Psychotic disorders, including schizophrenia, affect about 3% of the general population and are ranked among most important causes of disability worldwide. Interestingly, there are several biological alterations associated with psychotic disorders that can be found outside the central nervous system and might be related to symptomatic manifestation. For instance, it has been shown that subclinical inflammation, manifesting in elevated levels of various pro-inflammatory markers in the peripheral blood (cytokines, acute phase proteins or specific and non-specific antibodies) that remain in healthy ranges, occurs in patients with psychosis at various stages of illness. Similarly, patients with psychotic disorders, including unmedicated individuals, often present with low-grade metabolic disturbances in terms of slightly elevated levels of homocysteine, glucose, insulin or lipid profile alterations. Recently, it has also been shown that these alterations might be more robust in patients with the deficit schizophrenia subtype that captures individuals with persistent negative symptoms, such as blunting of emotional expression, apathy or social withdrawal. The exact mechanisms, underlying these observations, remain unknown. Several studies have found that a history of childhood traumatic events, including physical, emotional or sexual abuse might be strongly associated with inflammation and metabolic disturbances in patients with psychotic disorders. Emerging evidence indicates that the gut microbial environment might differ between individuals with psychotic disorders and healthy controls. These alterations of the gut microbial environment might compromise intestinal permeability and thus influence immune responses and metabolism. Moreover, there are numerous mechanisms by which gut microbiota and subsequent intestinal permeability might impact the brain functioning. Researchers have even captured these interactions as the gut-brain axis. However, studies investigating gut microbiota and intestinal permeability in psychosis are characterized by a number of methodological limitations and have not attempted to establish associations with certain environmental factors, such as traumatic life events, sedentary lifestyle or dietary habits. In addition, it has not been investigated whether deficit schizophrenia is associated with more pronounced alterations of the gut microbiota and intestinal permeability. Therefore, the project is based on the following objectives: 1) to investigate gut microbial diversity in patients with first-episode psychosis (FEP) and stable schizophrenia patients compared to healthy controls; 2) to explore gut permeability in patients with FEP patients and stable schizophrenia patients compared to healthy controls; 3) to investigate the associations between microbial gut diversity, gut permeability, subclinical inflammation and metabolic dysregulation in FEP and stable schizophrenia patients; 4) to examine the relationship between gut microbiota, gut permeability and symptoms of psychosis; 5) to investigate the association between stress throughout the lifespan, gut microbiota and permeability in patients with schizophrenia; 6) to test the hypothesis that deficit schizophrenia subtype might be associated with more robust alterations in gut microbiota and permeability and 7) to explore dynamics of gut microbiota diversity and ‘leaky gut’ markers in the course of pharmacological treatment.

In this project, 120 stable schizophrenia patients, 40 FEP patients and 160 healthy controls with a negative family history of psychotic and affective disorders, matched for age, sex and parental education as a measure of sociodemographic status will be recruited. Clinical assessment and sampling of biological material (peripheral blood serum and faecal samples) will be performed at baseline and after 24 weeks of antipsychotic treatment (the second assessment in case of FEP patients). Faecal samples will be obtained to examine gut microbial diversity, markers of intestinal permeability and inflammation (zonulin and calprotectin). Fasting levels of glucose, insulin, low- and high-density lipoproteins (LDL and HDL), total cholesterol and triglycerides, as well as pro-inflammatory markers, including interleukin-6 (IL-6), tumour necrosis factor-α (TNF-α) and interferon-γ (IFN-γ) will be determined in serum samples. Clinical assessment will include psychiatric examination (to record a severity of clinical symptoms), psychological assessment (to measure performance of attention, memory, language skills or visuospatial/constructional abilities) and self-report questionnaires regarding a history of stressful and traumatic events as well as stress coping strategies. Validated questionnaires will be also used to evaluate physical activity and dietary habits. Stable schizophrenia patients will be evaluated in terms of meeting the criteria of the deficit schizophrenia subtype.

Results of this project will provide insights into the mechanisms of subclinical inflammation and metabolic disturbances in patients with schizophrenia-spectrum disorders. Moreover, the project might contribute to develop novel treatment strategies that will ameliorate metabolic adversity of antipsychotic drugs and improve clinical outcomes in patients with schizophrenia-spectrum disorders.