



**The Translational Future of Stress Neurobiology and
Psychosis Vulnerability: A Review of the Evidence**

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The Translational Future of Stress Neurobiology and Psychosis Vulnerability: A Review of the evidence

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Abstract

Psychosocial stress is a well-established risk factor for psychosis, yet the neurobiological mechanisms underlying this relationship have yet to be fully elucidated. Much of the research in this field has investigated hypothalamic-pituitary-adrenal (HPA) axis function and immuno-inflammatory processes among individuals with established psychotic disorders. However, as such studies are limited in their ability to provide knowledge that can be used to develop preventative interventions, it is important to shift the focus to individuals with increased vulnerability for psychosis (i.e., high-risk groups). In the present article, we provide an overview of the current methods for identifying individuals at high-risk for psychosis and review the psychosocial stressors that have been most consistently associated with psychosis risk. We then describe a network of interacting physiological systems that are hypothesised to mediate the relationship between psychosocial stress and the manifestation of psychotic illness and critically review evidence that abnormalities within these systems characterise high-risk populations. We found that studies of high-risk groups have yielded highly variable findings, likely due to (i) the heterogeneity both within and across high-risk samples, (ii) the diversity of psychosocial stressors implicated in psychosis, and (iii) that most studies examine single markers of isolated neurobiological systems. We propose that to move the field forward, we require well-designed, large-scale translational studies that integrate multi-domain, putative stress-related biomarkers to determine their prognostic value in high-risk samples. We advocate that such investigations are highly warranted given that psychosocial stress is undoubtedly a relevant risk factor for psychotic disorders.

1. INTRODUCTION

Psychotic syndromes (most commonly, schizophrenia) include a diverse group of mental disorders characterised by distressing delusions and/or hallucinations (known as positive psychotic symptoms) and often accompanied by negative symptoms (e.g., affective flattening and anhedonia), cognitive impairment, and disorganised thinking and behaviour [1]. These disorders affect around 1% of the population during their lifetime [2] with a peak age at onset of 20.5 years [3] and chronic course if sub-optimally treated [4]. Consequently, there has been huge investment in understanding their complex aetiology and intervening during the early stages of illness, including preventive approaches [5].

Stress-vulnerability models of schizophrenia first emerged over 50 years ago [6, 7]. These models, which propose that psychosocial stress can contribute to psychosis onset among individuals with an underlying biological vulnerability for the disorder, have been hugely influential in shaping subsequent aetiological theories [8-14]. Whilst the fundamental principles of the stress-vulnerability model continue to have traction in both clinical and research settings, three major conceptual shifts have since occurred: First, our notion of what constitutes ‘vulnerability’ for psychosis has moved beyond one dominated by heritability, giving rise to new strategies for identifying individuals at increased risk for psychosis based on clinical features. Second, whilst early work in this field focused largely on major life events occurring proximal to illness onset, the range of psychosocial stressors that have been linked to psychosis has vastly expanded. Finally, increased consideration has been given to the neurobiological mechanisms that might underlie the relationship between stress and psychosis, particularly as such efforts might provide targets for intervention.

With regards to neurobiological mechanisms, there have been several excellent reviews on this topic [10, 15-19] which predominately focused on abnormal hypothalamic-pituitary-adrenal (HPA) function and immuno-inflammatory processes among individuals with established psychotic disorders and the influence of these systems on dopaminergic/glutamatergic function (two key neurotransmitters implicated in psychosis). Whilst the present article covers some of these topics, we shift the attention to the role of stress neurobiological mechanisms in promoting psychosis *vulnerability*. This is warranted given that studies of individuals with established psychosis are (i) retrospective in nature, and therefore cannot shed light on causality, (ii) confounded by antipsychotic medication and (particularly in populations with chronic schizophrenia) comorbid physical conditions and associated treatments, and (iii) limited in the extent to which they can provide knowledge that can be used to develop novel preventative interventions. In this critical review, we first describe the current strategies for identifying vulnerable individuals and psychosocial stressors that have been implicated in psychosis, before providing an extensive review of hypothesised neurobiological mechanisms and interventions targeting these mechanisms, [with particular focus on evidence provided by meta-analyses \(Tables 1-6\)](#). After discussing these findings, we provide suggestions for how to move the translational field forward.

2. IDENTIFYING VULNERABLE INDIVIDUALS

2.1. Familial/Genetic High-Risk Strategy

Since the 1920’s, prospective studies throughout the world have followed the development of offspring and siblings of individuals with psychotic disorders from early life into adulthood [20]. This familial high-risk (FHR), or so-called, genetic high-risk strategy emerged based on early family studies demonstrating that

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3 schizophrenia is highly heritable [21], indeed, more recent studies indicate that the risk of developing
4 schizophrenia is over seven times higher among offspring of individuals with the disorder [22]. Whilst genome-
5 wide association studies have confirmed that schizophrenia has a substantial genetic component [23], as many
6 offspring and siblings live with (or close to) their affected relatives, this increased risk likely reflects a
7 combination of genetic and environmental factors. Although the FHR approach has been a highly successful
8 research strategy, most individuals with schizophrenia do not have a relative with the disorder [24, 25], therefore
9 risk factors identified in these studies may relate to a more familial form of illness. Moreover, recent cross-
10 sectional studies often include adult relatives who have passed the age of peak risk for illness onset: As these
11 relatives likely remain illness-free (despite having substantial genetic and environmental risk) due to protective
12 factors, studying stress responsivity and neurobiological mechanisms in these older 'high-risk' populations has
13 limited relevance for determining the prognostic value of these factors.

19 **2.2. Schizotypal Personality Disorder and Traits**

21 A further strategy for identifying individuals at increased risk for psychotic disorders, is to study individuals
22 who fulfil criteria for schizotypal personality disorder (SPD) or who present high levels of schizotypal traits.
23 SPD is a disorder within the psychosis spectrum that is characterised by attenuated forms of many of the traits
24 and symptoms that define schizophrenia, most notably, odd beliefs, speech, and behaviour. Whilst SPD
25 symptoms can be distressing and pervasive, unlike those of schizophrenia, they do not typically confer the need
26 for long-term care [26]. Nevertheless, individuals with SPD and those with high schizotypy traits have been
27 found to share cognitive, neuroanatomical, and neurochemical features with individuals with schizophrenia [27].
28 Longitudinal studies show that around a third of individuals with SPD develop full-threshold psychotic disorder
29 within 2-3 years [28, 29].

34 **2.3. Clinical High-Risk Approach**

36 The clinical high-risk approach, which focuses on help-seeking individuals who present features consistent
37 with the prodromal phase of psychosis has become the dominant high-risk strategy in the past twenty years [30].
38 Individuals who meet clinical high-risk for psychosis (CHR-P) criteria present attenuated psychotic symptoms,
39 or (less commonly) brief, limited psychotic episodes, and/or trait vulnerability (first-degree relative with
40 psychosis or fulfilment of SPD criteria) with functional decline; functional and neurocognitive impairments are
41 also prevalent [31]. CHR-P individuals are typically detected in specialised, community-based clinics [32-35]
42 and assessed with CHR-P specific psychometric interviews, which have excellent prognostic accuracy, although
43 limited to group-level predictions [36]. The risk of transition to psychosis among CHR-P individuals varies over
44 time, cumulating to 0.20 (95% CI, 0.19-0.21) at 2 years and 0.35 (95% CI, 0.32-0.38) at 10 years [37].
45 Transition risk also varies across CHR-P subgroups [38], being highest in those presenting with a brief, limited
46 psychotic episode [39-42]. However, most of those who will not develop psychosis still present substantial
47 mental health burden at follow-up [43, 44]. The prevalence of CHR-P features is around 10-fold higher in
48 clinical samples (1.7%) than in the general population (19.2%) [45]. The combination of the relatively high risk
49 for psychosis transition, with a low prevalence in the population, yields an associated global population
50 attributable fraction of about 10% [46].

