-.681, .418]	-0.398, [-.785,.214]	-0.548, [-.849, .022]	-0.494, [-.838, .131]	**-0.587, [-.873, -.001]**
SNS ALO	0.162, [-.442, .665]	0.134, [-.465, .648]	0.017, [-.552, .575]	-0.067, [-.608, 516]	-0.402, [-.787, .209]	**-0.679*, [-.905, -.153]**	-0.360, [-.782, .287]
SNS AVO	0.303, [-.314, .740]	0.065, [-.518, .606]	0.508, [-.078, .833]	0.283, [-.334, .730]	0.232, [-.382, .703]	-0.079, [-.636, .532]	0.182, [-.453, .695]
SNS ANH	0.400, [-.211, .786]	0.434, [-.172, .801]	0.243, [-.371, .710]	0.145, [-.455, .655]	-0.104, [-.630, .488]	-0.036, [-.610, .563]	-0.239, [-.724, .405]
SNS TOT	0.479, [-.116, .821]	0.429, [-.177, .800]	0.338, [-.279, .757]	-0.030, [-.584, .542]	-0.300, [-.739, .318]	**-0.576*, [-.896, .015]**	-0.407, [-.802, .236]
ACC							
Left	0.423, [-.185, .797]	0.379, [-.235, .777]	0.516, [-.066, .837]	0.269, [-.347, .723]	0.319, [-.298, .748]	0.238, [-.406, .724]	0.119, [-.503, .660]
Right	0.374, [-.347, .723]	0.192, [-.416, .682]	0.511, [-.074, .834]	0.286, [-.331, .732]	0.424, [-.184, .797]	0.378, [-.269,.789]	0.249, [-.395, .729]

Note. RVEDV, right ventricular end-diastolic volume, measured in ml/m^2; RVESV, right ventricular end-systolic volume, measured in ml/m^2; RVSV, right ventricular stroke volume, measured in ml/m^2; RVEF, right ventricular ejection fraction, measured in percentage; BSA, body surface area, measured in m^2; BP, blood pressure, measured in mmHg; PANSS Pos, Positive and Negative Syndrome Scale – Positive Symptoms Only; PANSS Neg, Positive and Negative Syndrome Scale – Negative Symptoms Only; PANSS Tot, Positive and Negative Syndrome Scale – Total Symptoms; SNS SW, Self-Evaluation of Negative Symptoms – Social Withdrawal; SNS DE, Self-Evaluation of Negative Symptoms – Diminished Expression; SNS ALO, Self-Evaluation of Negative Symptoms – Alogia; SNS AVO, Self-Evaluation of Negative Symptoms – Avolition; SNS ANH, Self-Evaluation of Negative Symptoms – Anhedonia; SNS Tot, Self-Evaluation of Negative Symptoms – Total Symptoms; ACC, anterior cingulate cortex

** indicates correlation is significant at the .001 level (two tailed).

* indicates correlation is significant at the .05 level (two tailed).

Discussion

Overview

The present study set out to explore the relationships among the brain, the heart, and outcome; outcome was defined as being in a remitted state or not, and measures of the brain and heart were collected using MRI.

Participants who reached remission had significantly higher functioning as assessed by the GAF, significantly fewer positive and negative symptoms, and significantly decreased levels of alogia, compared to their non-remitted counterparts. This confirmed our hypothesis that negative symptoms would play a significant role in outcome. Participants had significantly increased LV concentricity compared to the general population, as well as significantly higher BSA; however, there were no significant differences in cardiac function or structure related to outcome status. This partially supports our hypothesis that cardiac function and structure in those diagnosed with schizophrenia is different than the general population; however, we did not confirm our hypothesis suggesting that the differences could also be such that people with better outcome could also have better cardiac function and structure. Finally, our assessments of brain volume in the ACC revealed that the left ACC was significantly lower in size for non-remitted participants, with trend-level volume decreases in the right ACC compared to their remitted counterparts, partially supporting our hypothesis that outcome status would be involved in brain volume. Likewise, partial correlations between brain volume and cardiac function and structure revealed positive correlations between cardiac function, and negative correlations between cardiac structure when controlling for remission status, indicating that better cardiac function and structure is associated with increased brain volume in both right and left ACC. Finally, while

brain volume did not relate to clinical outcome, cardiac function and structure was most related to social withdrawal; however, these relationships were inverse, such that as levels of social withdrawal scored higher, cardiac structure and function were healthier. This was an unexpected result.

Outcome

Remission rate in the current sample was 46.1%. This rate is in line with the wide range of heterogeneity remission rates observed in schizophrenia studies (AlAqeel & Margolese, 2013; Carpiniello et al., 2022; Huxley et al., 2021; Lambert et al., 2010a). Moreover, and as expected, people in remission showed better overall functioning, as determined by the GAF, and lower positive (PANSS) and negative (PANSS and SNS) symptoms.

When exploring individual negative symptoms with the SNS, the non-remitted group rated higher on social withdrawal and alogia; alogia significantly differed between the remitted and non-remitted groups. Unexpectedly, the two groups did not differ on ratings of avolition and, moreover, the remitted group rated higher on diminished expression and anhedonia. Because negative symptoms are considered the strongest predictor of remission status (Carpiniello et al., 2022; Foussias & Remington, 2010; Lambert et al., 2010b; Marchesi et al., 2014; Rammou et al., 2019), and where, of the negative symptoms, avolition is typically one of the most significant (Fervaha et al., 2014; Foussias & Remington, 2010; Martin et al., 2021), it is noteworthy to not see such differences within the current study. This may have been an issue of power due to the small sample size of this study or perhaps the chronic nature of the sample population, as Hovington et al. (2012) found that expressive symptoms including affect flattening and alogia symptoms improved after one-year follow-up, whereas symptoms of apathy/avolition did not. It is also important to note that clinical remission does not mean

symptom-free. An extensive review by Lambert et al. (2010b) demonstrated that a significant proportion of people with schizophrenia continue to have clinical symptoms despite reaching and maintaining remission. The findings in the present study demonstrate that participants in remission experience clinical symptoms less severe than their non-remitted counterparts.

Most interestingly, clinical symptom severity did not negatively relate to cardiac function and structure, but positively, which is the inverse of our expectations. It appears that as a person is more socially withdrawn, healthier cardiac structure and function is observed which seems counterintuitive. There is consistent evidence provided from a systematic overview indicating that social isolation and inhibition contribute to poor cardiovascular health outcomes (Leigh-Hunt et al., 2017). By synthesizing data from forty studies on the impacts of social isolation on health outcome, including studies from the general population (using all cause mortality studies) studies of participants with physical illnesses (cancer, musculoskeletal lower back pain) and those with mental illnesses (bipolar disorder, schizophrenia), the results consistently indicated that social isolation, as well as loneliness and fewer social relationships, was associated with poor cardiovascular outcome and increased mortality.

Left Ventricular Concentricity

People with schizophrenia have significant differences in cardiac structure as measured by left-ventricular concentricity compared to the general population. Changes in the geometry of the left ventricle is highly predictive of cardiovascular disease, whether the ratio is calculated as left ventricle mass over relative wall thickness (Krumholz et al., 1995) or as left ventricle mass over end-diastolic volume, as per more recent CMR-based measures (Khouri et al., 2010). The current study used the latter, similar to other recent publications by Osimo et al. (2020, 2021), where all results indicated increased concentricity compared to non-clinical volunteers. In such

instances where mass remains unaffected and the volume becomes abnormal (decreased), it is referred to as concentric cardiac remodelling. This is an adaptive response by the heart when faced with consistent and increasing systemic vascular resistance to push the blood from the heart into the rest of the body (Rosen et al., 2005). Of note, other studies (Osimo et al., 2020, 2021; Pillinger et al., 2019) found significantly lower LVEDV compared to non-clinical volunteers. In the present study, LVEDV values were smaller compared to the general population (as demonstrated by the large z-score) but significance was not attained; again, this may in part be due to the lack of the power. Nevertheless, significant differences in LV concentricity were observed.

