M20. CYTOKINE LEVELS THROUGHOUT PREGNANCY AND RISK FOR PSYCHOSIS IN ADULT OFFSPRING: EARLY PREGNANCY MATTERS

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Background: Schizophrenia has been associated with pregnancy and birth complications, and fetal exposure to inflammation is thought to be a common underlying mechanism. However, it is unclear whether the risk associated with inflammation is specific to particular phases of pregnancy, as no prior studies have examined maternal serum samples across multiple assessments from the first trimester onward. This study examined differences in longitudinal patterns of maternal serum levels of TNFα, IL-1β, IL-5, IL-6, IL-8, IL-10, and IL-17a across pregnancy for offspring who were later ascertained as having a psychotic disorder diagnosis, non-psychotic siblings of these cases, and unrelated, non-psychotic individuals who served as controls.

Methods: Participants included 90 offspring, 79 siblings, and 273 matched controls from the Philadelphia cohort of the National Collaborative Perinatal Project. Psychotic disorder diagnoses in adulthood were assessed with review of medical records and were confirmed with a validation study. Cytokine levels were assessed using a multiplex bead assay in archived maternal serum samples collected across prenatal visits and birth.

Results: Levels of pro-inflammatory TNFα, IL-1β, and IL-6 were significantly higher in maternal serum of offspring who later developed psychosis relative to maternal serum of non-psychotic siblings and matched controls. These differences were maximal in first half of pregnancy (7–20 weeks), tapering to non-significant during the second half of pregnancy.

Discussion: These findings elucidate the importance of exposure to elevated maternal pro-inflammatory cytokine levels in early pregnancy to the etiology of psychosis.

M21. THE STEP TRIAL: A SEQUENTIAL MULTIPLE ASSIGNMENT RANDOMISED TRIAL (SMART) OF INTERVENTIONS FOR PATIENTS AT ULTRA-HIGH RISK OF PSYCHOSIS - STUDY RATIONALE, DESIGN AND BASELINE DATA

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Background: Although approximately twenty randomised controlled trials have now been conducted with young people identified as being at high clinical risk of psychotic disorder, it remains unclear what the optimal type and sequence of treatments are for this clinical population. There has also been increased focus on clinical outcomes other than transition to psychotic disorder, such as psychosocial functioning, persistent attenuated psychotic symptoms and non-psychotic disorders. At Orygen, we are currently conducting a trial of a sequence of interventions consisting of two psychosocial therapies (support and problem solving [SPS] and cognitive-behavioural case management [CBCM]) and antidepressant medication.

The primary outcome of the study is functional outcome after 6 months. This presentation will outline the background, rationale, design, recruitment and retention data and preliminary baseline results.

Methods: STEP is a sequential multiple assignment randomised trial (SMART) of treatments for young people (12–25 year olds) who meet ultra high risk for psychosis (UHR) criteria. Participants were recruited from primary (headspace) and secondary/tertiary (Orygen Youth Health) mental health services in Melbourne, Australia. The trial consists of three steps: Step 1: SPS (1.5 months); Step 2: SPS vs Cognitive Behavioural Case Management (4.5 months); Step 3: Cognitive Behavioural Case Management + Antidepressant Medication vs Cognitive Behavioural Case Management + Placebo (6 months). Patients who do not respond by the end of each step graduate to the next step in treatment. Responders are randomised to SPS or monitoring. Treatment response is based a combination of reduced attenuated psychotic symptoms, rated using the Comprehensive Assessment of At-Risk Mental States (CAARMS), and functional improvement (Social and Occupational Functioning Assessment Scale [SOFAS]) at the end of the treatment step. A ‘fast fail’ option is built into Step 3, whereby patients who deteriorate or have not responded 3 months into Step 3 are offered a choice of continuing existing treatment or commencing omega-3 fatty acids or low-dose antipsychotic medication. The intervention is for 12 months, with follow up at 18 and 24 months. A pilot study using the same design is currently being conducted at The University of California Davis.

Results: Recruitment has recently completed, with 342 patients recruited over a 2.4 year period, representing the largest UHR treatment study conducted to date. Preliminary results indicate an 8% response rate to Step 1 and a 23% response rate to Step 2. Discontinuation rates are 15% (step 1), 43% (step 2), 32% (step 3), primarily due to participants being lost to follow-up or not wanting to start medication. The current transition to psychosis rate is 10.2%. Baseline clinical data are currently being analysed and will be presented at the conference.