52 Given that the prodromal phase of psychosis is retrospectively reported by ~50% of first-episode psychosis
53 (FEP) patients [47-50], the CHR-P strategy provides a unique opportunity to alter illness trajectory [51].

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3 Assessment, treatment, and clinical monitoring of CHR-P individuals are now considered essential components
4 of early intervention for psychosis in the UK [52]. Internationally, the CHR-P construct has been widely-
5 implemented with 47 specialist CHR-P services providing care to over 20,000 CHR-P individuals worldwide
6 [53]. These services aim to prevent transition to full-threshold psychotic disorder [54], reduce the severity of
7 attenuated positive and negative symptoms, and improve quality of life and functioning. Based on evidence that
8 a longer duration of untreated psychosis (DUP, defined as the length of time between psychosis onset and the
9 provision of adequate treatment) is associated with poorer clinical [55-59], cognitive [56, 60, 61], and social
10 outcomes [56, 62, 63] among patients with psychosis, a further aim is to reduce the DUP for CHR-P individuals
11 who do transition by facilitating prompt referral to FEP services. As such, CHR-P services can potentially
12 improve outcomes after psychosis onset [64, 65].
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18 **2.4. Psychotic-like Experiences**

19 Evidence emerging over the past decade indicates that psychosis exists on a continuum of severity, with
20 members of the general population exhibiting “psychotic-like experiences” (PLEs) [66-68], typically defined as
21 alterations in perception and reality that occur at the subclinical level [69]. These features are qualitatively
22 different to the psychotic symptoms that characterise individuals at CHR-P and those with psychotic disorders
23 [70] in that they are less commonly distressing and/or intrusive. PLEs are common in the general population,
24 with an average lifetime prevalence around 5% [71, 72], though estimates vary depending on assessment
25 method (i.e., self-report measures, which have questionable psychopathological validity, yielding higher
26 prevalence estimates than interview-based assessments) and factors such as age, sex, and country of residence. In
27 youth, PLEs are more common in younger children than adolescents (median prevalence ~17 vs. 8%,
28 respectively [73]), with longitudinal studies showing that most PLEs experienced during childhood and early
29 adolescence are transient [74-77]. Although the vast majority of individuals who experience PLEs are not help-
30 seeking, children and adolescents who report PLEs are nearly four times more likely to develop psychotic
31 disorders and three times more likely to develop any mental disorder [78], although the absolute risk is so low
32 that preventive interventions are infeasible. Furthermore, PLEs (at any age) appear to confer increased risk for
33 suicidal ideation and suicide attempts [79]. Given the potential to recruit large samples from the general
34 population (which are often free from medication and other confounds), the PLE strategy has been widely
35 utilised in studies examining stress neurobiology. However, it is important to note that PLEs are qualitatively
36 different from psychotic symptoms and disorders and cannot be used as a clinically valid proxy indicator [80].
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47 **3. PSYCHOSOCIAL STRESSORS**

48 Psychosocial stressors occurring throughout the lifespan have been associated with psychotic
49 symptomatology. This section considers the psychosocial stressors most-commonly examined in studies of
50 individuals with psychosis and high-risk populations.
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54 **3.1. Childhood adversity**

55 Childhood adversity is a broad term encompassing psychosocial stressors experienced throughout childhood
56 and early adolescence, which can include trauma/maltreatment, bullying, and parental death. These experiences
57 have been robustly associated with onset of psychosis (OR=2.87, 95%CI: 2.07 to 3.98) [81-86], even when
58 restricted to prospective studies (OR=2.52, 95%CI: 1.27 to 5.02) [82]. Meta-analytic evidence indicates that
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3 emotional abuse confers the highest risk for psychosis (OR=3.40, 95%CI: 2.06 to 5.62), followed by physical
4 abuse (OR=2.95, 95%CI: to 2.25 to 3.88), sexual abuse (OR=2.38, 95%CI: 1.98 to 2.87), bullying (OR=2.39,
5 95%CI:1.83 to 3.11), neglect (OR=2.90, 95%CI: 1.71 to 4.92), and parental death (OR=1.70, 95%CI: 0.82 to
6 3.53)[81]. Importantly, childhood adversities are a transdiagnostic risk factor for several mental disorders and
7 the one with the largest preventive capacity: For example, a recent meta-analysis [46] determined that reducing
8 childhood adversities would decrease the incidence of schizophrenia-spectrum disorders by 37.84% (global
9 population attributable fraction 95%CI: 26.77% to 48.40%).

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14 With regards to FHR studies, childhood trauma has been associated with subclinical psychotic symptoms in
15 both siblings of patients with psychosis and healthy controls [87], suggesting that this association may be
16 independent of underlying familial risk. CHR-P individuals are more likely to report childhood trauma than
17 healthy controls (OR=2.90, 95%CI: 2.90 to 12.2) [88]; which appears to be driven by higher rates of emotional
18 abuse (OR=5.84, 95%CI: 1.79 to 19.03) and physical neglect (OR=3.07, 95%CI: 1.04 to 9.01), with no
19 significant differences in other childhood trauma domains [88]. Childhood adversity also increases healthcare
20 costs in CHR-P individuals [89], as well the likelihood of presenting other comorbid mental disorders (including
21 depression, PTSD, panic disorder and social phobia) [90]. Whilst meta-analyses have shown no association
22 between childhood trauma and transition to psychosis in CHR-P individuals [91], childhood trauma has been
23 found to increase risk of subsequent PLEs in general population samples and mediate the relationship between
24 perinatal risk factors and these symptoms [92].

3.2. Stressful life events

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32 Experiencing stressful life events in adulthood, such as job loss, serious illness, divorce, death of a loved
33 one, or victimisation, substantially increases psychosis risk in the general population (OR=5.34, 95%CI: 3.84 to
34 7.43) [82], an effect that has been confirmed in prospective studies [93]. As these events can occur during a
35 wider time-frame than childhood adversity, there is heterogeneity across studies in the time-period investigated,
36 with some studies examining events in the past three months [94], and others including events occurring over
37 several years [93]. Early evidence from small studies suggested that stressful life events tended to increase in the
38 three weeks prior to the onset of psychotic symptoms [94] but this has not been replicated [95].

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42 With regards to high-risk samples, a study that included children at FHR and those presenting PLEs
43 (alongside other antecedents of schizophrenia) observed that both groups reported a greater number of negative
44 life events than their typically-developing peers [96]. Moreover, the PLE group experienced a higher frequency
45 of daily stressors than typically-developing children and were more distressed by these experiences. Similarly,
46 data from the North American Prodrome Longitudinal Study (NAPLS-2) suggests that CHR-P individuals are
47 more likely to experience both stressful life events and daily hassles than healthy controls, and report greater
48 subjective distress in relation to these events [97, 98]. However, a subsequent study from the NAPLS-2 cohort
49 found that neither stressful life events nor childhood trauma were independently associated with transition at 1-2
50 years in multivariable analyses, and that these variables made little contribution to the predictive models [99].
51 Thus, psychosocial stressors may have limited ability to predict transition in CHR-P youth over and above
52 baseline symptoms and demographic factors, perhaps because they are highly prevalent in this population.
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3.3. Momentary stress

Stress is a dynamic experience that fluctuates throughout the day, but these daily changes are difficult to assess retrospectively with clinical interviews or self-report questionnaires [100]. Advances in technology have allowed for repeated and momentary evaluation of stress and symptomatology, referred to as either experience sampling methods (ESM [101]) or ecological momentary assessment (EMA [102]). These methods typically assess stress associated with momentary activities using Likert scales, which the user is prompted to complete at randomly-timed intervals throughout the day. Many devices also include items capturing self-reported psychotic and depressive symptoms, which have been shown to correlate with standard researcher-assessed clinical instruments [103]. Consequently, there has been recent interest in using EMA devices in clinical settings to facilitate remote monitoring of symptoms and illness [104].