A factor that highly predicts increased LV concentricity is obesity (Abel et al., 2008; Gjesdal et al., 2011). The current study found body surface area (BSA) was significantly larger among the clinical participants compared to the general population. This was expected given that historical accounts of obesity and weight gain with the onset of symptoms noted by both Kraepelin and Bleuler (Bleuler, 1915; Kraepelin, 1899), and more so as per the well-established fact that both first- and second-generation antipsychotics commonly lead to weight gain (Wirshing, 2004). Although increased obesity in antipsychotic-treated schizophrenia is difficult to assess (Wirshing, 2004), there are some medications, such as clozapine and olanzapine, that lead to weight gain and impact the cardiometabolic system more severely than other antipsychotics (D'Errico et al., 2021; Pillinger et al., 2020; Sweeney et al., 2020). In the current study, regardless of remission status, 7 of the 13 participants took clozapine as their primary medication and 3 of the 13 took olanzapine. These medications may have had an inadvertent effect on the heart-related measures but could not be measured or assessed due to the chronic

nature and years of use by each of the participants. A future study would assess outcome in a first-episode sample where medication effects would be less of a confounding issue.

People with schizophrenia are often characterized as having lifestyle-related risk factors, such as poor diet, increased sedentary behaviour, and subsequent increased obesity, which are also risk factors for cardiovascular disease (Brown et al., 1999). Untangling the factors that lead to increased cardiac dysfunction, such as increased LV concentricity, are difficult due to the compounding factors of medications and lifestyle factors which can both lead to increased weight gain.

Nonetheless, BSA is important to note as it might be a potential mechanism for increased LV concentricity. Osimo et al. (2021) used MRI to assess differences in the whole-body adipose tissue and found abnormalities including lower levels of adiponectin in the blood. The authors also assessed the most common route to concentric cardiac remodelling: increased systemic vascular resistance, due to hypertension; however, they were not able to validate this. In fact, they found that people with schizophrenia were more likely to develop concentric cardiac remodelling by non-hypertensive means, such as low adiponectin and dyslipidemia. The current study did not collect these data but the presence of significantly increased LV concentricity and BSA suggest avenues for future directions of research to further elucidate the non-hypertensive pathway of cardiac dysfunction.

Anterior Cingulate Cortex

The present study identified significant differences in ACC volume between the remitted and non-remitted groups; the non-remitted group had significantly lower volume on the left and trend-level lower volume on the right. It is widely noted that people with schizophrenia have a reduced volume in the ACC compared to the general population, that is unbiased by sex and age

(Baiano et al., 2007; Bersani et al., 2014; Bouras et al., 2001; Devinsky et al., 1995b) Moreover, reduction in ACC volume has also been related to clinical outcome.

Mitelman et al. (2007) found decreased left ACC volume in people with a poor outcome compared to those with a good outcome. In this study, they assessed outcome following Keefe et al. (1987)'s protocol, which focused on illness duration, total symptom severity, daily functioning, and treatment responsiveness; they did not use the remission criteria operationalised by Andreasen et al. in (2005). Regardless, the two outcome groups displayed significant differences in positive and negative symptoms, similar with the current study, thus supporting a relationship between reduced ACC volume and outcome. Similarly, Takayanagi et al., (2013) found reduced bilateral volume in the ACC in people with 'deficit' schizophrenia compared to 'non-deficit' schizophrenia. Deficit schizophrenia is characterized by a person who displays negative symptoms in the absence of positive, depressive, anxious, and extrapyramidal symptoms; these are considered primary negative symptoms (Kirkpatrick et al., 1989). Due to the impactful nature of negative symptoms, people with deficit schizophrenia are more likely to experience a poorer outcome (Fenton & McGlashan, 1994; Tek et al., 2001). More recently, a study by G.W. Kim et al.(2017) found that decreased bilateral volume in the ACC was significantly and negatively correlated with primary negative symptoms such as emotional withdrawal and difficulty in abstract thinking, and trend-level correlated with social withdrawal ($p = .052$). These results indicate that increased negative symptoms related to decreased, total volume of the bilateral ACC. Similarly, Bègue et al. (2020) summarized that the primary negative symptoms that involve diminished expression, such as alogia, were found more strongly and negatively related to the volume in the rostral ACC; however, primary negative symptoms such as anhedonia, avolition, and social withdrawal were more strongly and negatively related to

the volume in the dorsal ACC. There remains a longstanding opinion that affective processes occur more prominently in the rostral ACC whereas cognitive processes occur in the dorsal ACC (Bush et al., 2000; Devinsky et al., 1995b), and with literature consistently supporting negative relationships between primary negative symptoms and ACC, it is likely that negative symptoms are related to volumetric differences in the ACC, and these differences may be regionally specific for different symptom domains.

While the ACC has been shown to be involved in affective processes, it also plays a role in modulating autonomic arousal, such as heart rate and blood pressure, during cognitive tasks (Critchley et al., 2003; Devinsky et al., 1995b). For example, during cognitive processing tasks involving arithmetic and attention speed, the dorsal ACC regulates heart rate and blood pressure to match the difficulty of the task – as mental stress increases, so does the autonomic response. A study involving participants with focal lesions in the ACC showed significant differences in maintaining sympathetic regulation during cognitive tasks despite performing the cognitive tasks well (Critchley et al., 2003). Moreover, these participants had decreased HRV that was sustained throughout testing.

Sympathetic dysregulation of the heart has been documented in schizophrenia as noted by decreased HRV under control of the ACC (Bengtsson et al., 2020). Moreover, this decrease in HRV has frequently been associated with clinical symptoms (K. J. Bär, 2015; K. J. Bär et al., 2017; K.-J. Bär et al., 2008; Benjamin et al., 2020; J.-H. Kim et al., 2011; Stogios et al., 2021). In some cases, an inverse relationship has been found with the negative symptoms (Chung et al., 2013; Huang et al., 2020; Quintana et al., 2016) and others have noted no relationship at all (Benjamin et al., 2021). The present study also identified an inverse relationship (i.e., negative symptoms were positively correlated with heart function and negatively correlated with heart

structure) suggesting that increased social withdrawal related to increased left ventricular functioning and structure, as well as lower heart rate and diastolic blood pressure. Further, increased symptoms of alogia related to lower systolic blood pressure. This evidence is counter-intuitive given the abundant research literature citing increased negative symptoms with cardiovascular disease (Bresee et al., 2010; Brown et al., 1999; Chiu et al., 2018; Fan et al., 2013; Kilicaslan et al., 2019; Storch Jakobsen et al., 2018b). Given that no associations between the ACC (bilaterally) were found with aggregated clinical symptoms, there may not be a role for the ACC in the volumetric and structural dysfunction of the heart; however, because of the small sample size, it is imperative to validate these findings in a larger study.

Strengths

This was the first study in psychosis to use CMR and MRI to explore the relationship among the brain, the heart, and clinical outcome. Currently, only three published studies to date have used CMR to its full extent to explore the global functioning parameters of the heart; however, these studies were all from a single centre (the Howes Lab of Kings' College, London, UK (Osimo et al., 2020, 2021; Pillinger et al., 2019)). Furthermore, this study supported the previous findings of functional and structural differences in the hearts of people with schizophrenia using CMR.

Including clinical outcome was an especially important strength of this study, given that there is a knowledge gap in relation to cardiac function and structure as assessed by CMR. Although remission status did not relate to cardiac dysfunction, our findings may be in line with Osimo et al. (2021) who suggested a non-hypertensive pathway to cardiac dysfunction in people with schizophrenia, such that dysfunctional adipose tissue from increased obesity may lead to increased inflammatory damage on cardiac myocytes, potentially leading to decreased cardiac functioning and structural changes

Limitations

Our research study recruited during the first few months leading up to the initial COVID-19 pandemic shut down and as such, our sample is small because of ongoing research closures. The small sample size restricted generalisability of the findings. Secondly, our sample was recruited from outpatients from the Royal Ottawa Hospital and was considered a convenience sample. As such, we did not have the funding nor infrastructure to expand the study beyond this region. Thirdly, the results obtained may have been due to chronic nature of the sample, which excluded people in first-episode psychosis due to restricted access to this population. This study could not control for all the life experiences and life-long care options people may have experienced. For example, the use of covariates such as age, or medication dosage, with such a small sample was not statistically viable. Nevertheless, interpretation of the results should be read with caution and should be verified in a first-episode, anti-psychotic naïve sample. Fourth, this study focused on the grey matter of the ACC, as this region has been linked to psychosis, outcome, and the heart. Analyses could have been expanded to the whole brain for exploratory purposes and also included white matter; however, these further analyses were limited due to the small sample size. Fifth, comparisons were limited to within the patient group in an attempt to make the results more straightforward. Relatedly, there was no control (non-clinical) group as recruitment was halted for COVID-19 reasons. This largely affects interpretations of the results, as we cannot fully comprehend how the clinical participants compare to people within the region.

