Cytokines, Oxidative Stress and Cellular Markers of Inflammation in Schizophrenia

Rachel Upthegrove[1, 2] and Golam M. Khandaker[3, 4]

[1] Institute for Mental Health, University of Birmingham, Birmingham, UK

[2] Birmingham Early Intervention Service, Birmingham Women's and Children's NHS Trust, UK

[3] Department of Psychiatry, University of Cambridge, Cambridge, UK

[4] Cambridgeshire and Peterborough NHS Foundation Trust, Cambridge, UK

Address for correspondence: Dr. Upthegrove, Institute for Mental Health, 52 Prichatts Rd Edgbaston Birmingham B152TT Email: r.upthegrove@bham.ac.uk

Abstract

In this article, we review current evidence linking immune dysfunction in schizophrenia and related psychotic disorders focusing particularly on circulating cytokines, oxidative stress and cellular markers of inflammation in various stages on illness from drug naïve first episode psychosis to chronic schizophrenia. Acute psychotic episode is associated with low-grade systemic inflammation in some patients, as reflected by increased concentrations of cytokines and other inflammatory markers in peripheral blood. Evidence from general population-based longitudinal cohort studies reporting an association between elevated inflammatory markers in childhood/adolescence and risk of schizophrenia and related psychosis subsequently in adulthood suggest that inflammation could be a causal risk factor for psychosis rather than simply be a consequence of illness. Mendelian randomization studies also suggest that associations between IL-6, CRP and schizophrenia are likely to be causal. In addition, we discuss evidence for disruptions in oxidative stress markers and CSF cytokine levels in schizophrenia, and potential reasons for reported trans-diagnostic associations for inflammatory cytokines including role of early-life adversity/maltreatment. We argue that low-grade inflammation is a clinically useful feature, because it is associated with poor response to antipsychotic medication in first episode psychosis. We discuss clinical implications for immunological understanding of schizophrenia including scope for clinical trials of anti-inflammatory agents, notable gaps in current knowledge, and offer suggestions for future research.

Introduction

Schizophrenia can be understood as a neurodevelopmental disorder [1, 2], with onset usually in early adulthood [3]. Biological research into the pathogenesis of schizophrenia has focused on brain structure, function and neurotransmitter abnormalities [4] and genetic risk [5]. However, there is also an accepted environmental impact, with a gene and environmental (GxE) combined effect related to increased risk, precipitation of illness and/or poorer outcomes. Notable environmental factors include childhood trauma, social and economic deprivation, minority status and stressful life events [6]. Increasing evidence suggests a role for the involvement of immunological processes in mediating the genetic and environmental risk for schizophrenia. Indeed, schizophrenia has been associated with an abnormal activation of the immune system for many years [7-9]. Previous reviews have summarised evidence linking schizophrenia with abnormalities in various components of the immune system; see [10, 11], but here, we focus primarily on the evidence on circulating inflammatory cytokines, oxidative stress and cellular markers of inflammation.

Cytokines as Key Mediators of Immune Response

Cytokines are the key signalling molecules that coordinate both innate and adaptive arms of the immune system and exert effects in the periphery and the brain. The immune response is a highly coordinated process involving an array of cell types that protect the body from harm while maintaining tolerance to self-antigens and beneficial organisms. The first arm is our "innate" defence mechanisms; older in evolutionary terms and considered to be a first line defence. Its cellular components include neutrophils, basophils and eosinophils, monocytes and macrophages, dendritic cells and natural killer (NK) cells, which recognise and promote defence against pathogens, but lack the sophistication to adapt compared to other more recent additions to the immune system [12]. The innate humoral component is made up of acute

phase proteins such as C Reactive Protein (CRP), cytokines such as interleukin 6 (IL-6), and the compliment cascade, which allow phagocytic cells to clear pathogens (see below).

The second arm of our immune system is the "adaptive" system, which acts on re-exposure to a known pathogen. The prime cellular components of the adaptive system include T and B lymphocytes. Antibodies produced by B lymphocytes comprise main humoral part of adaptive immunity. There is considerable "cross-talk" between the two major arms of the immune system. T cells comprise key components of the T Helper 1 (Th1) system and the T Helper 2 system (Th2). The Th1 system is polarised towards the production of pro inflammatory (activating) cytokines such as interleukin 2 (IL-2), interferon-γ (INF-γ), and tumour necrosis factor (TNFα). The Th2 system promotes the generation and maintenance of antibody-mediated immune responses as well as production of anti-inflammatory cytokines such as interleukin- 4 (IL-4), interleukin-10 (IL-10) and interleukin-13 (IL-13). However, cytokines often have pleotropic effect, as for example, IL-6 has both pro and anti-inflammatory properties. More recently, a key role for the Th17 system has been discovered, in regulation of immune response, so this system is important for pathogenesis of a number of immune-related disorders [13]. It is now understood that both innate and adaptive systems are able to form and retain memory, which influences immune response on re-exposure to a stimulus.

Changes in cytokines and their receptor levels have been reported in the blood and cerebrospinal fluid (CSF) of patients with schizophrenia [14] – see below. Previously, the brain was thought to be protected from peripheral inflammatory responses due to the blood-brain barrier (BBB). However, it is now clear that cytokines and other circulating inflammatory mediators can reach and influence the brain in a number of ways. Peripheral

immune-to-brain communication pathways include direct entry through leaky circumventricular areas in the BBB, the lymphatic system, infiltration of immune cells to brain, and retrograde axonal transport of immune signal via cranial nerves, for example, the Vagus nerve; for a review see [11]. Peripheral or systemic inflammation is therefore relevant for neuropsychiatric disorders such as schizophrenia.

Evidence for Cytokine Alteration in Different Stages of Schizophrenia

Here, we review the evidence for aberrant cytokines in peripheral blood and in CSF in patients with schizophrenia and related psychotic disorders. We also discuss evidence from epidemiological prospective cohort studies linking elevated inflammatory marker levels in childhood/adolescence with risk of psychosis subsequently in adulthood. There is notable heterogeneity in existing studies of inflammatory cytokines in schizophrenia as, for example, studies have used patients in different stages of illness. Levels of inflammatory markers could be influenced by neuroleptic and other drugs, alcohol and illicit drug use, sex, smoking, body mass index (BMI), and co-morbid physical illness [12]. Therefore, we have put particular emphasis on stage of illness and effects of potential confounders such as those listed above.

