

## SCHIZOPHRENIA AND PHYSICAL COMORBIDITY

Ivona Šimunović Filipčić<sup>1</sup> & Igor Filipčić<sup>1,2,3,4</sup>

<sup>1</sup>Department of psychological medicine, University Hospital Center Zagreb, Zagreb, Croatia

<sup>2</sup>Psychiatric Hospital "Sveti Ivan", Zagreb, Croatia

<sup>3</sup>Faculty of Dental Medicine and Health, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia

<sup>4</sup>School of Medicine, University of Zagreb, Zagreb, Croatia

### SUMMARY

Schizophrenia is a severe psychiatric disorder increasingly recognized as a systemic disorder. In addition to the burden and suffering caused by the mental illness itself, individuals with schizophrenia have a high risk for physical illnesses. The life expectancy gap remains 13 to 30 years wider in people with schizophrenia compared to the general population. This premature mortality is caused largely by deaths due to cardiovascular disease, cancer, diabetes mellitus, and other natural causes, poor diagnosis and treatment, and insufficient prevention of modifiable risk factors. Although the links between schizophrenia and physical illnesses are well established, in clinical practice, physical illnesses in patients with schizophrenia are often overlooked, and the mortality gap between general population and people with schizophrenia continues to widen. The physical health of people with schizophrenia is commonly self-neglected but also ignored by people around them and by health systems, resulting in significant physical health disparities and limited access to health services. The root of the problem of insufficient healthcare appear to lie in interrelated contributory factors from illness, patients, and medical and mental healthcare system. Furthermore, a growing body of literature has been indicating the effect of the chronic physical illness on the treatment outcome of psychosis. Premature mortality and disability could be reduced if there was a greater focus on the implementation of strategies that effectively prevent modifiable risk factors from the first psychotic episode and enhance early recognition of physical illnesses, reduce the burden of physical comorbidity and lead to improved health outcomes. Ultimately, to improve treatment outcome and to reduce the suffering of people with schizophrenia, it is crucial to treat physical comorbidity promptly and assertively from the appearance of the first symptoms of the psychotic disorder. The integrative approach and collaborative care within all levels of healthcare providers should be the imperative in clinical practice.

**Key words:** schizophrenia spectrum disorder – psychosis - serious mental illness – comorbidity - general medical condition - major noncommunicable disease

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### INTRODUCTION

It is well known that schizophrenia is associated with significant personal suffering, disability, family burden, and suboptimal treatment outcome (Salomon et al. 2012, Vos et al. 2012, Kahn et al. 2015). Moreover, poor physical health can substantially add to the increased disability, burden and poor quality of life (Filipčić et al. 2016). The fact is that patients with schizophrenia have about 10 to 30 years shorter life expectancy than the general population (Tiihonen et al. 2009, Laursen et al. 2011, Olfson et al. 2015). Unfortunately, the life expectancy gap between general population and people with schizophrenia continues to widen (Saha et al. 2007), and has increased 37% since the 1970s (Lee et al. 2017). This premature mortality is mainly caused by deaths due to cardiovascular disease, cancer, diabetes mellitus, and other natural causes (Saha et al. 2007, Olfson et al. 2015). The premature death from natural causes contribute approximately 60% to early mortality in people with severe mental illness mostly due to physical illnesses that occur more frequently, are not prevented adequately, are not identified early enough and are not treated efficiently (Saxena & Maj 2017). This mortality disparity is not confined to some regions and countries but seems to be a global reality (Saxena & Maj 2017). Although it has been known for more than

a century that schizophrenia is associated with markedly increased physical comorbidity and mortality, and that rate of physical illness in those with schizophrenia exceeds those of the general population, there is still a knowledge implementation gap (Björkenstam et al. 2012, Walker et al. 2015, Druss et al. 2018). In general, treatment of people with comorbidity and multimorbidity has become one of the most significant challenges faced by global healthcare (Sartorius 2018). Moreover, we need to adopt the approach that multimorbidities are indifferent to medical specialties, and implement it in routine clinical practice (Jakovljević & Ostojić 2013).