Conclusions and Future Directions

The differences in remission status in our sample was directly impacted by levels of clinical symptoms where remitted participants had significantly lower levels of both positive and negative symptoms compared to their non-remitted counterparts. The entire clinical sample,

regardless of remission status, showed cardiac structural differences compared to the general population such that participants with schizophrenia had greater LV Concentricity; however, cardiac measurements had an inverse relationship with some negative symptoms such as social withdrawal and alogia. Finally, left ACC volume was significantly greater for remitted participants, and bilateral ACC volume showed significant relationships with cardiac structure and function where larger ACC volume related to better cardiac function and structure; however, the ACC did not relate to any clinical symptoms.

Emerging health care data from this year suggests that chronic heart failure continues to be the most expensive comorbidity amongst people with chronic psychotic disorders in Ontario (Oliveira et al., 2022). Given that CMR is an excellent and more effective tool to diagnose cardiac dysfunction in schizophrenia than echocardiography, CMR should be an added routine assessment to assess manner of cardiac care considering the severity of differences in cardiac dysfunction between people with schizophrenia and the general population. An interesting potential future direction would be to determine if annual, or bi-annual, cardiac scanning and evaluation of people with schizophrenia would lead to reductions in health-care expenditures if cardiac dysfunction was assessed and treated earlier. Similarly, since the evidence suggests that cardiac dysfunction does not appear to be related to increased levels of clinical symptoms, it is imperative to investigate cardiac functioning and structure in the early stages of psychosis such during a first-episode or even before onset such as in ultra-high-risk people for psychosis. A potential future direction along this axis of research would be a longitudinal characterization of cardiac dysfunction in schizophrenia. An interesting hypothesis to investigate would be to determine whether cardiac dysfunction begins in ultra-high risk, first-episode psychosis, or in multiple-episode psychosis. Furthermore, validating a potential mechanism of this dysfunction

is paramount to developing an effective treatment. A replication of Osimo et al.'s (2021) research into the potential pathways to dysfunction, however designed longitudinally, would be an effective next step.

In any imaging study, or any study involving human participants, it is difficult to explore and find causal relationships with dysfunctional systems. Therefore, the goal of this study was to explore and find potential relationships between the heart and outcome as a means of developing new axes of research. While it appears that remitted patients have significantly more volume in the ACC than their non-remitted counterparts, and that the ACC positively related to cardiac dysfunction, the ACC did not relate to negative symptoms. Going forward, new imaging studies may seek to investigate functional differences, as the current study only examined the volume differences in the ACC. Furthermore, with larger samples, more brain regions may be explored to determine whether the brain exerts any influence over cardiac dysfunction and its association with clinical outcome.

Appendix

The Le Royal

Mental Health - Care & Research
Santé mentale - Soins et recherche

RESEARCH ETHICS BOARD LETTER OF APPROVAL

Date: 22 January 2019

Investigator Name: Dr. Michael Bodnar

Protocol ID Number: **2018055**

Study Title: ***A longitudinal, naturalistic exploration of outcome and recovery in schizophrenia and related psychoses using a clinically based research evaluation (CBRE)***

Submission Type: Initial Application

Review Type: ☐ Full Board Review ☒ Delegated Review

Date of Approval: 18 January 2019

Approval Expiry Date: **18 January 2020**

Dear Dr. Bodnar,

Thank you for submitting the above noted protocol to the Royal Ottawa Health Care Group Research Ethics Board for review. The study identified above has been reviewed by the REB and approval has been granted. This study is approved until the expiration date noted above.

The following documents have been approved:

Document Name/Title	Document Version Date
Research Protocol – version 2	9 January 2019
Information & Consent Form – version 2 (English)	9 January 2019
Information & Consent Form – version 2 (French)	9 January 2019
Recruitment Posters – version 2 (French & English)	8 January 2019
Screening Form – version 2 (French & English)	8 January 2019

No changes to, or deviations from the approved documents should be initiated prior to submitting an appropriate amendment and obtaining written approval from the Research Ethics Board, except when necessary to eliminate immediate hazard(s) to study participants.

An Annual Progress Report must be submitted a minimum of 30 days prior to the date of study expiration if the study will continue beyond the expiration date.

If the study is completed by the expiry date noted above, a Study Closure/Termination report must be submitted to the REB.

Sincerely,

Dr. Pierre Blier, MD, PhD
Chairperson

References

Abel, E. D., Litwin, S. E., & Sweeney, G. (2008). Cardiac remodeling in obesity. *Physiological Reviews*, *88*(2), 389–419.

Addington, D., Addington, J., & Maticka-Tyndale, E. (1993). Assessing depression in schizophrenia: the Calgary Depression Scale. *The British Journal of Psychiatry*, *163*(S22), 39–44.

AlAqeel, B., & Margolese, H. C. (2013). Remission in schizophrenia: critical and systematic review. *Harvard Review of Psychiatry*, *20*(6), 281–297.

an der Heiden, W., Leber, A., & Häfner, H. (2016). Negative symptoms and their association with depressive symptoms in the long-term course of schizophrenia. *European Archives of Psychiatry and Clinical Neuroscience*, *266*(5), 387–396. https://doi.org/10.1007/s00406-016-0697-2

Andreasen, N. C. (1984). The scale for the assessment of negative symptoms (SANS). *Rinsho Seishin Igaku*, *13*, 999–1010.

Andreasen, N. C., Carpenter, W. T. J., Kane, J. M., Lasser, R. A., Marder, S. R., & Weinberger, D. R. (2005). Remission in schizophrenia: proposed criteria and rationale for consensus. *The American Journal of Psychiatry*, *162*(3), 441–449. https://doi.org/10.1176/appi.ajp.162.3.441

Andreou, D., Saetre, P., Fors, B. M., Nilsson, B. M., Kullberg, J., Jönsson, E. G., Ebeling Barbier, C., & Agartz, I. (2020). Cardiac left ventricular ejection fraction in men and

women with schizophrenia on long-term antipsychotic treatment. *Schizophrenia Research*, *218*, 226–232. https://doi.org/10.1016/j.schres.2019.12.042

Baiano, M., David, A., Versace, A., Churchill, R., Balestrieri, M., & Brambilla, P. (2007). Anterior cingulate volumes in schizophrenia: A systematic review and a meta-analysis of MRI studies. *Schizophrenia Research*, *93*(1), 1–12. https://doi.org/https://doi.org/10.1016/j.schres.2007.02.012

Bär, K. J. (2015). Cardiac autonomic dysfunction in patients with schizophrenia and their healthy relatives - a small review. *Frontiers in Neurology*, *6*(JUN), 1–6. https://doi.org/10.3389/fneur.2015.00139

Bär, K. J., Schulz, S., & Voss, A. (2017). Cardiac autonomic dysfunction in patients with schizophrenia and their healthy relatives. *ECG Time Series Variability Analysis: Engineering and Medicine*, 345–358. https://doi.org/10.4324/9781315372921

Bär, K.-J. (2015). Cardiac autonomic dysfunction in patients with schizophrenia and their healthy relatives a small review. *Frontiers in Neurology*. https://doi.org/10.3389/fneur.2015.00139

Bär, K.-J., Wernich, K., Boettger, S., Cordes, J., Boettger, M. K., Löffler, S., Kornischka, J., & Agelink, M.-W. (2008). Relationship between cardiovagal modulation and psychotic state in patients with paranoid schizophrenia. *Psychiatry Research*, *157*(1–3), 255–257.

Barcones, M. F., MacDowell, K. S., García-Bueno, B., Bioque, M., Gutiirrez-Galve, L., González-Pinto, A., Parellada, M. J., Bobes, J., Bernardo, M., Lobo, A., & Leza, J. C. (2018). Cardiovascular Risk in Early Psychosis: Relationship with Inflammation and

Clinical Features 6 Months after Diagnosis. *International Journal of Neuropsychopharmacology*, *21*(5), 410–422. https://doi.org/10.1093/ijnp/pyx110

Bègue, I., Kaiser, S., & Kirschner, M. (2020). Pathophysiology of negative symptom dimensions of schizophrenia–current developments and implications for treatment. *Neuroscience & Biobehavioral Reviews*, *116*, 74–88.