Drug Naïve Psychosis

Studies of medication naive patients are particularly useful to gain a better understanding of inflammatory cytokine alteration in schizophrenia. It is well known that antipsychotic medication can influence the immune system. Drzyga and colleagues carried out an *in vitro* study showing that antipsychotic drugs affect immune cell function, which often occurs very shortly after initial exposure to drug [15]. However, there are mixed results and differing effects, including either stimulatory or inhibitory actions. Relatedly, other *in vitro* studies suggest that suppression of cytokine mediated microglial activity may partly underpin the

efficacy of some antipsychotic drugs [16]. For example, aripiprazole suppresses apoptosis of rodent oligodendrocytes by IFN-γ-activated microglia, and inhibition of TNF-α secretion from IFN-γ-activated microglia [17]. Clozapine, the most effective antipsychotic medication, influences the immune system. Its effects on white blood cell (WBC) count is well known. The drug may have immediate [18] and longer term effects on IL-6, CRP [19] and high sensitivity CRP (hs-CRP) levels [20] in schizophrenia patients.

In a systematic review and meta-analysis published in 2014, we included 14 studies that together assessed levels of 20 different cytokines and cytokine receptors in 570 neuroleptic naive patients. The majority of these patients had a diagnosis of schizophrenia or schizophreniform disorder (81%). Highly significant effect sizes were seen for IL-1β, IL-6, sIL2r and TNFα, suggesting that an increase in these cytokines in first episode psychosis (FEP) patients, compared with controls, is unrelated to antipsychotic drugs (Figure 1). These cytokines play key roles in orchestrating innate immune response; IL-1β and TNF-α are responsible for stimulating IL-6 production, while IL-6 signals hepatocytes to produce acute phase proteins such as CRP. Some increase in levels of IL-2, IL-4, and IFN-γ were also seen, but differecnes in these cytokine levels were not statistically significant. These cytokines were measured in studies with small samples, and in fewer studies altogether leading to low statistical power.

More recently, a study by Noto *et al* reported that comorbid depression might influence cytokine levels in FEP patients. While increased levels of IL-6, IL-10 and TNFα were found in 55 FEP patients overall, compared with controls, patients with depression showed higher IL-4 and TNFα levels compared with those without depression [21].

Acute Psychosis

In an extensive meta-analysis published in 2011, Miller *et al* explored cytokine function by phase of illness in schizophrenia. Assessing 40 studies, they found IL-1β, IL-6 and TGF-β were raised in the acute phase of illness (both in relapse patients and in first episode psychosis), and reduced with successful treatment [22]. IL-6 correlated to total level of psychopathology in 2 out of 5 studies [22]. TNF-α and IL-6 levels were analysed in most studies (97 and 156 total studies respectively). It was proposed that these cytokines could be state dependant markers of inflammation, resolving with symptom reduction. However, elevated levels of IL-6 in childhood measured years before onset of psychosis is associated with psychotic symptoms in early-adulthood [23] (see below). Levels of IL-6 and TNF-α are also associated with childhood maltreatment [24], so these cytokines could also be trait markers for psychosis.

In first episode psychosis, Mondelli *et al* measured BDNF, IL-6 and TNF-α in 46 patients. Compared to healthy controls, patients had reduced BDNF gene expression, and increased IL-6 and TNF-α. History of childhood trauma was associated with lower BDNF mediated through IL-6 [25]. In a more recent review, Goldsmith *et al* investigated acute and chronic cytokine changes in schizophrenia, bipolar disorder and depression, which included 40 studies on acute schizophrenia [26]. In meta-analysis, IL-6, sIL2r, IL-1RA and TNFα were all significantly raised in acute schizophrenia, bipolar disorder and depression. There was more heterogeneity in FEP samples than acute relapse of established schizophrenia. No publication bias was reported for IL-6 [27]. These findings suggest that the association of increased inflammatory cytokines transcend traditional diagnostic boundaries; for a discussion on the trans-diagnostic effect of inflammation please see below.

Another meta-analysis reported elevated serum levels of CRP in FEP and chronic schizophrenia irrespective of medication status [28]. With regards to association with specific symptoms, an association between CRP levels and positive symptoms, but not negative symptoms of psychosis was found. However, Johnsen *et al* investigated CRP in acute psychosis, reporting a particular association with cognitive dysfunctions rather than positive symptoms [29]. Studies in healthy volunteers and non-human primates have reported association of inflammatory markers with anhedonia-like behaviour and reward alterations [30, 31]. So overall, patient and animal studies indicate an association of inflammatory markers with positive, negative and cognitive symptoms.

Chronic Schizophrenia

TNF-α, IL-12, INF-γ and sIL2r have been reported to be elevated in both acute illness and stable 'outpatients' with chronic schizophrenia. Goldsmith *et al* found that, compared with controls, the levels of IL-6 were significantly increased in chronic schizophrenia, euthymic (but not depressed) bipolar disorder and major depressive disorder [26]. IL-1β and sIL2R were significantly increased in chronic schizophrenia and euthymic bipolar disorder. TNF-α has been suggested as a trait marker of neuroinflammation [27]. Goldsmith *et al* review confirmed that TNF-α was raised in acute schizophrenia compared to controls and remained so after treatment.

In meta-analysis of 5 studies, Miller and Culpeper found that 28% of patients with chronic schizophrenia have an elevated CRP [32]. In a recent study of 295 patients with schizophrenia and 192 with bipolar disorder, CRP was elevated in the schizophrenia even after adjusting for age, gender, race, maternal education, smoking status, and BMI but this was not found in bipolar disorder [33]. The association between CRP levels and cognitive

functioning in patients with predominantly chronic schizophrenia has been reported in one cross-sectional study [34]. Together these studies suggest poorer cognitive function may be associated with enduring neuroinflammation.

Population-based Longitudinal and Mendelian Randomization Studies Examining Causality

Psychological stress can active innate immune response [35], so cytokine elevation during acute psychosis could be a consequence of illness rather than be its cause (i.e., reverse causality). Therefore, longitudinal studies are need to establish, or refute, a potentially causal role of inflammation in the pathogenesis of psychosis. Evidence from population-based longitudinal cohort studies from the UK, Finland and Sweden has linked higher levels of IL-6, CRP and Erythrocyte Sedimentation Rate (ESR) in childhood/adolescence with risk of psychotic symptoms or diagnosis of schizophrenia subsequently in adulthood [23, 36, 37]. Using data from the Avon Longitudinal Study of Parents and Children (ALSPAC), a general population-representative birth cohort, Khandaker *et al* have reported that higher levels of IL-6 in childhood at age 9 years is associated with increased risk of psychotic symptoms at early adulthood at age 18 years in a linear dose-response fashion [23] (Figure 2). Evidence for this association remained after controlling for sex, BMI, social class, ethnicity and childhood psychological and behavioural problems preceding the measurement of IL-6. Although in ALSPAC, CRP was not associated with psychosis risk, Khandaker and colleagues found that in the Northern Finland Birth Cohort (NFBC) 1986 higher levels of CRP in adolescence was associated with increased risk of hospitalisation with a diagnosis of schizophrenia subsequently in adulthood. Furthermore, there was evidence that higher CRP levels in adolescence was associated with earlier age at illness onset [37]. These findings are consistent with a Danish study reporting that higher CRP at baseline is associated with

increased risk of late- and very-late-onset schizophrenia subsequently at follow-up [38]. More recently, we have conducted a longitudinal study based on Swedish male conscripts which found that higher ESR, a marker of systemic inflammation, in early-adulthood is associated with increased risk of schizophrenia subsequently in adulthood [36].