Early ESM studies reported that patients with psychotic disorder and CHR individuals exhibited higher levels of emotional stress reactivity (defined as a decrease in positive affect and increase in negative affect in response to stress) than healthy controls [105]. Moreover, increases in activity-related stress were associated with greater intensity of psychotic symptoms (referred to as psychotic stress reactivity) in patients and relatives but not controls [106]. Subsequent ESM studies have similarly observed that CHR-P individuals show increased emotional stress reactivity compared to healthy controls [107] and that the magnitude of emotional stress reactivity is associated with transition to psychosis [108]. Consistent with these findings, a large study in the general population observed that baseline emotional and psychotic stress reactivity were associated with persistence of PLEs over a 14-month follow-up [109].

3.4. Sociodemographic factors

Sociodemographic factors, such as ethnic minority and migrant status, are robustly associated with psychosis onset [82] an effect that is likely attributable in part to psychosocial stress [110]. For example, being a first-, second- or third-generation migrant is associated with higher rates of stressful life events and trauma and low sociodemographic status [111-113], whilst perceived racial discrimination increases severity of depression, anxiety, and stress as well as PLEs [114]. In contrast to studies of patients with established psychosis, CHR-P individuals are not more likely to be ethnic minorities compared to healthy controls [115]. Moreover, non-white ethnicity does not appear to increase psychosis risk in CHR-P populations [116], although there is some evidence that ethnic minority CHR-P individuals experience greater exposure to trauma [117]. Similarly, CHR-P individuals are less likely to be first-generation immigrants compared to healthy controls [118] and the evidence for an effect of migrant status on transition is mixed [119]. This discrepancy between ethnicity and migrant status increasing general population risk for psychosis, but having limited effect within CHR-P populations, could suggest differences in illness progression and/or sub-optimal identification of at-risk individuals in these population groups. Individuals from ethnic minority and/or migrant backgrounds may have a more acute progression of illness with a relatively short prodrome, making early detection more difficult. Indeed, migrant status is associated with delays in help-seeking and a longer duration of untreated psychosis [120, 121], potentially related to lack of understanding of local service provision [122], difficulty communicating in a non-native language [123], and low mental health literacy [123]. Together, these elements could result in delayed detection in these vulnerable populations. Living in an urban environment is likewise robustly associated with developing a psychotic disorder [82] but not with transition to psychosis in CHR-P

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3 individuals [116]. Conversely, neighbourhood level of social deprivation, however, does not appear to affect
4 psychosis risk in the general population [82] but is related to PLEs [124].
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6 7 **3.5. Interaction with substance use**

8 Substance use has become an increasingly important consideration for psychosis risk with cannabis [125,
9 126], tobacco [126] and novel psychoactive substances [127] (including synthetic cannabinoids) all shown to
10 increase the risk for psychotic disorders. This has been echoed by increased incidence of substance-induced
11 psychoses in recent years [128, 129]. In line with neurodevelopmental models, both prenatal and postnatal
12 substance use exposure has been associated with increased risk of psychosis [130]. While some of the variance
13 in risk may be explained by age at first use, frequency of use, and genetic factors [125, 131], psychosocial stress
14 exposure may also influence the extent to which substance use contributes to emerging psychopathological
15 states [132, 133]. For example, evidence suggests that childhood trauma and cannabis use interact to increase
16 the risk and frequency of PLEs in adolescents and young adults [134, 135].
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22 **4. NEUROBIOLOGICAL MECHANISMS**

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24 In the next section we discuss a network of interacting physiological systems that are hypothesised to
25 mediate the relationship between psychosocial stress and manifestation of psychotic illness.
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27 **4.1 HPA axis**

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29 The neural diathesis-stress model, proposed in 1997 by Walker and Diforio [9] and subsequently updated
30 [8, 10], was the first to suggest that the HPA axis may mediate the relationship between stress and psychosis. In
31 mammalian organisms, the physiological stress response is coordinated by the sympathetic branch of the
32 autonomic nervous system (triggering a rapid release of adrenaline which has immediate effects on heart rate,
33 vasoconstriction, and digestion), and subsequently, the HPA axis [136, 137]. Of the two systems, the HPA axis
34 has received particular attention from psychopathologists. In brief, the HPA axis responds to stress by eliciting a
35 cascade of hormonal reactions (release of corticotrophin-releasing hormone [CRH] from the paraventricular
36 nucleus of the hypothalamus and subsequently adrenocorticotrophic hormone [ACTH] from the pituitary),
37 resulting in the secretion of glucocorticoids from the adrenal cortex. Glucocorticoids (in humans, primarily
38 cortisol) facilitate behavioural and physiological responses to stress by interacting with various systems to
39 influence glucose metabolism, and immune, cardiovascular, and brain function [8]. The brain expresses two
40 forms of glucocorticoid receptor: high-affinity mineralocorticoid receptors (MRs) which are occupied at rest,
41 and low-affinity glucocorticoid receptors (GRs) that are typically occupied only under high glucocorticoid
42 conditions [137]. Glucocorticoids regulate HPA axis activity by binding to these receptors in the hypothalamus
43 and pituitary where they inhibit the secretion of CRH and ACTH respectively via negative feedback [138].
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51 HPA activity can be inferred from levels of cortisol and ACTH in bodily fluids, as cortisol can be measured
52 in blood, urine, saliva, and more recently, hair, it has become the most commonly-used HPA axis measure in
53 research settings. Cortisol can be measured under basal (i.e., unstimulated) conditions, in response to
54 awakening, following exposure to experimental psychosocial stressor tasks or pharmacological challenge, and
55 (using the ESM approaches described above), in response to naturally occurring stressors (for a comprehensive
56 review of cortisol measures see [10]). Pituitary volume has also been employed as a measure of HPA axis
57 function, albeit less commonly: enlargements are thought to reflect an increase in the size and ratio of ACTH-
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3 producing corticotroph cells within the anterior pituitary [139], thus indicating increased HPA axis activity.
4 Given that cortisol levels fluctuate substantially throughout the day, pituitary volume may provide a more stable
5 HPA axis measure [140].
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8 **4.1.1. Cortisol levels in high-risk populations**

