HHS Public Access

Author manuscript

Acta Psychiatr Scand. Author manuscript; available in PMC 2015 April 08.

Published in final edited form as:

Acta Psychiatr Scand. 2015 January ; 131(1): 18–20. doi:10.1111/acps.12309.

The thrifty psychiatric phenotype

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Van Ockenburg and colleagues (1) assessed the correlation between adverse life events and physiological status in a large population-based cohort, as psychosocial stress might correlate with adverse health outcomes. Although diverse methodological aspects were clinically considered (for instance, psychiatric conditions such as depressive symptoms, or diverse pharmacological treatments), their conclusions reflected no association with the stress-responsiveness conditions studied.

Nevertheless, it raised the issue of early programming in modern physiology and its translational relevance to psychiatry.

Current literature in developmental biology suggests that environmental factors acting early in life have consequences which become manifest as an altered disease risk in adulthood. This early programming research has mainly focused in the pathways that predict medical illnesses later in life such as adult cardiovascular diseases (CVD) and type 2 diabetes mellitus (T2DM). However, adverse developmental events can also affect the brain maturation, leading to impaired cognitive function and poor mental health (2).

Patients suffering from serious mental illnesses (SMI) exhibit a reduced average life span. An increased suicide rate, poor health habits, and limited access to medical care all contribute to the excess risk. However, the leading cause are medical-related diseases (3) such as the metabolic syndrome and other chronic pathologies, specially T2DM, atherosclerosis, and CVD.

Declaration of interest: Drs. Garcia-Rizo and Fernandez-Egea have nothing to disclose. Dr. Bernardo received consultant fees from Bristol-Meyer-Squibb and Wyeth, and honoraria from Janssen-Cilag, Eli Lilly, Pfizer, Synthelab, Glaxo Smith Kline and Astra-Zeneca. Dr. Kirkpatrick received consulting fees from Roche, Genentech, and he has financial relationship with Prophase, Inc.

The current state of evidence suggests that previous medical diseases are related not only to genetic and adult lifestyle factors but also to environmental factors acting early in life. This fetal origin of disease concept was initially described by Barker and Hales (4) and is referred to as the ‘thrifty phenotype hypothesis’. The concept relies on the fact that adverse gestational events (infections, placenta dysfunction, maternal stress, or malnourishment) interact with genetic factors and program the fetus to thrive in an environment in adult life that is characterized by poor nutrition. This developmental trade-off promotes early survival, through permanent changes (for instance, in glucose-insulin metabolism), but in an affluent society, those changes will lead to the development of T2DM and CVD. Later, epidemiological studies have shown that not only prenatal, but also postnatal factors can modify the early programming, setting up the present concept of ‘developmental origins of health and disease’ (DOHaD) (2).

Extensive research has focused on its pathophysiology; studies of the Dutch Hunger Winter and the 1959–1961 Chinese famine found that individuals exposed in utero during the famine had low birth weight and developed impaired glucose tolerance, suggesting glucose–insulin abnormalities (5) with different patterns depending on the stage of gestation when the fetus was affected by famine. Individuals exposed to these famines not only suffered from higher ratio of medical conditions but also had an increased risk of developing schizophrenia (6) and major affective disorders (7). Interestingly, besides the genetic risk of familiar inheritance, the most important known factor for SMI, obstetric complications account for an important risk of developing SMI over time.

With the previous rationale, we aim to defend the hypothesis that part of the increased prevalence of medical diseases in SMI, and consequent morbidity and mortality, is directly explained by the DOHaD model. Abnormal intrauterine and early postnatal growth, due to environmental disturbances, increase the risk of both metabolic abnormalities and SMI. We will focus on three SMI diagnoses, schizophrenia, major depressive disorder, and bipolar disorder, being the most prevalent and studied.