Although previous longitudinal studies have controlled for key confounders such as sex, BMI, social class, residual confounding still might explain the association between inflammatory markers and psychosis. Recently, Khandaker and colleagues have used genetic association analysis informed by Mendelian randomization (MR) which indicates that residual confounding is unlikely to explain the association between IL-6 and psychosis fully. MR is based on the idea that if a biomarker is causally related to an illness, genetic variant(s) regulating levels/activity of that biomarker should also be associated with the illness [39]. Using data from the ALSPAC birth cohort, we have shown that a genetic variant in the IL-6 receptor gene (*IL6R* Asp358Ala; rs2228145) that is known to dampen down inflammation by impairing the activity of IL-6 is protective for severe depression and/or psychosis [40]. The genetic variant is strongly associated with serum IL-6 and CRP levels, but not with any common confounders of the inflammation-psychosis relationship such as sex, social class, ethnicity, and BMI. Genetic variants segregate at random during meiosis and are unrelated to sociodemographic and other confounders. Therefore, an association between psychosis and a genetic variant that regulates IL-6 activity strongly indicates that the IL-6/IL-6R pathways are causally linked to psychosis. Similarly, using MR analysis of psychiatric genomic consortium (PGC) data, Hartwig *et al* has reported that IL-6 and CRP are likely to be causally linked with schizophrenia [41].

Together these studies suggest that reverse causality or residual confounding are unlikely explanations for previously observed association between inflammatory markers, particularly IL-6, CRP, and psychosis. These associations are likely to be causal, so these biomarkers could be novel targets for intervention and prevention of psychotic disorders.

CSF Cytokine Alteration in Schizophrenia

Meta-analysis of studies of CSF from patients with schizophrenia suggests that levels of inflammatory cytokines are increased in patients with psychosis. A meta-analysis of 16 studies published in 2018 by Wang *et al* reported that CSF levels of IL-1β, IL-6 and IL-8 were significantly elevated in schizophrenia patients compared with controls [42]. Similar findings were also observed for depression. Whether levels of inflammatory markers in peripheral blood corresponds with neuroinflammaton is an important question. This meta-analysis also reported that many CSF alterations are also concordant with those in the peripheral blood, particularly for schizophrenia [42]. This provides some validity to the use of peripheral markers of inflammation in schizophrenia research. This finding is consistent with a study by Coughlin *et al* that measured IL-6 in the CSF of patients with recent onset schizophrenia also undergoing a positron emission tomography (PET) study of translocator protein 18k Da (TSPO), a marker of microglial activation using [^{11}C] DPA-713[43]. Whilst non-significant results were seen in the TSPO analysis, IL-6 levels was significantly raised in patients compared to controls. Furthermore, the study found IL-6 levels in the CSF correlated significantly with circulating IL-6.

Oxidative Stress Markers in Acute and Chronic Schizophrenia

First Episode Psychosis

Decreased levels of the anti-oxidant, glutathione (GSH), have been reported in patients with acute psychosis compared with controls [44, 45]. GSH is an antioxidant which provides within cell protection, and when depleted contributes to oxidative stress. Flatlow, Buckly and Miller reported a decrease in GSH in acutely relapsed patients with schizophrenia together with other anti-oxidants such as superoxide dismutase (SOD) and catalase (CAT), however there was significant heterogeneity in reported studies such that SOD and CAT but not GSH was reduced in FEP [46]. This may suggest a more persevered oxidative defense earlier in the course of illness.

As a substantial minority of patients with FEP do not go on to develop an enduring mental illness, and it may be that those with a protective oxidative defense to cellular stress have better outcomes [47]. This hypothesis remains to be tested. However Wang *et al* investigated cysteine, a semi-essential amino acid and a precursor of GSH glutathione, as a potential indicator of preserved cognitive function in FEP with some positive findings [48]. The functional consequences of increased oxidative stress or reduced defence against this oxidative stress in the brain are still to be fully understood. Changes in neuronal membrane permeability eventually leading to cell death could contribute to grey matter volume (GMV) loss seen in schizophrenia [49]. In respect to known neurochemical changes in psychosis, it has been proposed that oxidative stress results in over activation of NMDA and altered dopamine receptor function. Whilst schizophrenia is no longer understood within a simplistic conclusion of hyperdopaminergia, rather consisting of regionally specific prefrontal hypodopaminergia and subcortical hyperdopaminergia, the cumulative effect of overactive or more readily available dopamine may account for positive symptoms [50]. NMDA glutamate

receptors are downregulated by oxidation leading to disinhibition of pyramidal cells and unregulated glutamatergic excess [51].

Chronic Schizophrenia

There is substantial evidence of impaired oxidative defense in chronic schizophrenia, as reviewed by Flatlow *et al* in 2013 [46]. Negative symptoms have been associated with low levels of GSH, and positive symptoms have been positively correlated with SOD activity. A study by Fraguas *et al* assessed the relationship between GMV and GSH in the brains of patients with schizophrenia, with a progressive decline in GMV correlated to declining circulating GSH [52]. Thus, the deficit state of some patients with schizophrenia may be related to a specific lack of defence against oxidative stress.

There is a great deal of clinical and phenomenological commonality between schizophrenia and depression [53]. In schizophrenia, there is substantial glutamate dysfunction including clear evidence for Glx abnormality in brain areas such as the posterior medial prefrontal cortex (pmPFC). Increased Glx is seen in younger patients or more acute phases of illness, whereas reduced Glx has been reported in patients who are older and have residual negative symptoms [54]. Just as in schizophrenia, there is substantial evidence for increase in peripheral markers of inflammation in MDD. However, co-morbid depression doesn't solely account for increased inflammation in schizophrenia, as evidence for association persists after excluding or controlling for depression [55]. Nevertheless, it is possible that the presence of both psychosis and depression has a greater impact on immune dysfunction than the sum of each individually. Poorer clinical outcomes including increased risk of relapse, low quality of life and poor functional outcomes for patients with comorbid depression and schizophrenia supports this idea [56].