Bengtsson, J., Bodén, R., Olsson, E. M. G., Mårtensson, J., Gingnell, M., & Persson, J. (2020). Autonomic modulation networks in schizophrenia: The relationship between heart rate variability and functional and structural connectivity in the brain. *Psychiatry Research - Neuroimaging*, *300*(March), 111079. https://doi.org/10.1016/j.pscychresns.2020.111079

Benjamin, B. R., Valstad, M., Elvsåshagen, T., Jönsson, E. G., Moberget, T., Winterton, A., Haram, M., Høegh, M. C., Lagerberg, T. V., Steen, N. E., Larsen, L. E., Andreassen, O. A., Westlye, L. T., & Quintana, D. (2020). Heart rate variability is associated with disease severity in psychosis spectrum disorders. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*. https://doi.org/10.1016/j.pnpbp.2020.110108

Benjamin, B. R., Valstad, M., Elvsåshagen, T., Jönsson, E. G., Moberget, T., Winterton, A., Haram, M., Høegh, M. C., Lagerberg, T. v, & Steen, N. E. (2021). Heart rate variability is associated with disease severity in psychosis spectrum disorders. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *111*, 110108.

Bersani, F. S., Minichino, A., Fojanesi, M., Gallo, M., Maglio, G., Valeriani, G., Biondi, M., & Fitzgerald, P. B. (2014). Cingulate Cortex in Schizophrenia: its relation with negative symptoms and psychotic onset. A review study. *European Review for Medical and Pharmacological Sciences*, *18*(22), 3354–3367.

Bjerregaard, P. (1983). Mean 24 hour heart rate, minimal heart rate and pauses in healthy subjects 40–79 years of age. *European Heart Journal*, *4*(1), 44–51.

Bleuler, E. (1915). Physisch und psychisch in der Pathologie. *Zeitschrift Für Die Gesamte Neurologie Und Psychiatrie*, *30*(1), 426–475.

Bogaert, J. (2011). Cardiac function. In *Clinical cardiac MRI* (pp. 109–165). Springer.

Bogaert, Jan., Dymarkowski, Steven., Taylor, A. M., & Muthurangu, Vivek. (2012). *Clinical Cardiac MRI* (2nd ed. 20). Springer Berlin Heidelberg. https://doi.org/10.1007/978-3-642-23035-6

Bouras, C., KÖVARI, E., HOF, P. R., RIEDERER, B. M., & GIANNAKOPOULOS, P. (2001). Anterior cingulate cortex pathology in schizophrenia and bipolar disorder. *Acta Neuropathologica*, *102*(4), 373–379. https://doi.org/10.1007/s004010100392

Bresee, L. C., Majumdar, S. R., Patten, S. B., & Johnson, J. A. (2010). Prevalence of cardiovascular risk factors and disease in people with schizophrenia: A population-based study. *Schizophrenia Research*, *117*(1), 75–82. https://doi.org/10.1016/j.schres.2009.12.016

Brown, S., Birtwistle, J., Roe, L., & Thompson, C. (1999). The unhealthy lifestyle of people with schizophrenia. *Psychological Medicine*, *29*(3), 697–701. https://doi.org/10.1017/s0033291798008186

Brown, S., Inskip, H., & Barraclough, B. (2000). Causes of the excess mortality of schizophrenia. *British Journal of Psychiatry*, *177*(SEPT), 212–217. https://doi.org/10.1192/bjp.177.3.212

Buchanan, R. W. (2007). Persistent Negative Symptoms in Schizophrenia: An Overview. *Schizophrenia Bulletin*, *33*(4), 1013–1022. https://doi.org/10.1093/schbul/sbl057

Bush, G., Luu, P., & Posner, M. I. (2000). Cognitive and emotional influences in anterior cingulate cortex. *Trends in Cognitive Sciences*, *4*(6), 215–222.

Carbon, M., & Correll, C. U. (2014a). Thinking and acting beyond the positive: the role of the cognitive and negative symptoms in schizophrenia. *CNS Spectrums*, *19*(S1), 35–53.

Carbon, M., & Correll, C. U. (2014b). Clinical predictors of therapeutic response to antipsychotics in schizophrenia. *Dialogues in Clinical Neuroscience*, *16*(4), 505–524. https://doi.org/10.31887/DCNS.2014.16.4/mcarbon

Carpiniello, B., Pinna, F., Manchia, M., Tusconi, M., Cavallaro, R., & Bosia, M. (2022). Sustained symptomatic remission in schizophrenia: Course and predictors from a two-year prospective study. *Schizophrenia Research*, *239*, 34–41. https://doi.org/10.1016/j.schres.2021.11.023

Chang, J. S., Hwang, S. S. H., Yi, S. H., Kim, Y., Kim, Y., Lee, Y. S., Kim, Y. S., & Jung, H.-Y. (2015). Evaluating subjective domains of antipsychotic-induced adverse effects using heart rate variability. *Psychiatry and Clinical Neurosciences*. https://doi.org/10.1111/pcn.12226

Chang, J. S., Yoo, C. S., Yi, S. H., Hong, K. H., Oh, H. S., Hwang, J. Y., Kim, S.-G., Ahn, Y. M., Kim, Y. S., & Kim, Y. S. (2009). Differential pattern of heart rate variability in patients with schizophrenia. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*. https://doi.org/10.1016/j.pnpbp.2009.05.004

Chang, W. C., Hui, C. L. M., Tang, J. Y. M., Wong, G. H. Y., Lam, M. M. L., Chan, S. K. W., & Chen, E. Y. H. (2011). Persistent negative symptoms in first-episode schizophrenia: A prospective three-year follow-up study. *Schizophrenia Research*, *133*(1), 22–28. https://doi.org/https://doi.org/10.1016/j.schres.2011.09.006

Chiu, M., Rahman, F., Vigod, S., Wilton, A. S., & Kurdyak, P. (2018). Temporal trends in cardiovascular disease risk factor profiles in a population-based schizophrenia sample: A repeat cross-sectional study. *Journal of Epidemiology and Community Health*, *72*(1), 71–77. https://doi.org/10.1136/jech-2017-209565

Chong, H. Y., Teoh, S. L., Wu, D. B. C., Kotirum, S., Chiou, C. F., & Chaiyakunapruk, N. (2016). Global economic burden of schizophrenia: A systematic review. *Neuropsychiatric Disease and Treatment*, *12*, 357–373. https://doi.org/10.2147/NDT.S96649

Chow, V., Yeoh, T., Ng, A. C. C., Pasqualon, T., Scott, E., Plater, J., Whitwell, B., Hanzek, D., Chung, T., Thomas, L., Celermajer, D. S., & Kritharides, L. (2014). Asymptomatic left ventricular dysfunction with long-term clozapine treatment for schizophrenia: A multicentre cross-sectional cohort study. *Open Heart*, *1*(1), 1–10. https://doi.org/10.1136/openhrt-2013-000030

Chung, M.-S., Yang, A. C., Lin, Y.-C., Lin, C.-N., Chang, F.-R., Shen, S., Ouyang, W.-C., Loh, E.-W., & Chiu, H.-J. (2013). Association of altered cardiac autonomic function with psychopathology and metabolic profiles in schizophrenia. *Psychiatry Research*, *210*(3), 710–715.

Clamor, A., Lincoln, T. M., Thayer, J. F., & Koenig, J. (2016). Resting vagal activity in schizophrenia: meta-analysis of heart rate variability as a potential endophenotype. *The British Journal of Psychiatry*, *208*(1), 9–16.

Concepcion, M., Otaduy, G., Steinmann, S. S., Federspiel, A., Weber, S., Hjelmervik, H., Craven, A. R., Johnsen, E., Kroken, R. A., Løberg, E.-M., Ersland, L., Kompus, K., & Hugdahl, K. (2021). Glutamate- and GABA-Modulated Connectivity in Auditory Hallucinations—A Combined Resting State fMRI and MR Spectroscopy Study. *Frontiers in Psychiatry | Www.Frontiersin.Org*, *12*, 643564. https://doi.org/10.3389/fpsyt.2021.643564

Correll, C. U., & Schooler, N. R. (2020). Negative symptoms in schizophrenia: A review and clinical guide for recognition, assessment, and treatment. *Neuropsychiatric Disease and Treatment*, *16*, 519–534. https://doi.org/10.2147/NDT.S225643

Crawford, M. J., Jayakumar, S., Lemmey, S. J., Zalewska, K., Patel, M. X., Cooper, S. J., & Shiers, D. (2014). Assessment and treatment of physical health problems among people with schizophrenia: National cross-sectional study. *British Journal of Psychiatry*, *205*(6), 473–477. https://doi.org/10.1192/bjp.bp.113.142521

Critchley, H. D., Mathias, C. J., Josephs, O., O'Doherty, J., Zanini, S., Dewar, B. K., Cipolotti, L., Shallice, T., & Dolan, R. J. (2003). Human cingulate cortex and autonomic control: Converging neuroimaging and clinical evidence. *Brain*, *126*(10), 2139–2152. https://doi.org/10.1093/brain/awg216

Curto, M., Comparelli, A., Ciavarella, G. M., Gasperoni, C., Lionetto, L., Corigliano, V., Uccellini, A., Mancinelli, I., Ferracuti, S., Girardi, P., & Baldessarini, R. J. (2015).