9 Meta-analyses (Table 1) indicate that individuals with psychotic disorders are characterised by increased
10 levels of unstimulated blood and salivary cortisol compared to healthy controls [141-143], but an
11 attenuated/blunted cortisol response during psychosocial stressor tasks and after awakening [144-147]. It has
12 been proposed that this pattern reflects repeated exposure to psychosocial stressors (leading to chronically
13 elevated cortisol levels) that, when exhausted, gives rise to a dysregulated system that is unable to mount a
14 sufficient response to acute stressors [19]. Consistent with this hypothesis, a small study measuring hair cortisol
15 levels (indexing chronic cortisol secretion) observed higher levels among 27 medication-naïve FEP patients
16 relative to controls [148], although a smaller study of 16 patients with schizophrenia (including 10 FEP) failed
17 to confirm these findings [149].
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23 Meta-analyses of cortisol levels in high-risk populations (Table 1) have, however, yielded inconsistent
24 results. In the first meta-analysis to examine salivary cortisol levels in CHR-P individuals [150], pooled data
25 from eight studies indicated a significant increase relative to controls. However, a more recent meta-analysis
26 [142] observed no significant differences in unstimulated salivary cortisol in CHR-P individuals relative to
27 controls (Hedges' $g=0.15$, 95%CI: -0.01 to 0.31) and no differences in blood cortisol levels (Hedges' $g=0.39$,
28 95%CI: -0.42 to 1.21). Moreover, neither of these meta-analyses observed differences in basal salivary cortisol
29 levels when comparing CHR-P individuals who subsequently transitioned to psychosis and those who did not
30 [142, 150]. With regards to dynamic cortisol measures, two meta-analyses, including three [150] and five
31 studies [142] respectively, both observed that the cortisol awakening response (CAR) was blunted, but not
32 significantly so. However, both reviews pooled data across diverse high-risk populations. Whilst no meta-
33 analysis has yet examined cortisol responses during psychosocial stressor tasks, significantly blunted responses
34 relative to controls have been observed in studies of CHR-P individuals [151] and those with high schizotypy
35 traits [152], but not in adult FHR populations [153]. Similarly, the few studies that have examined hair cortisol
36 in high-risk populations have yielded inconsistent results, with one study reporting increased hair cortisol among
37 CHR-P youth [154] but a subsequent study finding no differences between high-risk individuals (CHR-P and
38 FHR combined) and controls [155].
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46 More recently, it has been shown that incorporating salivary cortisol levels in multivariable models can
47 improve prediction of illness progression in high-risk samples. An analysis of data from the NAPLS-2 cohort
48 showed that the inclusion of basal salivary cortisol measured at baseline in a multivariable model (which
49 included baseline positive symptoms and functioning) significantly improved prediction of transition status
50 [156]. Consistent with this finding, in a cohort of children enriched for psychosis risk factors, diurnal cortisol
51 levels at age 11-14 years predicted development of attenuated psychotic symptoms at age 17-21 years in a
52 multivariable model that included demographic factors and baseline psychopathology [157]. Whilst these
53 findings require replication, they indicate that further research into the predictive utility of salivary cortisol in
54 psychosis high-risk groups is warranted, a topic that we will discuss in the Section 6.
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[Insert Table 1 here]

4.1.2. Pituitary volume in high-risk populations

While an early narrative review concluded that the onset of psychosis was associated with pituitary volume enlargement (independent of antipsychotic use) followed by a reduction in volume during chronic illness [139], subsequent studies have been inconsistent. A meta-analysis of nine studies (Table 1) observed no significant difference in pituitary volume when comparing patients with established psychosis (schizophrenia and FEP) and healthy controls [158], although a trend for larger volume was observed in the FEP group. In this review, effect sizes were positively correlated with the proportion of individuals receiving antipsychotic medication. With regards to high-risk populations, this same meta-analysis observed no differences in pituitary volume when all high-risk individuals (CHR-P and SPD) were compared with controls [158], although increased volume was reported in those who transitioned (SMD=0.37, 95%CI: 0.00 to 0.75). In a subsequent meta-analysis [159], a significant increase in pituitary volume was observed in high-risk individuals when data from 11 heterogenous samples were pooled (Hedges' $g=0.16$, 95%CI: 0.00 to 0.32), although sub-analyses performed for FHR and CHR-P groups showed no differences to controls. Moreover, individuals who later transitioned to psychosis showed even larger increases in pituitary volume (Hedges' $g=0.55$, 95%CI: 0.06 to 1.04) and consistent with the previous meta-analysis, larger effect sizes across all studies were positively associated with proportion of individuals receiving antipsychotic medication. As was the case with salivary cortisol, the largest study included in this review found that pituitary volume was a significant predictor of transition to psychosis in CHR-P individuals when included in a multivariable model accounting for baseline symptoms [160].

4.1.3. Concordance with stress measures

The neural diathesis-stress model posits that individuals with increased vulnerability are more sensitive to the effects of psychosocial stressors due to abnormalities within the HPA axis. As such, we might expect individuals on the psychosis spectrum to exhibit abnormal HPA axis responses to psychosocial stressors. Whilst this has been shown to some extent in laboratory studies using psychosocial stressor tasks (where individuals with established illness and some high-risk groups have been found to exhibit hypo-responsivity), far less is known about cortisol responses to the naturally-occurring psychosocial stressors that have been associated with psychosis risk.

Addressing this knowledge gap, a recent meta-analysis (Table 1) pooled data across studies examining the concordance between naturally-occurring psychosocial stressors and cortisol in individuals with established psychosis, high-risk individuals (CHR, FHR, SPD, PLEs), and healthy controls [161]. Analysis of 134 effect sizes from all three populations indicated that psychosocial stressors and cortisol measures were only weakly correlated [$r=0.05$, 95%CI: -0.00 to 0.10] and that neither established psychosis status [$r=0.01$ $p=0.838$] nor high-risk status [$r=0.02$, $p=0.477$] had a significant effect of the strength of correlation. Thus, there was no evidence to suggest that high-risk individuals or those with established psychosis exhibited either hypo- or hyper-responsivity to naturally-occurring psychosocial stressors. However, this review identified several major limitations with the extant literature, including, small samples, lack of adjustment for potential confounders, and failure to account for (or report) the time-lapse between stressor measurement and cortisol collection. The latter appears to be particularly important: in a further study from the NAPLS-2 consortium ($n=662$), the degree of concordance between psychosocial stressors and basal cortisol was found to be moderated by the lapse-of-time between collection of these measures, where daily stressors, life events, and childhood trauma were only associated with basal cortisol when these stress measures were completed on the same day as cortisol collection

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3 [98]. After accounting for the lapse-of-time between assessments, the degree of concordance was found to be
4 stronger among CHR-P individuals who later converted to psychosis when compared to those who did not [98].
5 These findings concur with those from studies using ESM to examine cortisol responses to daily stressors
6 (where cortisol measures are obtained within 10 minutes of rating stressful experiences). Indeed, two ESM
7 studies, which could not be included in the meta-analysis due to incomparable effect sizes [162, 163], reported
8 that event stress was correlated with salivary cortisol in individuals with psychosis and FHR groups but not in
9 healthy controls. Further studies, that address the methodological issues identified in this recent meta-analysis,
10 are required to determine whether stressor-cortisol concordance is a useful marker of psychosis risk.
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15 **[Insert Table 1 here]**

16 **4.2. Immuno-inflammatory processes**

17
18 There is growing interest in integrating immune and inflammatory mechanisms within diathesis-stress
19 models of psychosis risk for diagnostic, prognostic, and therapeutic purposes [164]. Alongside the HPA axis,
20 the immune system helps maintain homeostasis in response to acute and chronic stressors; indeed, cortisol is a
21 potent regulator of immune activity [165]. In brief, the immune system consists of molecular and cellular
22 components. Cytokines are the key signalling molecules, which, like other hormones, can signal at short
23 distances between cells but also systemically, coordinating physiological responses. Cellular components
24 include B and T lymphocytes with receptors to specific antigens and non-lymphocytic cells such as neutrophils,
25 macrophages, and dendritic cells. These are organised functionally into innate and adaptive arms: the former is
26 evolutionarily ancient and mediates broad and non-specific responses to infection and other physiologic
27 challenges by promoting inflammation (which acts to clear the challenge and prime adaptive immunity), whilst
28 adaptive immunity mediates antigen-specific responses via humoral (antibody) and cellular mechanisms. Acute
29 inflammation is usually useful and adaptive, turning off once resolved, whereas chronic inflammation is
30 typically maladaptive and associated with tissue-specific or systemic pathology. The most commonly-studied
31 immune markers in psychosis research are peripheral cytokines and markers of chronic low-grade inflammation
32 (e.g., C-reactive protein) [166, 167]. Although there has been recent interest in clotting and complement proteins
33 [168] and neuronal surface auto-antibodies [169].
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43 **4.2.1. Early life stress and inflammatory markers**