Early changes in neurochemicals such as Glx may result in more significant impact for those individuals with deficient defence against this inflammatory challenge [16]. The effect of inflammation includes the generation of reactive oxygen species such as superoxide, hydroxyl and peroxyl. The substantial evidence of impaired oxidative defense in early psychosis with diminished levels of GSH [44, 45, 57] show that the response of brain glutamate to inflammation and associated oxidative stress will also depend on the strength of defences against it. Thus, clinically poorer outcomes, such as seen with some subjects with depression and schizophrenia, may be related not just to the effect of chronic inflammation but also impaired defence against this.

Trans-diagnostic Effect of Inflammation and Potential Role of Early-Life Adversity

Studies of inflammatory markers in peripheral blood and CSF suggest that inflammation is associated with a number of psychiatric disorders including schizophrenia and related psychoses [10, 14, 42, 58, 59], depression [60, 61], anxiety [62], post-traumatic stress disorder (PTSD) [63], autism [64], Alzheimer's disease and other dementias [65]. However, possible reasons for this apparent trans-diagnostic association of inflammation are unknown. We have recently reported that the apparent trans-diagnostic effect may arise from association of inflammation with symptoms that are commonly shared between disorders [66]. Using a symptom-level data on 10 positive and 10 negative symptoms of psychosis assessed in adolescent participants from the from the ALSPAC birth cohort, we have shown at the at group level positive and negative symptom dimension scores were associated with serum CRP levels in a similar fashion. At individual symptom level, CRP was associated with particularly auditory hallucinations and anhedonia. Auditory hallucinations can occur in psychosis, depression and anxiety disorders [67]. Anhedonia is both an important negative symptom for psychosis and a core feature of depression [67].

Association between inflammation and anhedonia is supported by experimental studies. In non-human primates, chronic, low-dose peripheral interferon administration reduces striatal dopamine release in association with anhedonia-like behaviour [68]. In healthy volunteers, inflammation induces hedonic alterations (decreased preference for reward and increased avoidance of punishment) [30], which resemble anhedonia. Other reasons for this apparent trans-diagnostic effect could be shared genes that contributes to inflammation and risk of depression and schizophrenia. Genetic overlap between schizophrenia, bipolar disorder and depression is well established.

Shared risk factors, particularly early-life adversity, could be another explanation for the apparent trans-diagnostic effect of inflammation. Childhood abuse/maltreatment may program the immune system leading with increased concentrations inflammatory markers in adulthood [24], which in turn, may increase psychiatric risk. In the ALSPAC birth cohort, maternal parental depression is associated with higher levels of IL-6 and CRP in childhood and with higher risk of depression and psychosis in early-adulthood in offspring [69]. Furthermore, childhood IL-6 levels mediate the association between prenatal depression and offspring psychosis risk. These findings are consistent with the developmental programming hypothesis by David Barker, which posits that exposure to stress during critical period of development may program certain physiological system(s) leading to increased risk of chronic illnesses of adult life [70]. Early-life adversity is associated with coronary heart disease, type-two diabetes, which are common co-morbidities for schizophrenia and depression. Young adults with psychotic symptoms display evidence of dysglycaemia, which is linked with levels of IL-6 in childhood [71]. Therefore, whether programming of innate immune response by early-life adversity may explain the comorbidity between schizophrenia,

depression, coronary heart disease and type-two diabetes is an interesting hypothesis that needs investigating.

Therapeutic Implications for Low-grade Inflammation in Schizophrenia

Mondelli *et al* have reported an association between innate immune activation and poorer treatment response in 57 patients with FEP: non-responders (as defined by an absence of clinically significant symptom response in keep in with remission criteria at 12 weeks) had a significantly higher IL-6 and INF-γ at baseline. They also reported an aberrant cortisol wakening response and suggest this combination of markers may be an early signal of poor outcome [72]. Indeed, inflammatory mechanisms, as outlined above, have been cited as one of the potential mechanism of effect of Clozapine in treatment resistant schizophrenia.

As well as poor treatment response, makers of inflammation may indicate poorer physical health outcomes. Russell *et al* investigated 53 FEP patients and showed that FEP patients with raised CRP were at more risk of developing short-term metabolic abnormalities including dyslipidemia, independent of weight-gain [73]. As mentioned earlier, in the ALSPAC birth cohort young adults with psychotic symptoms displayed evidence of dysglycaemia, which was associated with childhood IL-6 levels [71]. Thus, the potential for stratifying treatment approach; early targeting of potential treatment resistance or heightened monitoring from adverse effects of antipsychotics shows some promise in a personalized approach to FEP and schizophrenia.

Because inflammation is associated with BMI, smoking, alcohol use, physical comorbidity, antipsychotic treatment and treatment induced weight gain, further work is needed to understand whether and how measuring inflammation in clinical setting could be useful for

predicting response to antidepressant/ antipsychotic treatment, and for identifying patients who are likely to benefit from immunomodulatory treatments.

Inflammation is unlikely to be relevant for illness pathogenesis in all patients with psychosis. For depression, clinical trials indicate that anti-inflammatory drugs may be helpful for patients who show evidence of inflammation [74, 75]. Existing RCTs of anti-inflammatory drugs for schizophrenia have yielded mixed results [76-78], possibly due to imprecise targeting of patients. Patients with psychosis who do show evidence of inflammation may be more suitable candidate for RCTs of anti-inflammatory drugs in future.

Conclusions and Future Directions

For a number of years now there have been considerable efforts to have a better understanding of the immunological and inflammatory aspects of schizophrenia, in the hope that this might lead to novel approaches to diagnosis and treatment. See text box for key clinical findings and questions for future research. Some aspects are becoming clearer. For example, accumulating evidence now confirms that inflammation could play a causal role in psychosis rather than being an epiphenomenon or result of treatment, other confounders or illness itself. An immunological understanding of schizophrenia could be clinically useful. Inflammation is associated with poor response to antipsychotics, co-morbid physical illness, such as type-two diabetes mellitus [79], and increased all-cause mortality [80]. Therefore, measuring inflammation levels (e.g., CRP test) as part of routine clinical assessment of psychosis could identify treatable causes of inflammation and potentially guide antipsychotic treatment decision. However, the “one size fits all” approach to drug therapy is unlikely to be effective for immune-therapies, so more personalised approach is needed.