Discussion: Preliminary results indicate high non-response rates following SPS and moderate non-response rates following extended SPS or CBCM, possibly partly due to the stringent definition of response, which required substantial and persistent improvement in both attenuated psychotic symptoms and functioning. Discontinuation rates are low to moderate, reflecting the complexity and severity of this clinical population. The recruitment and retention data show that it is possible to conduct large-scale and complex stepped care trials with this high risk population in a primary mental health care setting (headspace services). Outcomes will inform the most effective type and sequence of treatments for improving psychosocial functioning, symptoms and reducing risk of developing psychotic disorder in this group, as well as identify predictors of treatment response.

M22. IGG ANTIBODIES TO TOXOPLASMA GONDII ARE ASSOCIATED WITH INCREASED LONG-TERM RISK FOR PSYCHOSIS IN INDIVIDUALS AT ULTRA-HIGH RISK FOR PSYCHOSIS

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Background: The prevalence of antibodies to Toxoplasma gondii, a ubiquitous parasitic protozoan causing the infectious disease toxoplasmosis, is increased in patients with psychotic disorders compared to the general
population. We have previously shown that antibody titer for T. gondii correlate with the severity of positive symptoms in young people at ultra-high risk (UHR) for psychosis, suggesting that infection with T. gondii may be relevant to the manifestation of psychosis. However, it is unclear if T. gondii antibodies represent a risk factor for psychosis onset or non-psychotic outcome in UHR individuals. The aim of the present study was to examine whether seropositivity for T. gondii is associated with transition to psychosis and other outcomes in young people at UHR for psychosis.

**Methods:** The study sample consisted of 96 individuals at UHR for psychosis who were referred to the Personal Assistance and Crisis Evaluation (PACE) clinic in Melbourne, Australia, between 2001 and 2004, consented to optional blood tests for infected agents and were followed up for up to 10 years after baseline (median interquartile range duration of follow-up: 7.15 (3.14 – 7.72) years). Serum IgG antibodies to six viral and parasitic pathogens (Toxoplasma gondii, Herpes Simplex Virus Type 1 and 2, Cytomegalovirus, Epstein Barr Virus, Varicella-Zoster Virus) were measured at baseline. Outcome measures included transition to psychosis, general psychiatric symptomatology and positive psychotic symptoms (BPRS), negative symptoms (SANS), depressive symptoms (HAM-D), anxiety symptoms (HAM-A) and functioning (SOFAS and GAF). Cox proportional hazards regression and linear regression models were used to examine the associations of seropositivity and antibody titers at baseline and transition to psychosis and other outcomes at follow-up.

**Results:** A total of 17 individuals (17.7%) were seropositive for Toxoplasma gondii at baseline. The rate of transition to psychosis was higher among seropositive (35.7%) compared to seronegative participants (14.6%), although this was not statistically significant (p=0.101). Antibody titers (IgG) for Toxoplasma gondii were significantly higher at baseline in participants who later transitioned to psychosis (1.34 ± 1.36 vs. 0.79 ± 0.73, p=0.027). Seropositivity for T. gondii IgG at baseline significantly predicted transition to psychosis within the follow-up duration (hazard ratio [HR]=3.61, 95%CI 1.08 – 12.00, p=0.036). Toxoplasma IgG at baseline were significantly associated with higher BPRS scores at follow-up in participants who were seropositive at baseline (Beta=6.38, 95%CI 0.43 – 12.34, p=0.038). No significant associations were found between antibodies to other pathogens and outcome, or between antibodies to Toxoplasma gondii and any other outcomes.

**Discussion:** Our findings suggest that the presence of IgG class antibodies for Toxoplasma gondii is associated with a higher risk for psychosis transition in individuals at UHR for psychosis, but not with risk for other long-term outcomes. These observations provide support for the hypothesis that infection with Toxoplasma gondii may be an environmental risk factor for psychosis and suggest that IgG antibodies for Toxoplasma gondii in individuals at UHR for psychosis have prognostic relevance.