Patients with schizophrenia exhibit an increased risk of obstetric complications, with maternal diabetes and low birth weight conferring a large and medium effect size respectively (8). Diverse environmental factors, both prenatal (infections, hypertension during pregnancy, and placental abnormalities) (9) and postnatal (10) increase the risk of psychosis. Patients diagnosed with schizophrenia exhibit a reduced life expectancy, mainly due to an increased prevalence of diseases and medical conditions (11). In between those, T2DM has been historically related to schizophrenia; Sir Henry Maudsley stated in his book ‘The Pathology of Mind’ (1879) that ‘diabetes is a disease that often shows itself in families where insanity prevails’. Since Maudsley, several other contemporary authors (12) delved deeper into the association with diverse methodological difficulties till the appearance of the studies in naïve first episode psychosis, which avoided the confounding factor of pharmacological treatment. Those studies described abnormal glucose metabolism (higher fasting glucose values and an insulin resistant state) (13); however, higher cortisol values might have biased the results. Nevertheless, the physiological challenge of an oral glucose tolerance test did confirm the underlying glucose disturbances (14), suggesting an abnormal

glucose homeostasis in individuals quite young to be affected by regular risk factors associated with mental health (unhealthy habits, obesity, and sedentary lifestyle) (15).

Patients with major affective disorders have repeatedly been associated with obstetric difficulties, specially stressful events during the second and third trimester (7). Some data even suggest that an earlier onset of affective disorder is directly associated with obstetric abnormalities (16). A review of obstetric complications in bipolar disorder did not find any robust conclusion (17); however, methodological inadequacies might have biased the conclusions; irrespective a critical review of those studies does suggest an unexpected relationship with bipolar disorder.

Depression will be the second contributor to the global burden of disease by 2020 according to the World Health Organization, due not only to psychiatric disability but also to the associated comorbidity with physical diseases (18). As early as the 17th century, Thomas Willis, the physician who described glycosuria as a sign of diabetes, stated that it was caused by ‘sadness or long sorrow and other depressions’ (19). Later, epidemiological studies confirmed the relationship between T2DM and major depression disorder, even suggesting a directionality from depression toward the onset of T2DM (20) in young patients. Studies in naïve population affected from major depression disorder have shown several metabolic disturbances, including an abnormal glucose metabolism state (21).

The interest of research with respect to CVD, T2DM, and metabolic disturbances in manic-depressive illness began with a seminal study by Derby in 1933 (22). Increased morbidity and mortality in bipolar disorder has been justified mainly due to an increase ratio of medical-related pathologies (18). In between those, glycemic abnormalities are a consistent finding, recalling pre-antipsychotic studies that highlighted an unexpected relationship between manic-depressive illness and glucose metabolism (12). Although to date, we have conducted the only one study in drug-naïve bipolar subjects, describing glucose abnormalities through an increased 2-h glucose load (23). Indeed, altered glucose homeostasis (insulin dysfunction) has been theorized as the reason of the increased amount of medical comorbidities found in bipolar disorder (24).

The available research data in SMI suggest that part of the relationship between these neuropsychiatric disorders and metabolic abnormalities might be explained by the DOHaD model. We have focused in the glucose-insulin metabolism as it was the initial pathway studied. Glycemic abnormalities have been described to have a familial background besides being associated with factors such as obesity and sedentary lifestyle. However, studies in young naïve psychiatric patients, well matched with regard to body mass index and other potentially confounding factors (14, 21, 23), may suggest that their impaired glucose tolerance is related to the same early environmental factors that led to their psychiatric disorder.

Although the ‘thrifty phenotype hypothesis’ is one of the several models proposed to explain the mechanism of the early programming of diverse medical conditions, we have adopted its name, first as a tribute to the seminal work of Barker and Hales (4) and second as a comprehensive explanation of the idea. The ‘thrifty psychiatric phenotype’ concept does not

aim to explain all the relationship between these neuropsychiatric disorders and their medical comorbidity and mortality. However, it does lend itself to specific hypothesis testing. For instance, other major psychiatric disorders, such as obsessive–compulsive disorder or autism spectrum disorders have been described to present an increased prevalence of medical conditions. Are these also related to adverse early events?

SMI, from a metabolic point of view, might represent a selection bias of patients who, after known or unknown early life stressors, develop cardiovascular and metabolic related pathologies (3) with a later augmented risk due to pharmacological treatments (antipsychotics, mood stabilizers, and antidepressants). The psychiatric diagnose would be the factor that makes us, clinicians, conduct a complete metabolic assessment (biochemical and anthropometric) and alerts us of the increased risk of cardiovascular events.

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