A ley challenge for future is to determine precisely which patients are likely to benefit from anti-inflammatory therapies. This would require a consorted approach including immune target identification using genomic and other methods, deep immuno-phenotyping of psychosis patients to identify cellular source of inflammation, clinical studies to identify effect of inflammation on symptom dimensions, followed by experimental medicine and animal studies to examine the effects of novel immune-modulating agents on brain and behaviour. With regards to certain pathways where there is sufficient evidence for a causal association with schizophrenia, e.g., IL-6/IL-6R pathway, the field now needs experimental medicine studies based on selected patient groups to test whether targeting these pathways with immuno-modulating drugs improve clinical/clinically relevant outcome measures.

Another important avenue for future research would be to understand how inflammation influences developmental trajectories of neuropsychiatric symptoms, cognition or functional outcome over the life course. Population-based prospective studies and animal experiments would be useful for this purpose.

In summary, many of the major advances in our understanding of the links between immune system and schizophrenia suggest that immuno-psychiatry is a promising field, which could transform our understanding of illness pathogenesis and approaches to treatment and prevention for schizophrenia. To be successful, the field requires collaborative working among many experts including those from psychiatry, neuroscience, immunology, neurobiology, genomics, data science, epidemiology and clinical trial.

Abbreviations

BBB: Blood–brain barrier

CRP: C-reactive protein

TNF-α: Tumour necrosis factor alpha

IL6: Interleukin-6

IL-8: Interleukin 8

CNS: Central nervous system

MHC: Major histocompatibility complex

ALSPAC: Avon longitudinal study of parents and children

CSF: Cerebrospinal fluid

HPA: Hypothalamic-pituitary-adrenal

ROS: Reactive Oxygen Series

Glx: Gutamate/Glutamine ratio

GSH: Glutathione

FEP: First Episode Psychosis

Textbox

Key Clinical Findings

- Patients with schizophrenia show evidence of low-grade inflammation detectable in in peripheral blood.
- Inflammation appears to pre-date the onset of illness and be independent of medication treatment.
- Inflammation is associated with poor response to antipsychotic medication.

Key Clinical Questions

- What is the relationships between peripheral markers of inflammation and structural or functional brain changes?
- Which patients could benefit from anti-inflammatory therapies?
- Could measuring inflammation levels in clinical practice help better monitoring of psychiatric and physical health?

Acknowledgement

Dr Khandaker acknowledges funding support from the Wellcome Trust (201486/Z/16/Z), MQ: Transforming Mental Health (MQDS17/40), and MRC, UK (MC_PC_17213).

Declaration of Interest

The authors have no competing financial interests in relation to the work described.

References

1. Murray, R.M. and S.W. Lewis, *Is schizophrenia a neurodevelopmental disorder?* BMJ (Clinical Research Edition), 1987. **295**(6600): p. 681- 682.
2. Weinberger, D.R., *Implications of normal brain development for the pathogenesis of schizophrenia.* Arch Gen Psychiatry, 1987. **44**(7): p. 660-9.
3. Van Os, J., et al., *A systematic review and meta-analysis of the psychosis continuum: evidence for a psychosis proneness-persistence-impairment model of psychotic disorder.* Psychological medicine, 2009. **39**(2): p. 179.
4. Jones, A.L., et al., *Immune dysregulation and self-reactivity in schizophrenia: do some cases of schizophrenia have an autoimmune basis?* Immunology and Cell biology, 2005. **83**(1): p. 9-17.
5. Consortium, S.P.G.-W.A.S., *Genome-wide association study identifies five new schizophrenia loci.* Nature genetics, 2011. **43**(10): p. 969-976.
6. van Os, J., G. Kenis, and B.P. Rutten, *The environment and schizophrenia.* Nature, 2010. **468**(7321): p. 203-212.
7. Dameshek, W., *White blood cells in dementia praecox and dementia paralytica.* Arch Neurol Psychiatry, 1930. **24**: p. 855.
8. Müller, N., et al., *Impaired monocyte activation in schizophrenia.* Psychiatry Research, (0).
9. Ganguli, R., et al., *Serum interleukin-6 concentration in schizophrenia: elevation associated with duration of illness.* Psychiatry Res, 1994. **51**(1): p. 1-10.
10. Khandaker, G.M., et al., *Inflammation and immunity in schizophrenia: implications for pathophysiology and treatment.* The Lancet Psychiatry, 2015. **2**(3): p. 258-270.
11. Khandaker, G.M. and R. Dantzer, *Is there a role for immune-to-brain communication in schizophrenia?* Psychopharmacology (Berl), 2016. **233**(9): p. 1559-73.

12. Upthegrove, R. and N.M. Barnes, *The immune system and schizophrenia: an update for clinicians.* Advances in Psychiatric Treatment, 2014. **20**(2): p. 83-91.

13. Janeway, C.A., et al., *Immunobiology: The Immune System in Health and Disease*. 5th ed. 2001, New York: Garland Science.

14. Upthegrove, R., N. Manzanares-Teson, and N.M. Barnes, *Cytokine function in medication-naive first episode psychosis: a systematic review and meta-analysis.* Schizophrenia research, 2014. **155**(1-3): p. 101-108.

15. Drzyzga, Ł., et al., *Cytokines in schizophrenia and the effects of antipsychotic drugs.* Brain, behavior, and immunity, 2006. **20**(6): p. 532-545.

16. Bian, Q., et al., *The effect of atypical antipsychotics, perospirone, ziprasidone and quetiapine on microglial activation induced by interferon-γ.* Progress in Neuro-Psychopharmacology and Biological Psychiatry, 2008. **32**(1): p. 42-48.

17. Seki, Y., et al., *Pretreatment of aripiprazole and minocycline, but not haloperidol, suppresses oligodendrocyte damage from interferon-gamma-stimulated microglia in co-culture model.* Schizophr Res, 2013. **151**(1-3): p. 20-8.

18. Røge, R., et al., *Immunomodulatory effects of clozapine and their clinical implications: what have we learned so far?* Schizophrenia research, 2012. **140**(1): p. 204-213.

19. Kluge, M., et al., *Effects of clozapine and olanzapine on cytokine systems are closely linked to weight gain and drug-induced fever.* Psychoneuroendocrinology, 2009. **34**(1): p. 118-128.

20. Löffler, S., et al., *Clozapine therapy raises serum concentrations of high sensitive C-reactive protein in schizophrenic patients.* International clinical psychopharmacology, 2010. **25**(2): p. 101-106.