It is reality that there is a lack of an integrative approach in clinical practice because of the configuration of healthcare systems, which focus on individual diseases rather than on multimorbidities (Vogeli et al. 2007, Barnett et al. 2012, Sinnige et al. 2013, Prados-Torres et al. 2014). Mental disorders still carry stigma, which makes access to healthcare more difficult, and the quality of care inadequate – both of which contribute to the probability of complications of physical illnesses (Sartorius 2018).

The primary objective of this paper is to raise awareness of the importance of prevention, detection and assertive treatment of physical illnesses in people with schizophrenia, and to reduce premature mortality and enhance treatment outcomes.

## **MODIFIABLE HEALTH RISK BEHAVIORS**

Unhealthy lifestyles, including sedentary living, poor dietary habits, smoking, and alcohol/substance use, enhance rapid deterioration of physical health and early mortality of individuals with schizophrenia (Liu et al. 2017). Smoking is the most common substance use disorder in people with schizophrenia, and prevalence rates are two to four times higher than of the general population (Rüther et al. 2014, Stubbs et al. 2015, Šagud et al. 2018). Researchers have found that even the population of ultra-high risk for psychosis display high rates of behavioral cardiometabolic risk factors with elevated rates of smoking, physical inactivity and alcohol abuse (Carney et al. 2016). In the past decades, smoking in the general population has markedly declined, while the smoking rate of persons with schizophrenia remains at a much higher level (Stubbs et al. 2015). Furthermore, smoking increases the risk of natural cause mortality more than two times, and there is an additive effect of smoking to both cardiac and a respiratory condition (Dickerson et al. 2018). Notably, researchers have found high cardiovascular risk mostly as a result of lifestyle factors, even before the onset of psychosis (Carney et al. 2016).

It is well known that multisystem adverse effects of antipsychotic medications play a role in increased physical morbidity, and there is a large amount of evidence that they may cause metabolic dysregulation such as diabetes, weight gain and obesity (Vancampfort et al. 2015). However, recent large population-based study showed the highest mortality among patients not receiving any antipsychotics, while the lowest mortality was among those receiving a long-acting injectable second-generation antipsychotic (Taipale et al. 2017).

## **THE GENETIC LINK**

Even before the onset of the first psychotic episode, young patients with schizophrenia already suffer from wide variety of physical conditions (Sørensen et al. 2015). Studies have shown that patients with schizophrenia show raised fasting plasma glucose levels, reduced glucose tolerance, raised fasting plasma insulin levels, and increased insulin resistance at illness onset even before exposure to psychotropic medications (Pillinger et al. 2017). Evidence from recent genetic studies implicates shared genetic risk (pleiotropy) for cardiovascular risk factors and psychotic disorders (Andreassen et al. 2013, Barcones et al. 2017). These findings may indicate that individuals with schizophrenia present at the early course of illness already have a vulnerable phenotype for development of particular physical illnesses, and suggest genetic, physiological and immunological or developmental overlap between schizophrenia and physical illnesses (Andreassen et al. 2013, Sørensen et al. 2015, Pillinger et al. 2017).