Impairment of left ventricular function early in treatment with clozapine: A preliminary study. *International Clinical Psychopharmacology*, *30*(5), 282–289. https://doi.org/10.1097/YIC.0000000000000085

D'Errico, S., la Russa, R., Maiese, A., Santurro, A., Scopetti, M., Romano, S., Zanon, M., Frati, P., & Fineschi, V. (2021). Atypical antipsychotics and oxidative cardiotoxicity: Review of literature and future perspectives to prevent sudden cardiac death. *Journal of Geriatric Cardiology*, *18*(8), 663–685. https://doi.org/10.11909/j.issn.1671-5411.2021.08.002

Devinsky, O., Morrell, M. J., & Vogt, B. A. (1995a). Contributions of anterior cingulate cortex to behaviour. In *Brain* (Vol. 118). https://academic.oup.com/brain/article/118/1/279/342045

Devinsky, O., Morrell, M. J., & Vogt, B. A. (1995b). Contributions of anterior cingulate cortex to behaviour. *Brain*, *118*(1), 279–306. https://doi.org/10.1093/brain/118.1.279

Diagnostic and statistical manual of mental disorders : DSM-5. (2013). In *DSM-5* (5th ed.). American Psychiatric Association.

Dingemans, P. M. (1990). The brief psychiatric rating scale (BPRS) and the nurses' observation scale for inpatient evaluation (NOSIE) in the evalution of positive and negative symptoms. *Journal of Clinical Psychology*, *46*(2), 168–174. https://doi.org/10.1002/1097-4679(199003)46:2<168::AID-JCLP2270460207>3.0.CO;2-L

Dollfus, S., Mach, C., & Morello, R. (2016). Self-evaluation of negative symptoms. *Schizophrenia Bulletin*, *42*(3), 571–578. https://doi.org/10.1093/schbul/sbv161

Drevets, W. C., Savitz, J., & Trimble, M. (2008). The subgenual anterior cingulate cortex in mood disorders. *CNS Spectrums*, *13*(8), 663–681. https://doi.org/10.1017/s1092852900013754

Eckel, R. H., Grundy, S. M., & Zimmet, P. Z. (2005). The metabolic syndrome. *The Lancet*, *365*(9468), 1415–1428.

Fan, Z., Wu, Y., Shen, J., Ji, T., & Zhan, R. (2013). Schizophrenia and the risk of cardiovascular diseases: A meta-analysis of thirteen cohort studies. *Journal of Psychiatric Research*, *47*(11), 1549–1556. https://doi.org/10.1016/j.jpsychires.2013.07.011

Fenton, W. S., & McGlashan, T. H. (1994). Antecedent, symptoms progression, and long-term outcome of the deficit syndrome in schizophrenia. *The American Journal of Psychiatry*.

Fervaha, G., Foussias, G., Agid, O., & Remington, G. (2014). Motivational and neurocognitive deficits are central to the prediction of longitudinal functional outcome in schizophrenia. *Acta Psychiatrica Scandinavica*, *130*(4), 290–299.

Foussias, G., & Remington, G. (2010). Negative symptoms in schizophrenia: avolition and Occam's razor. *Schizophrenia Bulletin*, *36*(2), 359–369.

Garrido-Torres, N., Rocha-Gonzalez, I., Alameda, L., Rodriguez-Gangoso, A., Vilches, A., Canal-Rivero, M., Crespo-Facorro, B., & Ruiz-Veguilla, M. (2021). Metabolic syndrome in antipsychotic-naïve patients with first-episode psychosis: a systematic review and meta-analysis. *Psychological Medicine*, *51*(14), 2307–2320. https://doi.org/10.1017/S0033291721002853

Gatov, E., Rosella, L., Chiu, M., & Kurdyak, P. A. (2017). Trends in standardized mortality among individuals with schizophrenia, 1993-2012: A population-based, repeated cross-sectional study. *Cmaj*, *189*(37), E1177–E1187. https://doi.org/10.1503/cmaj.161351

Germain, P., Roul, G., Roul, G., Kastler, B., Kastler, B., Jm, M., Mossard, J.-M., Mossard, J. M., Bareiss, P., & Sacrez, A. (1992). Inter-study variability in left ventricular mass measurement. Comparison between M-mode echography and MRI. *European Heart Journal*. https://doi.org/10.1093/oxfordjournals.eurheartj.a060307

Gjesdal, O., Bluemke, D. A., & Lima, J. A. (2011). Cardiac remodeling at the population level—risk factors, screening, and outcomes. *Nature Reviews Cardiology*, *8*(12), 673–685.

Goeree, R., Farahati, F., Burke, N., Blackhouse, G., O'Reilly, D., Pyne, J., & Tarride, J. E. (2005). The economic burden of schizophrenia in Canada in 2004. *Current Medical Research and Opinion*, *21*(12), 2017–2028. https://doi.org/10.1185/030079905X75087

Hall, R. C. W. (1995). Global Assessment of Functioning: A Modified Scale. *Psychosomatics*, *36*(3), 267–275. https://doi.org/10.1016/S0033-3182(95)71666-8

Hennekens, C. H., Hennekens, A. R., Hollar, D., & Casey, D. E. (2005). Schizophrenia and increased risks of cardiovascular disease. *American Heart Journal*, *150*(6), 1115–1121. https://doi.org/10.1016/j.ahj.2005.02.007

Hovington, C. L., Bodnar, M., Joober, R., Malla, A. K., & Lepage, M. (2012). Identifying persistent negative symptoms in first episode psychosis. *BMC Psychiatry*, *12*, 224. https://doi.org/10.1186/1471-244X-12-224

Howell, S., Yarovova, E., Khwanda, A., & Rosen, S. D. (2019). Cardiovascular effects of psychotic illnesses and antipsychotic therapy. *Heart (British Cardiac Society)*, *105*(24), 1852–1859. https://doi.org/10.1136/heartjnl-2017-312107

Huang, W., Liu, W., Liu, W., Liu, W.-S., Chen, T., Chen, T.-T., Chen, W., Chen, W., Chen, W.-H., & Huang, W.-L. (2020). Parasympathetic activity as a potential biomarker of negative symptoms in patients with schizophrenia. *Asia-Pacific Psychiatry*. https://doi.org/10.1111/appy.12392

Hundley, W. G., Bluemke, D. A., Finn, J. P., Flamm, S. D., Fogel, M. A., Friedrich, M. G., Ho, V. B., Jerosch-Herold, M., Kramer, C. M., Manning, W. J., Patel, M., Pohost, G. M., Stillman, A. E., White, R. D., Woodard, P. K., Harrington, R. A., Anderson, J. L., Bates, E. R., Bridges, C. R., … Wesley, D. J. (2010). ACCF/ACR/AHA/NASCI/SCMR 2010 expert consensus document on cardiovascular magnetic resonance: A report of the american college of cardiology foundation task force on expert consensus documents. *Circulation*, *121*(22), 2462–2508. https://doi.org/10.1161/CIR.0b013e3181d44a8f

Huxley, P., Krayer, A., Poole, R., Prendergast, L., Aryal, S., & Warner, | Richard. (2021). Schizophrenia outcomes in the 21st century: A systematic review. *Brain and Behavior*, *11*. https://doi.org/10.1002/brb3.2172

Jin, H., & Mosweu, I. (2017). The Societal Cost of Schizophrenia: A Systematic Review. *PharmacoEconomics*, *35*(1), 25–42. https://doi.org/10.1007/s40273-016-0444-6

Joober, R., Rouleau, G. A., Lal, S., Dixon, M., O'Driscoll, G., Palmour, R., Annable, L., Bloom, D., Lalonde, P., & Labelle, A. (2002). Neuropsychological impairments in neuroleptic-

responder vs.-nonresponder schizophrenic patients and healthy volunteers. *Schizophrenia Research*, *53*(3), 229–238.