21. Noto, C., et al., *Effects of depression on the cytokine profile in drug naive first-episode psychosis.* Schizophrenia research, 2015. **164**(1): p. 53-58.

22. Miller, B.J., et al., *Meta-Analysis of Cytokine Alterations in Schizophrenia: Clinical Status and Antipsychotic Effects.* Biological Psychiatry, 2011. **70**(7): p. 663-671.

23. Khandaker, G.M., et al., *Association of serum interleukin 6 and C-reactive protein in childhood with depression and psychosis in young adult life: a population-based longitudinal study.* JAMA Psychiatry, 2014. **71**(10): p. 1121-8.

24. Baumeister, D., et al., *Childhood trauma and adulthood inflammation: a meta-analysis of peripheral C-reactive protein, interleukin-6 and tumour necrosis factor-alpha.* Mol Psychiatry, 2016. **21**(5): p. 642-9.

25. Mondelli, V., et al., *Cortisol and Inflammatory Biomarkers Predict Poor Treatment Response in First Episode Psychosis.* Schizophrenia Bulletin, 2015. **41**(5): p. 1162-1170.

26. Goldsmith, D.R., M.H. Rapaport, and B.J. Miller, *A meta-analysis of blood cytokine network alterations in psychiatric patients: comparisons between schizophrenia, bipolar disorder and depression.* Mol Psychiatry, 2016. **21**(12): p. 1696-1709.

27. Goldsmith, D., M. Rapaport, and B. Miller, *A meta-analysis of blood cytokine network alterations in psychiatric patients: comparisons between schizophrenia, bipolar disorder and depression.* Molecular psychiatry, 2016. **21**(12): p. 1696-1709.

28. Fernandes, B., et al., *C-reactive protein is increased in schizophrenia but is not altered by antipsychotics: meta-analysis and implications.* Molecular psychiatry, 2016. **21**(4): p. 554-564.

29. Johnsen, E., et al., *The serum level of C-reactive protein (CRP) is associated with cognitive performance in acute phase psychosis.* BMC psychiatry, 2016. **16**(1): p. 60.

30. Harrison, N.A., et al., *A Neurocomputational Account of How Inflammation Enhances Sensitivity to Punishments Versus Rewards.* Biol Psychiatry, 2016. **80**(1): p. 73-81.

31. Capuron, L., et al., *Dopaminergic mechanisms of reduced basal ganglia responses to hedonic reward during interferon alfa administration.* Arch Gen Psychiatry, 2012. **69**(10): p. 1044-53.

32. Miller, B.J., N. Culpepper, and M.H. Rapaport, *C-reactive protein levels in schizophrenia: a review and meta-analysis.* Clinical schizophrenia & related psychoses, 2013. **7**(4): p. 223-230.

33. Dickerson, F., et al., *C-reactive protein is elevated in schizophrenia.* Schizophrenia research, 2013. **143**(1): p. 198-202.

34. Dickerson, F., et al., *C-reactive protein is associated with the severity of cognitive impairment but not of psychiatric symptoms in individuals with schizophrenia.* Schizophrenia research, 2007. **93**(1): p. 261-265.

35. Maes, M., et al., *The effects of psychological stress on humans: increased production of pro-inflammatory cytokines and a Th1-like response in stress-induced anxiety.* Cytokine, 1998. **10**(4): p. 313-8.

36. Kappelmann, N., et al., *Systemic inflammation and intelligence in early adulthood and subsequent risk of schizophrenia and other non-affective psychoses: a longitudinal cohort and co-relative study.* Psychol Med, 2018: p. 1-8.

37. Metcalf, S.A., et al., *Serum C-reactive protein in adolescence and risk of schizophrenia in adulthood: A prospective birth cohort study.* Brain Behav Immun, 2017. **59**: p. 253-259.

38. Wium-Andersen, M.K., D.D. Orsted, and B.G. Nordestgaard, *Elevated C-reactive protein associated with late- and very-late-onset schizophrenia in the general population: a prospective study.* Schizophr Bull, 2014. **40**(5): p. 1117-27.

39. Davey Smith, G. and S. Ebrahim, *'Mendelian randomization': can genetic epidemiology contribute to understanding environmental determinants of disease?* Int J Epidemiol, 2003. **32**(1): p. 1-22.

40. Khandaker, G.M., et al., *Association between a functional interleukin 6 receptor genetic variant and risk of depression and psychosis in a population-based birth cohort.* Brain Behav Immun, 2018. **69**: p. 264-272.

41. Hartwig, F.P., et al., *Inflammatory Biomarkers and Risk of Schizophrenia: A 2-Sample Mendelian Randomization Study.* JAMA Psychiatry, 2017. **74**(12): p. 1226-1233.

42. Wang, A.K. and B.J. Miller, *Meta-analysis of Cerebrospinal Fluid Cytokine and Tryptophan Catabolite Alterations in Psychiatric Patients: Comparisons Between Schizophrenia, Bipolar Disorder, and Depression.* Schizophr Bull, 2018. **44**(1): p. 75-83.

43. Coughlin, J., et al., *In vivo markers of inflammatory response in recent-onset schizophrenia: a combined study using [11 C] DPA-713 PET and analysis of CSF and plasma.* Translational psychiatry, 2016. **6**(4): p. e777.

44. Wood, S.J., et al., *Neurobiology of schizophrenia spectrum disorders: the role of oxidative stress.* Ann Acad Med Singapore, 2009. **38**(5): p. 396-401.

45. Raffa, M., et al., *Decreased glutathione levels and impaired antioxidant enzyme activities in drug-naive first-episode schizophrenic patients.* BMC psychiatry, 2011. **11**(1): p. 1.

46. Flatow, J., P. Buckley, and B.J. Miller, *Meta-analysis of oxidative stress in schizophrenia.* Biological psychiatry, 2013. **74**(6): p. 400-409.

47. Lally, J., et al., *Remission and recovery from first-episode psychosis in adults: systematic review and meta-analysis of long-term outcome studies.* The British Journal of Psychiatry, 2017: p. bjp. bp. 117.201475.

48. Wang, L.-J., et al., *Increased serum levels of cysteine in patients with schizophrenia: A potential marker of cognitive function preservation.* Schizophrenia Research, 2017.

49. Mahadik, S.P. and S. Mukherjee, *Free radical pathology and antioxidant defense in schizophrenia: a review.* Schizophrenia research, 1996. **19**(1): p. 1-17.