## **INFLAMMATION, OXIDATIVE STRESS, AND ACCELERATED AGING**

There is an increasing recognition of elevated inflammation and oxidative stress in persons with schizophrenia, and that the accelerated biological aging may also play an important role in the premature morbidity observed in individuals with psychosis (Kirkpatrick & Miller 2013, Lindqvist et al. 2015, Nguyen et al. 2018). The evidence implicating biological pathways potentially affecting both body and brain is increasing (Dieset et al. 2016). This includes overlapping genes between schizophrenia and physical illness, prenatal risk factors such as hypoxia and infections, and increased cardiovascular disease risk in drug-naïve patients at illness onset (Dieset et al. 2016). Exposure to early trauma and chronic stress may also be a risk factor for both schizophrenia and physical illnesses (Ruby et al. 2014, Riley et al. 2018). It is well known that exposure to stressors is linked to a weakening of the immune system and an increase in the inflammatory response (Black 2003). Furthermore, it seems that physiological changes seen throughout the body with normal aging occur at an earlier age in people with schizophrenia than in general population (Kirkpatrick et al. 2008). Understanding alterations in the aging process within schizophrenia is clearly imperative, but attempts to address systemic biological defects in schizophrenia failed because of the lack of specific and sensitive systemic biomarkers of aging (Nguyen et al. 2018). There are strong evidences of abnormal physiological biomarkers in schizophrenia (Nguyen et al. 2018). The current biomarker literature suggests that aging is altered in schizophrenia, and the mechanisms are likely to be multifactorial. The observed aging patterns may be a result of the pathophysiology of schizophrenia or, given the oft-observed correlations with duration of illness, due to the wear and tear on the body from factors associated with the illness, such as medication effects, stress of psychotic episodes, stress of lower functional status, weak social support, poor healthcare, childhood abuse/trauma, lower socioeconomic status, and lifestyle factors such as unhealthy diet, sedentary behavior, and heavy smoking. From the available literature, aging processes may begin early in the lifespan through abnormalities in genetic factors and altered synaptic function, which may then be exacerbated by inflammation and oxidative stress associated with illness-related factors (Nguyen et al. 2018). Thus far, the emerging literature provides initial exciting evidence suggesting that the gut microbiome is altered in schizophrenia and, importantly, is associated with clinical features of mental illness (Nguyen et al. 2018). Understanding the relationship of the microbiome to other markers of physiological abnormalities may help to identify mechanisms by which the gut ecosystem impacts the brain and physical morbidity (Nguyen et al. 2018). As schizophrenia has been characterized by chronic, low-grade inflammation, suggesting a process of immunosenescence or “inflammaging” (Kennedy et

al. 2014), it has been hypothesized that the gut microbiome may be an important mechanism involved in this process (Nguyen et al. 2018). To sum up, schizophrenia is a risk factor for physical illness, and its presence increases the chance that an individual will also suffer from one or more chronic physical illnesses.

## **DISPARITY IN HEALTHCARE**

Individuals with schizophrenia are less likely to seek help for physical illnesses, and symptoms may affect adherence to treatment as well as prognosis (Saxena & Maj 2017). Physical health of people with schizophrenia is commonly ignored not only by themselves and people around them, but also by health systems, resulting in crucial physical health disparities and limited access to health services (Saxena & Maj 2017). In the paper published in this issue of *Psychiatria Danubina* by Jeleč et al. the findings indicated that utilization of specialist healthcare in patients with schizophrenia is relatively lower than in general population, and absolutely lower than in other mental disorders, and therefore not adequate in the prevention of increased mortality (Jeleč et al. 2018).

Reasons for this are many and varied as people with schizophrenia often face barriers which interfere with timely and optimal access to healthcare. These barriers are dependent on different factors relative to the organization of healthcare systems, providers and patients (Lawrence & Kisely 2010, Druss & Walker 2011, Gervais et al. 2018). At healthcare system level, this includes systematic separation of mental and somatic healthcare and lack of clarity and consensus about who should be responsible for detecting and managing physical problems in patients with mental illnesses (Druss & Walker 2011, Gervais et al. 2018). At the provider level, time and resource constraints and stigma can also lead to a poor quality of care offered by clinicians to patients with schizophrenia (Lawrence & Kisely 2010, De Hert et al. 2011, Gervais et al. 2018). At the patients level, the barriers include modifiable health risk factors and unhealthy lifestyles (e.g. substance abuse, poor diet, smoking and lack of exercise), side effects of medications, cognitive impairment, suspiciousness, difficulties communicating physical needs and poor social circumstances (De Hert et al. 2011, Gervais et al. 2018). In this perspective, the problem that exists independently of us – high prevalence of physical comorbidities - we aggravate by inadequate healthcare strategies and clinical practice.