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45 Converging evidence suggests that the immune system may mediate the effect of early life stress on
46 neurodevelopment and psychosis risk. Studies using rodent maternal immune activation (MIA) models show
47 that offspring of pregnant mice subjected to peripheral inflammatory stimuli exhibit structural, functional, and
48 behavioural features relevant to psychosis risk, including changes in ventricular size, pre-pulse inhibition, HPA
49 axis sensitivity, and locomotive and social behaviour [170]. In humans, early-life stress has been shown to
50 influence immune set-points and response to inflammatory challenges. For example, young children from
51 families with high psychosocial stress were found to show low spontaneous immune activity as indexed by
52 peripheral cytokines when compared to children from low-stress families, but an increased immune response
53 when cells were stimulated *in vitro* [171]. As children in the high-stress group were also characterised by
54 elevated cortisol, these findings suggest that psychological stress can influence immune system parameters and
55 HPA axis markers. In terms of psychosis risk, an analysis of data from the ALSPAC study (a prospective
56 longitudinal cohort of children from the general population) observed that higher levels of IL-6 measured at age
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9 were associated with psychotic experiences and disorder at age 18 [172]. However, this effect was not disorder-specific, as risk of depression was also elevated. In the same cohort, proteomic analysis indicated that elevations in complement proteins at age 12 were associated with risk of psychotic experiences at age 18 [173].

4.2.2. First episode psychosis and state markers

Meta-analyses (Table 2) indicate that medication-naïve FEP patients are characterised by elevations in several cytokines (e.g., IFN- γ , IL-6, IL-17, TGF- β , and TNF- α) [174-176]. Whilst it has been hypothesised that these alterations may be specific to a subgroup of psychosis patients, examination of the distribution of immune markers does not support this [174]. Meta-analytic evidence also indicates that treatment with antipsychotic medication is associated with a reduction in with IL-6, whereas IL-12 and TNF- α remain raised despite treatment [176], suggesting that cytokines may function as both state and trait markers of psychosis. Moreover, elevations in IL-6 and IFN- γ have been associated with poorer responses to antipsychotic treatment [177]. Studies of medication-naïve psychosis patients have also observed raised B cells and reduced T cells with a raised CD4:CD8 sub-set ratio, which has been shown to normalise with antipsychotic treatment [175, 178]. Furthermore, some (but not all) studies have shown that CRP levels are associated with symptom severity and acute-phase illness among patients with schizophrenia [167]. With regards to how these immune markers might relate to psychosocial stress, studies observing elevated cytokine levels in FEP patients have also found that stress measures (life events and childhood trauma) are associated with raised cytokine levels, including TNF- α , IL-1 β , IFN- γ , IL-6 [179] and TGF- β [180] in patients and/or controls.

[Insert Table 2 here]

4.2.3. High risk and transition to first episode psychosis

In contrast to findings in patients with established psychosis, meta-analyses have provided no convincing evidence of abnormal immuno-inflammatory process in high-risk individuals. A recent meta-analysis (Table 2) of 12 immuno-inflammatory markers observed no significant differences in any marker when all high-risk groups (CHR-P and FHR) were compared with controls [181]; although subgroup analyses showed significantly increased IL-6 levels in the CHR-P group only ($g=0.33$, 95%CI: 0.06 to 0.60).

Some promising findings have been obtained using multivariable prediction models. For example, a study utilising data from small subset of the NAPLS-2 cohort (including 72 individuals at CHR) found that cortisol and several cytokines were among the 15 markers (of 117 tested) that best distinguished individuals at CHR-P who transitioned to psychosis from those who did not and healthy controls [182]. More recently, proteomic analysis of the ALSPAC and EU-GEI cohorts combined with clinical data was used to derive a model with an area under the curve (AUC) of 0.95 [183], where complement and coagulation proteins were highly implicated in the proteomic differences. Conversely, autoantibodies against the NMDA receptor [detectable in a small proportion of the EU-GEI cohort, but not more commonly than controls (8.3% vs. 5.2%; OR=1.50, 95% CI: 0.58-3.90)] were not associated with transition to psychosis [184].

4.3. Brain structure

4.3.1. Influence of HPA and immuno-inflammatory systems on the brain

As described in Section 4.1, cortisol exerts its functions in the CNS by binding to MRs and GRs. Both receptors are highly expressed in the human hippocampus, although GRs are also distributed in other regions

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3 such as the amygdala and prefrontal cortex. These regions influence glucocorticoid release and behavioural
4 responses to stress [185]: the hippocampus and prefrontal cortex inhibit HPA axis activity and participate in the
5 regulation of the HPA axis by means of glucocorticoid feedback inhibition, whilst the amygdala can influence
6 HPA axis when activated by emotional and physiological stressors.
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10 These brain regions also determine how the brain adapts to stress, with the amygdala and hippocampus
11 involved in emotional and contextual aspects, respectively, whilst the prefrontal cortex is involved in planning
12 and control. There is some evidence to suggest that chronic stress induces structural changes in brain regions.
13 Whilst low-stress or low-cortisol concentrations have particular neurotrophic effects, prolonged high stress (in
14 dose or time) is thought to induce neurotoxicity by different mechanisms such as the glutamate cascade, the
15 inhibition of glucose transport, and reducing brain-derived neurotrophic factor (BDNF) expression [186].
16 Chronic exposure to stress hormones has been shown to adversely affect the brain structures involved in
17 cognition and psychiatric disorders, where the timing and duration of the exposure is a crucial factor [187, 188].
18 Specific brain areas may be more sensitive to the effects of stress hormones during periods when they are
19 undergoing development; for example, the hippocampus (which undergoes significant development during the
20 first two years of life) may be more vulnerable to early-life stressors [187] whereas stress exposure during late
21 childhood and adolescence might lead to changes in amygdala volume and the frontal cortex, respectively (as
22 these regions continue to develop in these developmental periods).
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30 While the brain was long considered to be an immune-privileged site (due to the blood-brain barrier),
31 evidence of complex interactions between the brain and immune system has emerged. In addition to vagal
32 afferents (crucial for bidirectional communication in the gut-brain axis) and circumventricular organs (small
33 ventricular structures which lack a blood-brain barrier), there is evidence that meningeal lymphatic vessels are
34 rich in immune cells and can play a role in regulating neuronal networks [189]. Moreover, brain-resident glial
35 cells can transduce and integrate multiple signals, including from stress and systemic inflammation, leading to
36 changes in neurobiology both structurally and functionally, for example by synaptic pruning [190]. These
37 findings lend support to the notion that immuno-inflammatory processes can contribute to neuroanatomical and
38 neurofunctional changes relevant to diathesis-stress models of psychosis.
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42 **4.3.2. The impact of early life stress on the brain**