50. Howes, O.D. and S. Kapur, *The dopamine hypothesis of schizophrenia: version III—the final common pathway.* Schizophrenia bulletin, 2009. **35**(3): p. 549-562.

51. Traynelis, S.F., et al., *Glutamate receptor ion channels: structure, regulation, and function.* Pharmacological reviews, 2010. **62**(3): p. 405-496.

52. Fraguas, D., et al., *Decreased glutathione levels predict loss of brain volume in children and adolescents with first-episode psychosis in a two-year longitudinal study.* Schizophrenia research, 2012. **137**(1): p. 58-65.

53. Upthegrove, R.M., S; Birchwood, Max, *Depression and schizophrenia: cause, consequence or trans-diagnostic issue?* Schizophrenia Bulletin, 2016. **online ahead of print**.

54. Marsman, A., et al., *Glutamate in schizophrenia: a focused review and meta-analysis of 1H-MRS studies.* Schizophrenia bulletin, 2013. **39**(1): p. 120-129.

55. Khandaker, G.M., R. Dantzer, and P.B. Jones, *Immunopsychiatry: important facts.* Psychological medicine, 2017. **47**(13): p. 2229-2237.

56. McGinty, J., M.S. Haque, and R. Upthegrove, *Depression during first episode psychosis and subsequent suicide risk: A systematic review and meta-analysis of longitudinal studies.* Schizophrenia research, 2017.

57. Jiménez-Fernández, S., et al., *Oxidative stress and antioxidant parameters in patients with major depressive disorder compared to healthy controls before and after antidepressant treatment: results from a meta-analysis.* The Journal of clinical psychiatry, 2015. **76**(12): p. 1658-1667.

58. Miller, B.J., et al., *Meta-analysis of cytokine alterations in schizophrenia: clinical status and antipsychotic effects.* Biol Psychiatry, 2011. **70**(7): p. 663-71.

59. Upthegrove, R., N. Manzanares-Teson, and N.M. Barnes, *Cytokine function in medication-naive first episode psychosis: a systematic review and meta-analysis.* Schizophr Res, 2014. **155**(1-3): p. 101-8.

60. Dantzer, R., et al., *From inflammation to sickness and depression: when the immune system subjugates the brain.* Nat Rev Neurosci, 2008. **9**(1): p. 46-56.

61. Miller, A.H., V. Maletic, and C.L. Raison, *Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression.* Biol Psychiatry, 2009. **65**(9): p. 732-41.

62. Wohleb, E.S., et al., *Re-establishment of anxiety in stress-sensitized mice is caused by monocyte trafficking from the spleen to the brain.* Biol Psychiatry, 2014. **75**(12): p. 970-81.

63. Eraly, S.A., et al., *Assessment of plasma C-reactive protein as a biomarker of posttraumatic stress disorder risk.* JAMA Psychiatry, 2014. **71**(4): p. 423-31.

64. Brown, A.S., et al., *Elevated maternal C-reactive protein and autism in a national birth cohort.* Mol Psychiatry, 2014. **19**(2): p. 259-64.

65. Schmidt, R., et al., *Early inflammation and dementia: a 25-year follow-up of the Honolulu-Asia Aging Study.* Ann Neurol, 2002. **52**(2): p. 168-74.

66. Khandaker, G.M., et al., *Positive and Negative Symptoms of Psychosis Associated with Circulating C-Reactive Protein: Unravelling Trans-diagnostic Effect of Inflammation* (under review), 2018.

67. APA, *Diagnostic and statistical manual of mental disorders (5th ed.)*, 2013, American Psychiatric Publishing: Arlington, VA.

68. Felger, J.C., et al., *Chronic interferon-alpha decreases dopamine 2 receptor binding and striatal dopamine release in association with anhedonia-like behavior in nonhuman primates.* Neuropsychopharmacology, 2013. **38**(11): p. 2179-87.

69. Khandaker, G.M., et al., *Influence of Prenatal Maternal Depression on Circulating Inflammatory Markers and Risks of Depression and Psychosis in Offspring: a prospective birth cohort study.* Psychoneuroendocrinology, 2018 (in press).

70. Barker, D.J.P., *Fetal and Infant Origins of Adult Disease*. 1993, London: British Medical Journal.

71. Perry, B.I., et al., *Dysglycaemia, Inflammation and Psychosis: Findings From the UK ALSPAC Birth Cohort.* Schizophr Bull, 2018.

72. Mondelli, V., et al., *Cortisol and inflammatory biomarkers predict poor treatment response in first episode psychosis.* Schizophrenia bulletin, 2015. **41**(5): p. 1162-1170.

73. Russell, A., et al., *Inflammation and metabolic changes in first episode psychosis: preliminary results from a longitudinal study.* Brain, behavior, and immunity, 2015. **49**: p. 25-29.

74. Raison, C.L., et al., *A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: the role of baseline inflammatory biomarkers.* JAMA Psychiatry, 2013. **70**(1): p. 31-41.

75. Kappelmann, N., et al., *Antidepressant activity of anti-cytokine treatment: a systematic review and meta-analysis of clinical trials of chronic inflammatory conditions.* Mol Psychiatry, 2018. **23**(2): p. 335-343.

76. Deakin, B., et al., *The benefit of minocycline on negative symptoms of schizophrenia in patients with recent-onset psychosis (BeneMin): a randomised, double-blind, placebo-controlled trial.* The Lancet Psychiatry, 2018. **5**(11): p. 885-894.

77. Girgis, R.R., et al., *A Randomized, Double-Blind, Placebo-Controlled Clinical Trial of Tocilizumab, An Interleukin-6 Receptor Antibody, For Residual Symptoms in Schizophrenia.* Neuropsychopharmacology, 2018. **43**(6): p. 1317-1323.

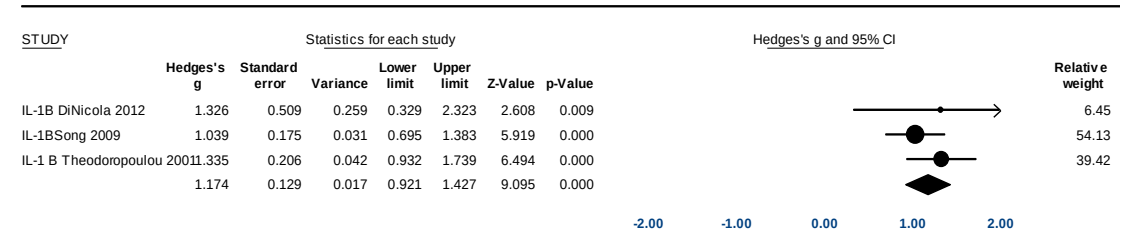
78. Miller, B.J., et al., *An open-label, pilot trial of adjunctive tocilizumab in schizophrenia.* J Clin Psychiatry, 2016. **77**(2): p. 275-6.