## **IMPACT OF PHYSICAL COMORBIDITY ON TREATMENT OUTCOMES**

To the best of our knowledge, only a few studies addressed the problem of the association of physical comorbidities with the outcomes of treatment of psychosis. These studies used different outcome measures, but

the prevalence of patients with chronic physical comorbidities and the main guiding principles are similar. Researchers have found that physical comorbidities were significantly associated with a higher psychiatric symptom ratings at hospital discharge and an increased risk of relapse (Douzenis et al. 2012, Köhler et al. 2016). Furthermore, a growing body of literature suggested the effect of the chronic physical illness on the treatment outcome of psychosis indicated by higher rate of psychiatric readmission and poorer health-related quality of life (Filipčić et al. 2016, 2017, Šprah et al. 2017, Gervais et al. 2018). It seems that chronic physical illness is associated with higher rates of psychiatric readmission independently of psychiatric comorbidities and other clinical, sociodemographic, and lifestyle factors (Filipčić et al. 2017). In this perspective, to treat psychosis effectively, it may be necessary to enhance prevention of modifiable risk factors and early recognition of physical illnesses, and to address physical illnesses promptly and assertively from the appearance of the first symptoms of mental disorders.

## **STRATEGIES AND INTERVENTION SERVICES TO IMPROVE PHYSICAL HEALTH**

In recent years, several reports and action plans have been developed to address poor physical health in people with mental disorders (Druss & Walker 2011, McGinty et al. 2016, Cohen 2017). Over the past decade, studies have provided substantial evidence for the effectiveness of both pharmacologic and behavioral interventions to target modifiable risk factors among persons with schizophrenia (McGinty et al. 2016). In particular, effective interventions are available to support smoking cessation and to promote weight loss among obese individuals, addressing the two leading causes of preventable mortality (McGinty et al. 2016, Druss et al. 2018). However, for addressing physical health of people with schizophrenia it is crucial to integrate multimodal interventions including pharmacologic, behavioral, somatic, and social services (McGinty et al. 2015), and the utmost priority in clinical practice should be given to primary and secondary prevention through regular screening, health promotion programs and reduction of cardiometabolic risk factors.

The first pharmacological and behavioral intervention program in Croatia was established in Psychiatric Hospital „Sveti Ivan” under the umbrella of the Centre for integrative psychiatry (CIP) in 2015. The CIP is a multimodal model for integration of pharmacological, behavioral, somatic, and social services for people with severe mental illnesses. The primary aim is to reduce morbidity and mortality of people with mental disorders through prevention of modifiable cardiovascular risk factors, early recognition and intervention, and assertive treatment of physical comorbidity. The secondary aim is to accelerate re-socialization and rehabilitation through existing new socio-rehabilitation

programs, to increase the quality of life and work productivity of psychiatric patients, and to implement educational-preventive programs for patients, families and health workers (school of non-smoking, diet nutrition program, how to live with mental illness etc.)

Notably, the prevention and early intervention to maintain the physical health of those with severe mental disorders is an investment that can reduce the costs of treating more advanced diseases for the Croatian health system and the whole Croatian society. Creating the National strategy and Clinical Guidelines for the prevention and treatment of physical illness in people with mental illness has the potential to significantly improve health and well-being, and reduce premature mortality among persons with severe mental illness on the national level. The CIP health programs are a promising model for integration of behavioral, somatic, and social services for people with mental disorders, but may be strengthened by additional policy and implementation supports.

## CONCLUSION

The current greatest barrier to increasing the life expectancy of persons with severe mental illnesses is no longer a knowledge gap - it is an implementation gap. Premature mortality and disability could be reduced if there was a greater focus on the implementation of strategies that effectively prevent modifiable risk factors from the first psychotic episode, and enhance early recognition of physical illnesses, reduce the burden of physical comorbidity and lead to improved health outcomes. Ultimately, to improve treatment outcomes and to reduce the suffering of people with schizophrenia, it is crucial to treat physical comorbidity promptly and assertively from the appearance of the first symptoms of psychotic disorder. The integrative approach and collaborative care within all levels of healthcare providers should be the imperative in clinical practice.

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### Contribution of individual authors:

Ivona Šimunović Filipčić & Igor Filipčić equally contributed to the conception of this manuscript, the literature search, and participated in drafting and revising the article critically.

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Correspondence:

Ivona Šimunović Filipčić, MD  
Department of Psychological Medicine, University Hospital Center Zagreb  
Kišpatićeva 12, HR 10 000 Zagreb, Croatia  
E-mail: ivonasf@gmail.com