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44 Stressors experienced during early life, including those occurring before (prenatal stress) and after birth
45 (postnatal stress, childhood, and adolescence), have been shown to impact on brain structure and function.
46 Converging evidence indicates that prenatal stress influences the brain and HPA axis by means of programming
47 effects [191]. For example, prenatal stress has been associated with decreased functional connectivity and
48 increased structural connectivity between the amygdala and the medial prefrontal cortex [192]. Moreover, foetal
49 exposure to elevated placental CRH levels has been related to increased cortical thinning of temporal and frontal
50 regions [193], an effect that may be more pronounced in females. With regards to postnatal stressors, childhood
51 maltreatment has been found to correlate with structural and functional brain changes. Meta-analyses (Table 3)
52 have shown reduced grey matter in the right dorsolateral prefrontal cortex and right hippocampus among adults
53 with a history of childhood trauma [194], as well as significantly increased activation in the left superior frontal
54 gyrus and left middle temporal gyrus, and decreased activation in the left superior parietal lobule and the left
55 hippocampus [195]. Studies also suggest that there might be sex-differences in the sensitivity of brain regions to
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3 childhood maltreatment [196], as early-life stress has been associated with lower hippocampus-subgenual
4 cingulate resting-state functional brain connectivity (rs-FC) in both adolescent females and males, but lower
5 amygdala-subgenual cingulate rs-FC in females.
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8 [\[Insert Table 3 here\]](#)
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10 With regards to psychosis high-risk populations, a recent study reported that childhood sexual abuse was
11 associated with reduced cortical thickness in bilateral middle temporal gyri and the left superior frontal gyrus in
12 CHR-P individuals, whilst physical abuse was associated with increased cortical thickness in the right middle
13 frontal gyrus [197]. Other studies exploring adversity in CHR-P youth have reported volume losses in the cortex
14 and hippocampus in people with a history of deprivation but not threat [198]. Moreover, severity of childhood
15 maltreatment has been correlated with resting cerebral blood flow (rCBF) in the bilateral hippocampus and
16 negatively associated with rCBF in the left prefrontal cortex in CHR-P individuals [199].
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20 **4.3.3. Stress biomarkers and brain structure in psychosis**

21 Stress biomarkers may contribute to some of the neuroanatomical features associated with psychosis. An
22 early longitudinal study observed that diurnal cortisol levels were inversely correlated with left hippocampal
23 volume in patients with FEP [200]. In a further study from this group, childhood maltreatment and stressful life
24 events were both found to contribute to a reduction in BDNF mRNA levels in FEP patients, possibly through a
25 stress-induced increase in IL-6 expression [201]. Other studies have reported that a decreased CAR is associated
26 with reduced hippocampal volumes in male FEP patients [202] and male CHR-P individuals [203]. With regards
27 to immuno-inflammatory markers, a recent review of 14 publications concluded that there was reasonably
28 consistent evidence that increased peripheral inflammation is associated with smaller hippocampal volume and
29 reduced cortical thickness among patients with psychosis [204]. Psychosocial stress may also impact on brain
30 function: a recent fMRI study observed that the relationship between cortisol reactivity (the slope between pre-
31 and post-imaging salivary concentrations) and brain activation in the bilateral temporo-parieto-insular junctions,
32 right middle cingulum, right pre/postcentral gyri, left cerebellum and right lingual gyrus during an emotional
33 face-matching task was moderated by the severity of childhood maltreatment and these effects were different in
34 patients with schizophrenia and healthy controls [205]. Moreover, data from a large sample of CHR-P
35 individuals observed that that higher levels of proinflammatory cytokines at baseline were associated with
36 greater prefrontal cortical thinning in the total sample, and that this association was even more pronounced
37 among those who transitioned to psychosis within two-years [206]. Thus, models incorporating markers of
38 immuno-inflammatory processes may have utility in predicting neuroanatomical changes as well as symptom
39 progression.
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50 **4.4. Cognition**

51 **4.4.1. Glucocorticoids and cognition in non-psychiatric populations**

52 Studies of patients with endocrine disorders (e.g., Cushing's syndrome) and healthy individuals indicate that
53 chronic stress and excess glucocorticoids are associated with cognitive impairments. For example, patients with
54 Cushing's syndrome, where there is an excess of glucocorticoids (due to exogenous or endogenous factors),
55 show deficits in verbal, visual, and working memory domains [207, 208] which improve following successful
56 treatment. Some brain changes associated with Cushing's syndrome, such as hippocampal atrophy, are also
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3 reversible with treatment [209, 210], although longer periods of glucocorticoid excess are associated lower
4 likelihood of improvement [211]. Consistent with these findings, a longitudinal study of healthy subjects
5 observed that individuals characterised by an increasing/high pattern of cortisol secretion (i.e., year-to-year
6 increases in cortisol with currently high levels) showed significant impairments in declarative memory and
7 selective attention compared to individuals with increasing/moderate or decreasing/moderate cortisol levels
8 [212]. These results suggest that cognitive deficits linked to glucocorticoid excess are not specific to
9 hippocampal function, since they also target the process of selective attention sustained by the frontal lobes.
10 Several cohort studies have investigated whether cortisol may accelerate cognitive decline in humans. In a meta-
11 analysis including 19 prospective studies (see Table 4 [213]), higher morning cortisol was considered a risk
12 factor for cognitive decline in mild cognitive impairment or mild Alzheimer's Disease patients, although the
13 results in cognitively healthy adults were inconsistent.

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22 [Insert Table 4 here]

23 4.4.2. Glucocorticoids and cognition in psychosis

24 Cognitive abnormalities are considered a core feature of schizophrenia and related psychoses [214]. These
25 abnormalities are present (albeit to a lesser degree) in CHR-P populations before the psychosis onset [215],
26 although these deficits appear to be attributable to those who subsequently transition to psychosis [216]. The
27 neurotoxic hypothesis proposes that stress-induced HPA axis hyperactivity leads to an increase in cortisol which
28 has neurotoxic effects on specific brain regions that express high levels of GRs (hippocampus and prefrontal
29 cortex), thereby leading to cognitive impairments in domains attributed to these regions (e.g., memory and
30 executive function) [10]. In support of this hypothesis, elevations in afternoon cortisol levels have been
31 associated with poorer verbal memory in males with first-episode schizophrenia [217] whilst higher hair cortisol
32 concentrations have been associated poorer working memory in psychosis patients and healthy controls,
33 independent of diagnosis [218]. In contrast, a lower CAR has been related to a poorer processing speed and
34 verbal memory performance in FEP patients [219]. Consistent with these findings, a study of children at
35 elevated risk for psychosis (children at FHR and those presenting PLEs and other antecedents) observed that
36 more pronounced HPA axis abnormalities (higher diurnal cortisol levels and reduced CAR) were associated
37 with poorer verbal memory and executive functioning in high-risk groups, but this effect was not present in
38 typically-developing children [220]. As these findings go against the neurotoxic hypothesis, the authors
39 concluded that altered neurodevelopmental trajectories may have contributed to structural and functional
40 abnormalities in regions that mediate both cognitive and HPA axis function. However, in a further study
41 supporting the neurotoxic hypothesis, sex differences in the relationship between the CAR and verbal memory
42 and processing speed were observed (a higher CAR was associated with poorer cognitive outcomes in female
43 patients), as well as with the diurnal cortisol slope and spatial working memory (a flattened cortisol slope was
44 associated with poorer working memory in female patients) [221]. [Immuno-inflammatory might plausibly
45 contribute to the cognitive impairments that characterise individuals with psychosis \[222\]; however, findings
46 have been mixed \(see Table 4\). A recent systematic review observed that CRP levels were inconsistently
47 associated with cognitive impairment in patients with psychosis \[167\], similarly, a meta-analysis that included
48 studies of patients with psychotic and mood disorders found limited evidence to suggest that immune markers
49 were associated with cognitive performance in the combined patient analysis or when stratified by diagnostic
50 subgroup \[223\]. In contrast, a subsequent meta-analysis of studies examining patients with schizophrenia](#)