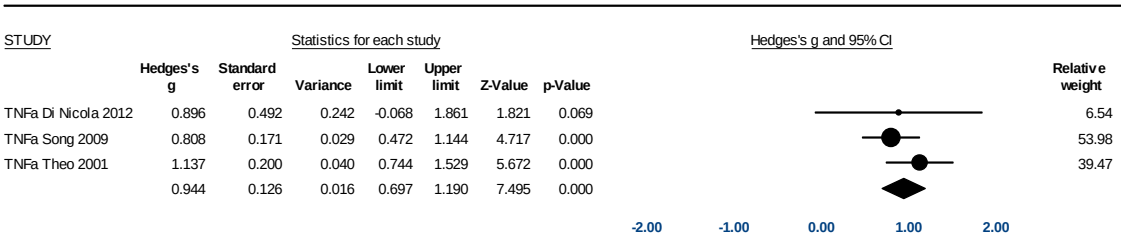
79. Pradhan, A.D., et al., *C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus.* JAMA, 2001. **286**(3): p. 327-34.

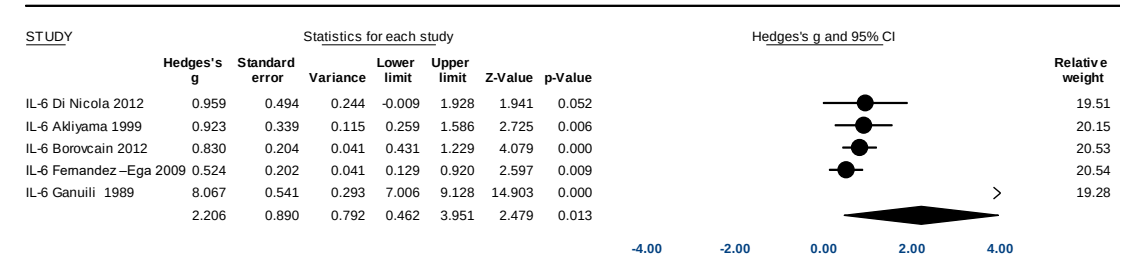
80. Zacho, J., A. Tybjaerg-Hansen, and B.G. Nordestgaard, *C-reactive protein and all-cause mortality--the Copenhagen City Heart Study.* Eur Heart J, 2010. **31**(13): p. 1624-32.

Figure 1: Cytokine Profile in Medication Naive First Episode Psychosis: patients have higher IL-1β, TNF-α, IL-6 and sIL-2r levels compared with controls

Modified from Upthegrove *et al*. *Schizophrenia Research.* 2014 May;155(1-3):101-8.







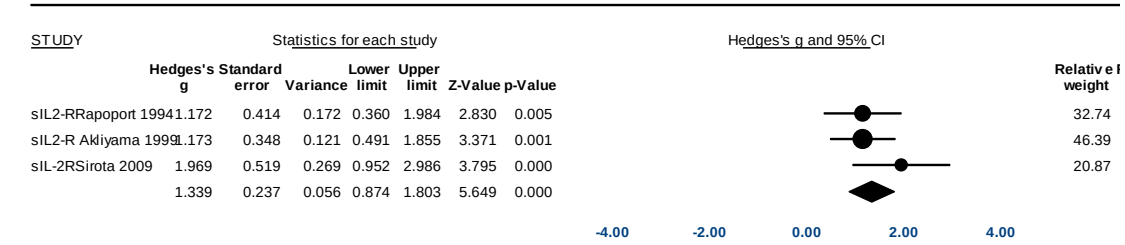
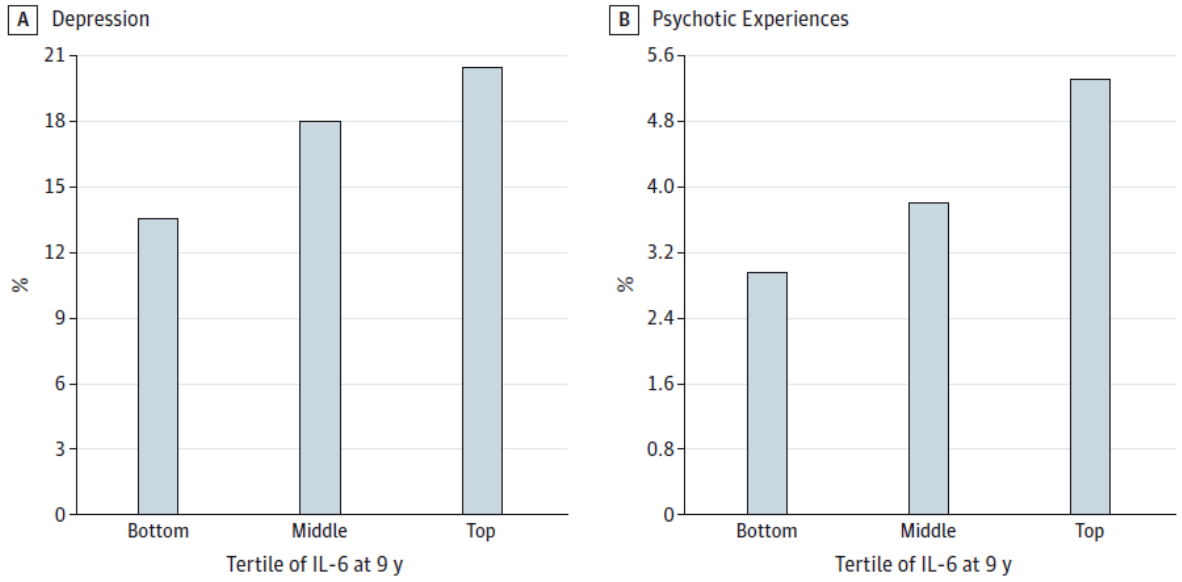


Figure 2: Depression and Psychotic Experiences at Age 18 Years in the Avon Longitudinal Study of Parents and Children

Reproduced with permission from: Khandaker *et al*. *JAMA Psychiatry.* 2014;71(10):1121-1128.



Note: Samples of depression (A) and psychotic experiences (B) were divided by tertiles of interleukin 6 (IL-6) in participants at age 9 years. Cutoff values for the top and bottom thirds of the distribution of IL-6 values in the total sample (cases and noncases combined) were 1.08 and 0.57 pg/mL, respectively.