Kawel-Boehm, N., Hetzel, S. J., Ambale-Venkatesh, B., Captur, G., Francois, C. J., Jerosch-Herold, M., Salerno, M., Teague, S. D., Valsangiacomo-Buechel, E., van der Geest, R. J., & Bluemke, D. A. (2020). Reference ranges ("normal values") for cardiovascular magnetic resonance (CMR) in adults and children: 2020 update. In *Journal of Cardiovascular Magnetic Resonance* (Vol. 22, Issue 1). BioMed Central. https://doi.org/10.1186/s12968-020-00683-3

Kay, S. R., Fiszbein, A., & Opler, L. A. (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophrenia Bulletin*, *13*(2), 261–276. https://doi.org/10.1093/schbul/13.2.261

Kay, S. R., Opler, L. A., & Lindenmayer, J. P. (1988). Reliability and validity of the positive and negative syndrome scale for schizophrenics. *Psychiatry Research*, *23*(1), 99–110. https://doi.org/10.1016/0165-1781(88)90038-8

Keefe, R. S., Mohs, R. C., Losonczy, M. F., Davidson, M., Silverman, J. M., Kendler, K. S., Horvath, T. B., Nora, R., & Davis, K. L. (1987). Characteristics of very poor outcome schizophrenia. *The American Journal of Psychiatry*.

Kern, R. S., Green, M. F., Nuechterlein, K. H., & Deng, B.-H. (2004). NIMH-MATRICS survey on assessment of neurocognition in schizophrenia. *Schizophrenia Research*, *72*(1), 11–19. https://doi.org/10.1016/j.schres.2004.09.004

Khouri, M. G., Peshock, R. M., Ayers, C. R., de Lemos, J. A., & Drazner, M. H. (2010). *A 4-Tiered Classification of Left Ventricular Hypertrophy Based on Left Ventricular Geometry The Dallas Heart Study*. https://doi.org/10.1161/CIRCIMAGING.109.883652

Kilicaslan, E. E., Karakilic, M., & Erol, A. (2019). The Relationship between 10 Years Risk of Cardiovascular Disease and Schizophrenia Symptoms: Preliminary Results. *Psychiatry Investigation*, *16*(12), 933–939. https://doi.org/10.30773/pi.2019.0063

Kim, G.-W., Kim, Y.-H., & Jeong, G.-W. (2017). Whole brain volume changes and its correlation with clinical symptom severity in patients with schizophrenia: A DARTEL-based VBM study. *PLOS ONE*, *12*(5), e0177251. https://doi.org/10.1371/journal.pone.0177251

Kim, J.-H., Ann, J.-H., & Lee, J. (2011). Relationship between heart rate variability and the severity of psychotic symptoms in schizophrenia. *Acta Neuropsychiatrica*, *23*(4), 161–166.

Kim, J.-H., Yi, S. H., Yoo, C. S., Yang, S. A., Yoon, S. C., Yoon, S. C., Lee, K. Y., Ahn, Y. M., Kang, U. G., & Kim, Y. S. (2004). Heart rate dynamics and their relationship to psychotic symptom severity in clozapine-treated schizophrenic subjects. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*. https://doi.org/10.1016/j.pnpbp.2003.11.007

Kirkpatrick, B., Buchanan, R. W., McKenny, P. D., Alphs, L. D., & Carpenter Jr, W. T. (1989). The schedule for the deficit syndrome: an instrument for research in schizophrenia. *Psychiatry Research*, *30*(2), 119–123.

Kirkpatrick, B., Fenton, W. S., Carpenter Jr., W. T., & Marder, S. R. (2006). The NIMH-MATRICS Consensus Statement on Negative Symptoms. *Schizophrenia Bulletin*, *32*(2), 214–219. https://doi.org/10.1093/schbul/sbj053

Kisely, S., Smith, M., Lawrence, D., Cox, M., Campbell, L. A., & Maaten, S. (2007). Inequitable access for mentally ill patients to some medically necessary procedures. *Cmaj*, *176*(6), 779–784. https://doi.org/10.1503/cmaj.060482

Korkmaz, S., Korkmaz, H., Ozer, O., & Atmaca, M. (2016). Assessment of left ventricle systolic and diastolic functions in schizophrenia patients. *Psychiatry Research*, *240*, 348–351. https://doi.org/10.1016/J.PSYCHRES.2016.04.025

Kraepelin, E. (1899). Psychiatrie. Ein Lehrbuch für Studierende und Ärzte., 6. vollstandig umgearbeitete Auflage edn. JA Barth, Leipzig. *Ref ID*, *134*.

Kraepelin, E. (1919). *Dementia praecox and paraphrenia*. Livingstone.

Kraynak, T. E., Marsland, A. L., & Gianaros, P. J. (2018). Neural Mechanisms Linking Emotion with Cardiovascular Disease. *Current Cardiology Reports*, *20*(12), 128. https://doi.org/10.1007/s11886-018-1071-y

Krumholz, H. M., Larson, M., & Levy, D. (1995). Prognosis of left ventricular geometric patterns in the Framingham heart study. *Journal of the American College of Cardiology*, *25*(4), 879–884. https://doi.org/10.1016/0735-1097(94)00473-4

Lambert, M., Karow, A., Leucht, S., Schimmelmann, B. G., & Naber, D. (2010a). Remission in schizophrenia: validity, frequency, predictors, and patients' perspective 5 years later. *Dialogues in Clinical Neuroscience*, *12*(3), 393–407. https://doi.org/10.31887/DCNS.2010.12.3/mlambert

Lambert, M., Karow, A., Leucht, S., Schimmelmann, B. G., & Naber, D. (2010b). Remission in schizophrenia: validity, frequency, predictors, and patients' perspective 5 years later.

Dialogues in Clinical Neuroscience, *12*(3), 393–407. https://doi.org/10.31887/DCNS.2010.12.3/MLAMBERT

Lambert, M., Karow, A., Leucht, S., Schimmelmann, B. G., & Naber, D. (2022). Remission in schizophrenia: validity, frequency, predictors, and patients' perspective 5 years later. *Dialogues in Clinical Neuroscience*.

Lang, X., Liu, Q., Fang, H., Zhou, Y., Forster, M. T., Li, Z., & Zhang, X. (2021). The prevalence and clinical correlates of metabolic syndrome and cardiometabolic alterations in 430 drug-naive patients in their first episode of schizophrenia. *Psychopharmacology*, *238*(12), 3643–3652. https://doi.org/10.1007/s00213-021-05983-9

Laursen, T. M., Plana-Ripoll, O., Andersen, P. K., McGrath, J. J., Toender, A., Nordentoft, M., Canudas-Romo, V., & Erlangsen, A. (2019). Cause-specific life years lost among persons diagnosed with schizophrenia: Is it getting better or worse? *Schizophrenia Research*, *206*, 284–290. https://doi.org/10.1016/j.schres.2018.11.003

Lee, D. S., Gona, P., Vasan, R. S., Larson, M. G., Benjamin, E. J., Wang, T. J., Tu, J. v, & Levy, D. (2009). Relation of disease pathogenesis and risk factors to heart failure with preserved or reduced ejection fraction: insights from the framingham heart study of the national heart, lung, and blood institute. *Circulation*, *119*(24), 3070–3077.

Leigh-Hunt, N., Bagguley, D., Bash, K., Turner, V., Turnbull, S., Valtorta, N., & Caan, W. (2017). An overview of systematic reviews on the public health consequences of social isolation and loneliness. *Public Health*, *152*, 157–171. https://doi.org/10.1016/J.PUHE.2017.07.035

Leucht, S. (2014). Measurements of Response, Remission, and Recovery in Schizophrenia and Examples for Their Clinical Application. *J Clin Psychiatry*, *75*(1), 8–14. https://doi.org/10.4088/JCP.13049su1c.02

Leucht, S., Kane, J. M., Kissling, W., Hamann, J., Etschel, E., & Engel, R. R. (2005). What does the PANSS mean? *Schizophrenia Research*, *79*(2–3), 231–238. https://doi.org/10.1016/J.SCHRES.2005.04.008

Lin, C.-H., Lin, H.-S., Lin, S.-C., Kuo, C.-C., Wang, F.-C., & Huang, Y.-H. (2018). Early improvement in PANSS-30, PANSS-8, and PANSS-6 scores predicts ultimate response and remission during acute treatment of schizophrenia. *Acta Psychiatrica Scandinavica*, *137*(2), 98–108. https://doi.org/10.1111/acps.12849

Liu, Y., Huang, Y., Zhou, J., Zhou, J., Zhou, J., Zhou, J., Li, G., Chen, J., Chen, J., Xiang, Z., Wu, F., Wu, F., & Wu, K. (2021). Altered Heart Rate Variability in Patients With Schizophrenia During an Autonomic Nervous Test. *Frontiers in Psychiatry*. https://doi.org/10.3389/fpsyt.2021.626991

Marchesi, C., Affaticati, A., Monici, A., de Panfilis, C., Ossola, P., & Tonna, M. (2014). Predictors of symptomatic remission in patients with first-episode schizophrenia: a 16 years follow-up study. *Comprehensive Psychiatry*, *55*(4), 778–784.