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3 concluded that cognitive deficits were associated with elevations in pro-inflammatory markers in this population
4 [224]. Given the inconsistency of findings across studies, further research investigating the interplay between
5 early-life stress, stress biomarkers, and cognitive outcome is an important area for future research.
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8 **4.5. Gut microbiome**

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10 The gut microbiome is a complex and dynamic ecosystem of microorganisms present in the intestinal tract
11 [225]. Humans host around 500-1000 bacterial species, with a total genes set 150 times larger than the human
12 genome [226, 227]. Gut bacteria contribute to many of the host's physiological functions, including nutrient
13 metabolism, immunomodulation, and permeability of biological barriers [227]; in turn, the host sends signals to
14 the gut and modulates the composition and functionality of gut bacteria [225]. A consistent body of evidence
15 now suggests that the gut microbiome can affect brain chemistry and development, including key nodes of the
16 physiological stress system [228-230]; however, most of this work is preclinical, with few studies in humans.
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20 **4.5.1. Effects of the stress system on the gut microbiome**

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22 Converging evidence indicates that several psychosis risk factors can modify the composition and
23 functionality of the gut microbiome [231], which in turn, can affect specific gut-brain pathways believed to
24 contribute to the pathophysiology of psychosis. In prenatal life, a recent study in humans showed that infants
25 from mothers who exhibited high levels of self-reported stress and salivary cortisol during pregnancy had lower
26 levels of Lactobacilli and Bifidobacteria in the gut [232]. Similar findings were obtained in newborn pups of
27 pregnant mice exposed to severe stress during pregnancy [233] where gut microbiome shifts were accompanied
28 by modifications in the levels of metabolites and essential amino acids in the hippocampus and thalamus of the
29 pups. Similarly, adverse childhood experiences (e.g., parent-child dysfunctions, lower socioeconomic status, and
30 childhood trauma) have also been associated with altered gut microbiome composition in humans [234, 235].
31 Consistent with these observations, early maternal separation in non-human animals induces significant shifts in
32 the gut microbiome of the offspring [236, 237] which is accompanied by increased peripheral inflammation
33 (IFN- γ and IL-6) and altered central neurotransmission [237]. With regards to other psychosis-relevant risk
34 factors, migration [238] and urbanisation [239] have both been associated with reduced gut microbiome
35 diversity.
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42 **4.5.2. Effects of the gut microbiome on the stress system**

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44 The most convincing evidence that the gut microbiome influences the stress system comes from studies of
45 mice never exposed to bacteria (germ-free mice, GFM) and antibiotic-depleted mice. Studies of GFM indicate
46 that these animals exhibit abnormal activation of the HPA axis (increases in stress hormones and locomotor
47 activity) when exposed to stressors [240]. However, as GFM have an abnormal brain development, and are often
48 raised in social isolation (germ-free environment), some authors questioned the validity of these findings [240].
49 This criticism was recently addressed in studies using co-caged antibiotic-depleted mice, which have a
50 physiological brain development and avoid the germ-free environment bias. Consistent with the findings from
51 GFM, antibiotic-depleted mice also showed a heightened activation of the HPA axis in response to a range of
52 different stressors [241, 242]. These studies also demonstrate that the lack of bacteria induced by antibiotic
53 depletion in mice is associated with hippocampal atrophy and reduced neuroplasticity [242], features which
54 have been consistently associated with both heightened stress exposure and psychosis [243]. Importantly, these
55 central detrimental effects could be prevented by modulating the gut microbiome with different interventions
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3 (e.g., probiotics and faecal transfer from non-antibiotic-depleted mice) [244]. Such findings are in line with
4 those obtained in humans, where probiotics and prebiotics can reduce stress perception and cortisol release in
5 otherwise healthy individuals [245, 246].
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8 Animal studies indicate that the efficacy of gut microbiome-based interventions is dependent on
9 developmental stage, with earlier interventions resulting in more consistent and long-lasting neuroprotective
10 effects [244]. This is not surprising, given that the timeline of the development of the mammalian stress system
11 coincides with the acquisition and consolidation of the gut microbiome [229]. In humans, the circadian rhythm
12 of cortisol release consolidates in the early postnatal period, approximately six months after birth [247], this
13 period also represents a key window for the colonisation of the gut by bacteria. Evidence suggests that the infant
14 gut is sterile at birth [248], although recent work shows that initial bacterial colonisation might occur as early as
15 10 weeks after conception when the foetus begins to swallow amniotic fluid [249]. Immediately after birth, the
16 gut of the infant is colonised by bacteria coming either from the mother's vagina (in case of vaginal delivery) or
17 from the mother's/carer's skin (in case of C-section) [249]. Once feeding commences, additional bacteria can be
18 acquired from breast milk [249]. These initial steps of bacterial colonisation introduce a high degree of
19 interindividual variability in gut microbiome composition. For example, formula-fed and C-section born infants
20 have a lower abundance of *Bifidobacteria* and *Bacteroidetes* (essential for the digestion of human milk
21 oligosaccharides) and greater levels of Proteobacterial groups (known to contain pathogens) [250]. These
22 differences might result in reduced absorption of essential nutrients and increased activation of the immune
23 system, both having important effects on the brain and specific HPA axis components (namely, cytokine-
24 induced release of CRH from the hypothalamus) [251], especially during this critical developmental period.
25 Indeed, C-section and formula-feeding are associated with an altered stress response that persists into adulthood
26 and with an increased risk of immunological disorders [252, 253], but the link with psychotic disorders is more
27 tenuous [254]. It is plausible that these associations might be mediated by alterations of the gut microbiome,
28 although this remains to be tested. Other critical periods for the development of the HPA axis are childhood and
29 early adolescence [247], where the gut microbiome is reaching its final and more stable composition [225].
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40 **4.5.3. The gut microbiome in psychotic disorders**

41 Accumulated evidence suggests that reduced microbiome diversity may contribute to a number of
42 detrimental health outcomes, including psychiatric disorders, although meta-analyses (see Table 5) have yielded
43 variable findings depending on the microbiome measure and psychiatric population examined [255, 256].
44 Nevertheless, studies have shown that gut microbiome composition is altered in psychosis patients [257-259]
45 and individuals at CHR-P [260] when compared to controls, independent of medication [255, 257]. Moreover,
46 gut microbiome samples obtained from medication-naive patients can cause brain and behavioural abnormalities
47 in recipient mice that resemble those of schizophrenia [255]. Of translational relevance, recent studies suggest
48 that gut microbiome features can be used to predict treatment response [261] and functional deterioration [259]
49 in patients with psychosis.
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55 [\[Insert Table 5 here\]](#)

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57 Multiple mechanisms have been hypothesised to explain these findings. For example, the gut microbiome is
58 a key regulator of immune system development [262]; shifts in the gut microbiome have been associated with
59 modifications of the activity of the complement system and increased production and release of cytokines and
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3 autoantibodies with anti-glutamatergic action [262-264]. This enhanced immunological activation is a well-
4 established feature of novel psychopathological models of psychotic disorders [169]. Other mechanisms include
5 the regulation by bacteria of the circulating levels of kynurenate, an NMDA receptor antagonist [265]; the
6 synthesis of short-chain fatty-acids (acetate, butyrate, propionate) that modulate the permeability of the blood
7 brain barrier [266]; the synthesis of endocannabinoids and other neurotransmitters [267]; and the regulation of
8 the activity of the enteric nervous system and the stress system [268]. However, studies in clinical samples are
9 needed test these hypothesised mechanisms.
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14 **5. IMPLICATIONS FOR PREVENTION AND TREATMENT**