Marczak, B. T., & Paprocki, A. (2001). Blood pressure variability on the basis of 24-hour ambulatory blood pressure monitoring in a group of healthy persons. *Przeglad Lekarski*, *58*(7–8), 762–766.

Martin, E. A., Jonas, K. G., Lian, W., Foti, D., Donaldson, K. R., Bromet, E. J., & Kotov, R. (2021). Predicting Long-Term Outcomes in First-Admission Psychosis: Does the

Hierarchical Taxonomy of Psychopathology Aid DSM in Prognostication? *Schizophrenia Bulletin*, *47*(5), 1331–1341. https://doi.org/10.1093/schbul/sbab043

Messinger, J. W., Trémeau, F., Antonius, D., Mendelsohn, E., Prudent, V., Stanford, A. D., & Malaspina, D. (2011). Avolition and expressive deficits capture negative symptom phenomenology: Implications for DSM-5 and schizophrenia research. *Clinical Psychology Review*, *31*(1), 161–168. https://doi.org/https://doi.org/10.1016/j.cpr.2010.09.002

Mitchell, A. J., & Lord, O. (2010). Do deficits in cardiac care influence high mortality rates in schizophrenia a systematic review and pooled analysis. *Journal of Psychopharmacology*. https://doi.org/10.1177/1359786810382056

Mitelman, S. A., Brickman, A. M., Shihabuddin, L., Newmark, R. E., Hazlett, E. A., Haznedar, M. M., & Buchsbaum, M. S. (2007). A comprehensive assessment of gray and white matter volumes and their relationship to outcome and severity in schizophrenia. *Neuroimage*, *37*(2), 449–462.

Montaquila, J. M., Trachik, B. J., & Bedwell, J. S. (2015). Heart rate variability and vagal tone in schizophrenia: A review. *Journal of Psychiatric Research*. https://doi.org/10.1016/j.jpsychires.2015.07.025

Mosteller, R. D. (1987). Simplified calculation of body surface area. *N Engl J Med*, *317*, 1098.

Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., Cummings, J. L., & Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society*, *53*(4), 695–699.

Nosir, YoussefF. M., Lequin, M., Kasprzak, J., Domburg, RonT. van, Vletter, W., Yao, J., Stoker, J., Cate, FolkertJ. T., & Roelandt, JosR. T. C. (1998). Measurements and day-to-day variabilities of left ventricular volumes and ejection fraction by three-dimensional echocardiography and comparison with magnetic resonance imaging. *American Journal of Cardiology*. https://doi.org/10.1016/s0002-9149(98)00306-3

Oliveira, C. de, Iwajomo, T., & Kurdyak, P. (2022). *Health Care Expenditures Among Individuals With Chronic Psychotic Disorders in Ontario: An Analysis Over Time*. https://doi.org/10.3389/frhs.2022.848072

Osborn, D. P. J., Baio, G., Walters, K., Petersen, I., Limburg, H., Raine, R., & Nazareth, I. (2011). Inequalities in the provision of cardiovascular screening to people with severe mental illnesses in primary care: cohort study in the United Kingdom THIN Primary Care Database 2000-2007. *Schizophrenia Research*, *129*(2–3), 104–110. https://doi.org/10.1016/j.schres.2011.04.003

Osimo, E. F., Brugger, S. P., de Marvao, A., Pillinger, T., Whitehurst, T., Statton, B., Quinlan, M., Berry, A., Cook, S. A., O'Regan, D. P., & Howes, O. D. (2020). Cardiac structure and function in schizophrenia: cardiac magnetic resonance imaging study. *The British Journal of Psychiatry*, 1–8. https://doi.org/10.1192/bjp.2019.268

Osimo, E. F., Sweeney, M., de Marvao, A., Berry, A., Statton, B., Perry, B. I., Pillinger, T., Whitehurst, T., Cook, S. A., O'Regan, D. P., Thomas, E. L., & Howes, O. D. (2021). Adipose tissue dysfunction, inflammation, and insulin resistance: alternative pathways to cardiac remodelling in schizophrenia. A multimodal, case–control study. *Translational Psychiatry*, *11*(1). https://doi.org/10.1038/s41398-021-01741-9

Østergaard, S. D., Lemming, O. M., Mors, O., Correll, C. U., & Bech, P. (2016). PANSS-6: A brief rating scale for the measurement of severity in schizophrenia. *Acta Psychiatrica Scandinavica*, *133*(6), 436–444. https://doi.org/10.1111/acps.12526

Patel, R., Jayatilleke, N., Broadbent, M., Chang, C.-K., Foskett, N., Gorrell, G., Hayes, R. D., Jackson, R., Johnston, C., Shetty, H., Roberts, A., McGuire, P., & Stewart, R. (2015). Negative symptoms in schizophrenia: a study in a large clinical sample of patients using a novel automated method. *BMJ Open*, *5*(9), e007619. https://doi.org/10.1136/bmjopen-2015-007619

Perry, B. I., Stochl, J., Upthegrove, R., Zammit, S., Wareham, N., Langenberg, C., Winpenny, E., Dunger, D., Jones, P. B., & Khandaker, G. M. (2021). Longitudinal Trends in Childhood Insulin Levels and Body Mass Index and Associations with Risks of Psychosis and Depression in Young Adults. *JAMA Psychiatry*, *78*(4), 416–425. https://doi.org/10.1001/jamapsychiatry.2020.4180

Pillinger, T., McCutcheon, R. A., Vano, L., Mizuno, Y., Arumuham, A., Hindley, G., Beck, K., Natesan, S., Efthimiou, O., Cipriani, A., & Howes, O. D. (2020). Comparative effects of 18 antipsychotics on metabolic function in patients with schizophrenia, predictors of metabolic dysregulation, and association with psychopathology: a systematic review and network meta-analysis. *The Lancet Psychiatry*, *7*(1), 64–77. https://doi.org/10.1016/S2215-0366(19)30416-X

Pillinger, T., Osimo, E. F., de Marvao, A., Berry, M. A., Whitehurst, T., Statton, B., Quinlan, M., Brugger, S., Vazir, A., Cook, S. A., O'Regan, D. P., & Howes, O. D. (2019). Cardiac

structure and function in patients with schizophrenia taking antipsychotic drugs: an MRI study. *Translational Psychiatry*, *9*(1). https://doi.org/10.1038/s41398-019-0502-x

Quintana, D. S., Westlye, L. T., Kaufmann, T., Rustan, Ø. G., Brandt, C. L., Haatveit, B., Steen, N. E., & Andreassen, O. A. (2016). Reduced heart rate variability in schizophrenia and bipolar disorder compared to healthy controls. *Acta Psychiatrica Scandinavica*, *133*(1), 44–52.

Rammou, A., Fisher, H. L., Johnson, S., Major, B., Rahaman, N., Chamberlain-Kent, N., & Stone, J. M. (2019). Negative symptoms in first-episode psychosis: Clinical correlates and 1-year follow-up outcomes in London Early Intervention Services. *Early Intervention in Psychiatry*, *13*(3), 443–452. https://doi.org/10.1111/eip.12502

Raucher-Chéné, D., Bodnar, M., Lavigne, K. M., Malla, A., Joober, R., & Lepage, M. (2022). Dynamic interplay between insight and persistent negative symptoms in first episode of psychosis: A longitudinal study. *Schizophrenia Bulletin*, *48*(1), 211–219.

Rødevand, L., Steen, N. E., Elvsåshagen, T., Quintana, D. S., Reponen, E. J., Mørch, R. H., Lunding, S. H., Vedal, T. S. J., Dieset, I., Melle, I., Lagerberg, T. v., & Andreassen, O. A. (2019). Cardiovascular risk remains high in schizophrenia with modest improvements in bipolar disorder during past decade. *Acta Psychiatrica Scandinavica*, *139*(4), 348–360. https://doi.org/10.1111/acps.13008

Rosen, B. D., Edvardsen, T., Lai, S., Castillo, E., Pan, L., Jerosch-Herold, M., Sinha, S., Kronmal, R., Arnett, D., Crouse, J. R., Heckbert, S. R., Bluemke, D. A., & Lima, J. A. C. (2005). Left Ventricular Concentric Remodeling Is Associated With Decreased Global and

Regional Systolic Function. *Circulation*, *112*(7), 984–991. https://doi.org/10.1161/CIRCULATIONAHA.104.500488

Sauvé, G., Brodeur, M. B., Shah, J. L., & Lepage, M. (2019). The Prevalence of Negative Symptoms Across the Stages of the Psychosis Continuum. *Harvard Review of Psychiatry*, *27*(1), 15–32. https://doi.org/10.1097/HRP.0000000000000184

Scharfetter, C. (2001). Eugen Bleuler's schizophrenias - Synthesis of various concepts. *Schweizer Archiv Fur Neurologie Und Psychiatrie*, *152*(1), 34–37. https://doi.org/10.4414/sanp.2001.01199

Schulz-Menger, J., Bluemke, D. A., Bremerich, J., Flamm, S. D., Fogel, M. A., Friedrich, M. G., Kim, R. J., von Knobelsdorff-Brenkenhoff, F., Kramer, C. M., Pennell, D. J., Plein, S., & Nagel, E. (2013). Standardized image interpretation and post processing in cardiovascular magnetic resonance: Society for Cardiovascular Magnetic Resonance (SCMR) Board of Trustees Task Force on Standardized Post Processing. *Journal of Cardiovascular Magnetic Resonance*, *15*(1), 1–19. https://doi.org/10.1186/1532-429X-15-35

Shaffer, F., & Ginsberg, J. P. (2017). An Overview of Heart Rate Variability Metrics and Norms . In *Frontiers in Public Health* (Vol. 5). https://www.frontiersin.org/article/10.3389/fpubh.2017.00258

Singh, M. M., & Kay, S. R. (1975). A comparative study of haloperidol and chlorpromazine in terms of clinical effects and therapeutic reversal with benztropine in schizophrenia. Theoretical implications for potency differences among neuroleptics. *Psychopharmacologia*, *43*(2), 103–113. https://doi.org/10.1007/BF00421012

Smith, D. J., Langan, J., McLean, G., Guthrie, B., & Mercer, S. W. (2013). Schizophrenia is associated with excess multiple physical health comorbidities but low levels of recorded cardiovascular disease in primary care cross sectional study. *BMJ Open*. https://doi.org/10.1136/bmjopen-2013-002808

Stahl, S. M., Mignon, L., & Meyer, J. M. (2009). Which comes first: Atypical antipsychotic treatment or cardiometabolic risk? *Acta Psychiatrica Scandinavica*, *119*(3), 171–179. https://doi.org/10.1111/j.1600-0447.2008.01334.x

Stanculete, M. F. (2022). *The Many Faces of Negative Symptoms in Schizophrenia* (O. C. E.-K. Fukao, Ed.; p. Ch. 4). IntechOpen. https://doi.org/10.5772/intechopen.98412

Stewart, A. J., Patten, S. B., Fiest, K. M., Williamson, T. S., Wick, J. P., & Ronksley, P. E. (2022). 10-Year Trends in Healthcare Spending among Patients with Schizophrenia in Alberta, Canada. *The Canadian Journal of Psychiatry*, 070674372210828. https://doi.org/10.1177/07067437221082885

Stogios, N., Gdanski, A., Gerretsen, P., Chintoh, A. F., Graff-Guerrero, A., Rajji, T. K., Remington, G., Hahn, M. K., & Agarwal, S. M. (2021). Autonomic nervous system dysfunction in schizophrenia: impact on cognitive and metabolic health. *NPJ Schizophrenia*, *7*(1), 22. https://doi.org/10.1038/s41537-021-00151-6

Storch Jakobsen, A., Speyer, H., Nørgaard, H. C. B., Hjorthøj, C., Krogh, J., Mors, O., & Nordentoft, M. (2018a). Associations between clinical and psychosocial factors and metabolic and cardiovascular risk factors in overweight patients with schizophrenia spectrum disorders - Baseline and two-years findings from the CHANGE trial. *Schizophrenia Research*, *199*, 96–102. https://doi.org/10.1016/j.schres.2018.02.047

Storch Jakobsen, A., Speyer, H., Nørgaard, H. C. B., Hjorthøj, C., Krogh, J., Mors, O., & Nordentoft, M. (2018b). Associations between clinical and psychosocial factors and metabolic and cardiovascular risk factors in overweight patients with schizophrenia spectrum disorders – Baseline and two-years findings from the CHANGE trial. *Schizophrenia Research*, *199*, 96–102. https://doi.org/10.1016/J.SCHRES.2018.02.047

Sweeney, M., Whiskey, E., Patel, R. K., Tracy, D. K., Shergill, S. S., & Plymen, C. M. (2020). Understanding and managing cardiac side-effects of second-generation antipsychotics in the treatment of schizophrenia. *BJPsych Advances*, *26*(1), 26–40. https://doi.org/10.1192/bja.2019.49

Takayanagi, M., Wentz, J., Takayanagi, Y., Schretlen, D. J., Ceyhan, E., Wang, L., Suzuki, M., Sawa, A., Barta, P. E., & Ratnanather, J. T. (2013). Reduced anterior cingulate gray matter volume and thickness in subjects with deficit schizophrenia. *Schizophrenia Research*, *150*(2–3), 484–490.

Tan, X. W., Chan, C. Y. W., Lum, A. W. M., Lee, E. S., Mok, Y. M., Fung, D. S. S., & Tor, P. C. (2022). Association of cardiovascular metabolic risk factor measurements with psychiatric readmission among in-hospital patients with severe mental illness: a retrospective study. *BMC Psychiatry*, *22*(1), 43. https://doi.org/10.1186/s12888-022-03704-w

Taylor, A. J., Salerno, M., Dharmakumar, R., & Jerosch-Herold, M. (2016). T1 Mapping: Basic Techniques and Clinical Applications. *JACC: Cardiovascular Imaging*, *9*(1), 67–81. https://doi.org/10.1016/J.JCMG.2015.11.005

Tek, C., Kirkpatrick, B., & Buchanan, R. W. (2001). A five-year followup study of deficit and nondeficit schizophrenia. *Schizophrenia Research*, *49*(3), 253–260.

Thayer, J. F., Yamamoto, S. S., & Brosschot, J. F. (2010). The relationship of autonomic imbalance, heart rate variability and cardiovascular disease risk factors. *International Journal of Cardiology*, *141*(2), 122–131.

Toichi, M., Kubota, Y., Murai, T., Kamio, Y., Sakihama, M., Toriuchi, T., Inakuma, T., Sengoku, A., & Miyoshi, K. (1999). The influence of psychotic states on the autonomic nervous system in schizophrenia. *International Journal of Psychophysiology*, *31*(2), 147–154.

Unsal, C., Oran, M., Tureli, H. O., Alpsoy, S., Yeşilyurt, S., Arslan, M., Topcu, B., Karakaya, O., & Kurt, E. (2013). Detection of subclinical atherosclerosis and diastolic dysfunction in patients with schizophrenia. *Neuropsychiatric Disease and Treatment*, *9*, 1531–1537. https://doi.org/10.2147/NDT.S52030

Verbraecken, J., van de Heyning, P., de Backer, W., & van Gaal, L. (2006). Body surface area in normal-weight, overweight, and obese adults. A comparison study. *Metabolism*, *55*(4), 515–524.

Verdoux, H., Lengronne, J., Liraud, F., Gonzales, B., Assens, F., Abalan, F., & Os, J. van. (2000). Medication adherence in psychosis: predictors and impact on outcome. A 2-year follow-up of first-admitted subjects. *Acta Psychiatrica Scandinavica*, *102*(3), 203–210.

Verdoux, H., Liraud, F., Assens, F., Abalan, F., & van Os, J. (2002). Social and clinical consequences of cognitive deficits in early psychosis: a two-year follow-up study of first-admitted patients. *Schizophrenia Research*, *56*(1–2), 149–159.

Weber, S., Scott, J. G., & Chatterton, M. lou. (2022). Healthcare costs and resource use associated with negative symptoms of schizophrenia: A systematic literature review. *Schizophrenia Research*, *241*, 251–259. https://doi.org/10.1016/J.SCHRES.2022.01.051

Wechsler, D. (1955). Wechsler adult intelligence scale--. *Archives of Clinical Neuropsychology*.

Wirshing, D. A. (2004). Schizophrenia and obesity: impact of antipsychotic medications. *Journal of Clinical Psychiatry*, *65*(Suppl 18), 13–26.

Yung, N. C. L., Wong, C. S. M., Chan, J. K. N., Chen, E. Y. H., & Chang, W. C. (2021). Excess Mortality and Life-Years Lost in People With Schizophrenia and Other Non-affective Psychoses: An 11-Year Population-Based Cohort Study. *Schizophrenia Bulletin*, *47*(2), 474–484. https://doi.org/10.1093/schbul/sbaa137