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17 We now turn our attention to the real-world implications, that is, how might our understanding of the stress
18 neurobiological mechanisms be used to improve outcomes for those at risk for psychosis. However, a major
19 limitation is that work in this field has thus far focused on individuals with established psychosis.
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22 **5.1. Antipsychotic medication**

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24 There is some evidence to suggest that antipsychotic medications may influence the physiological systems
25 described in the preceding sections, and that these actions may partially explain their therapeutic effects. With
26 regards to the HPA axis, an observational study of FEP patients found that those with < 2 weeks of
27 antipsychotic treatment were characterised by significantly higher diurnal cortisol levels when compared to
28 patients with > 2 weeks of treatment and healthy controls [269]. Experimental studies have confirmed this
29 pattern, for example, a double-blind randomised controlled trial (RCT) examined the effect of antipsychotic
30 administration vs. placebo in healthy controls (n=11) and found that quetiapine and olanzapine significantly
31 reduced levels of plasma cortisol and ACTH levels [270]. A larger double-blind RCT of patients with treatment-
32 resistant schizophrenia (n=78) observed that 12-weeks treatment with risperidone or haloperidol both resulted in
33 a decrease in serum cortisol levels and that cortisol levels at follow-up were associated with negative symptoms
34 [271]. Similar findings have been observed for cytokines; indeed, this same trial observed that risperidone and
35 haloperidol were both associated with a reduction in IL-2 (but not IL-6) levels and that pre-treatment IL-2 levels
36 were associated with positive symptoms. Moreover, a meta-analysis of eight observational studies (Table 6)
37 observed that IL-2 and IL-6 levels were significantly decreased (with moderate effect sizes) in FEP patients
38 following four weeks of antipsychotic treatment [272]. With regards to the gut-microbiome, there appears to be
39 a reciprocal relationship, in that antipsychotic medications directly affect the composition of the gut-
40 microbiome, and in turn, microbiota influence the absorption (and hence efficacy) of antipsychotics [273].
41 Specifically, a large *in vitro* study that investigated more than 1,000 non-antibiotic medications, found that
42 antipsychotic medications were among the three classes of medications that were found to inhibit gut bacteria to
43 a greater degree than other medications [274]. Moreover, as this study also found that gut microbes targeted by
44 different antipsychotics were more similar than would be expected based on the structural similarity of these
45 medications, the authors concluded that these bactericidal effects may be part of the therapeutic action rather
46 than simply a side effect.
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57 **5.1. Treatments targeting the HPA axis**

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59 Evidence of cortisol abnormalities in patients with psychosis has generated interest in assessing the
60 therapeutic benefit antigluocorticoid treatments (either as a sole or adjunctive treatment) in this population.

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3 These treatments typically inhibit cortisol synthesis (e.g., metyrapone, aminoglutethimide, ketoconazole) or act
4 as GR antagonists (e.g., mifepristone) thereby suppressing cortisol secretion [275]. A Cochrane review of RCTs
5 found insufficient evidence to indicate that antiglucocorticoid medications improved psychotic symptoms (either
6 positive or negative) when administered as an adjunctive treatment [276]. However, the largest of these studies
7 (n=221) examined outcomes among patients with psychotic depression after seven days of mifepristone
8 treatment (followed by treatment-as-usual) and reported that these patients were significantly more likely to
9 achieve treatment response (defined as a 30% reduction in global symptoms) than those receiving placebo [277].
10 As noted in this review, study quality was highly variable (many studies had small samples and short follow-up
11 periods), thereby limiting the ability to draw conclusions regarding the potential utility of targeting the HPA axis
12 system. It is possible that any potential benefits of antiglucocorticoid medications might be restricted to a subset
13 of individuals with HPA axis abnormalities at treatment commencement. Indeed, a recent meta-analysis (see
14 [Table 6](#)) examining the efficacy of antiglucocorticoid treatment in mood disorders reported that patients who
15 responded to treatment with cortisol synthesis inhibitors had significantly higher peripheral cortisol levels at
16 baseline than non-responders [278], suggesting that only those with HPA axis abnormalities at baseline might
17 benefit from treatment.
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25 **5.2. Therapies targeted at immune and inflammatory abnormalities**

26 Since there are extensive therapeutics direct against inflammatory mediators that could be repurposed, there
27 has been interest in evaluating whether this may have a treatment role in psychosis. Early studies investigated
28 broad anti-inflammatory treatments such as aspirin or non-steroidal anti-inflammatory drugs, observing modest
29 effects ([279, 280], see [Table 6](#)). More recently, specific therapies have been tested; however, a small placebo-
30 controlled RCT of tocilizumab, a monoclonal antibody against IL-6, observed no effect on symptom severity at
31 12 weeks in patients with schizophrenia [281]. The authors proposed that future trials might consider enriching
32 samples with individuals presenting inflammatory biomarker abnormalities at recruitment, targeting earlier in
33 the illness, and treating those with more severe symptoms. A further perspective is to consider trans-diagnostic
34 subsyndromal aspects of psychosis such as anhedonia, that associate with differential cytokine signatures, and
35 investigate the effects of anti-inflammatory medications on these specific symptoms in trials across psychosis
36 and mood disorders [282, 283].
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43 **5.3. Treatments targeting the gut-microbiome**

44 Treatments targeting the gut-microbiome include probiotics (live microorganisms that confer health benefits
45 to the host when administered in sufficient quantities) and prebiotics (substrates that benefit the host by
46 selectively stimulating growth and/or activity of gut microorganisms) [284]. There has been substantial interest
47 in evaluating the effect of these nutritional supplements in patients with psychiatric disorders, with an initial
48 review the literature (including studies published between 2014-2019) concluding that there was some evidence
49 to suggest that probiotics may improve depression, but not anxiety or schizophrenia [285]. Similarly, a
50 subsequent [meta-analysis \(Table 6\)](#) found that across 28 RCTs evaluating add-on strategies targeting the gut-
51 microbiome (of which 21 examined antibiotics, with only three investigating pre-and/or probiotics) there was no
52 evidence to suggest that augmentation was significantly superior to placebo in improving symptom severity in
53 patients with schizophrenia [286].
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[Insert Table 6 here]

6. DISCUSSION

We have described a network of integrated systems that are relevant to understanding how psychosocial stressors contribute to risk of psychosis. Our review shows that whilst there is reasonably consistent evidence that individuals with established illness are characterised by higher levels of traditional stress biomarkers (namely cortisol and cytokines), studies of high-risk groups have yielded highly variable findings. Moreover, treatments targeting the HPA axis, immuno-inflammatory processes, and the gut-microbiome have yet to be convincingly shown to improve treatment outcomes among those with established psychosis, although some of the beneficial effects of antipsychotics may be through these systems.

Whilst these findings are somewhat discouraging, the lack of consistency is unsurprising for several reasons. First, the mode of onset, treatment course, and long-term prognosis for psychotic disorders is highly variable [1], thus, it is implausible that a single underlying biological mechanism could be associated with illness onset, symptom expression, and treatment response. *Indeed, there is evidence to suggest that psychotic disorder subtypes are associated with distinct neurobiological features: for example, shared and distinct brain regions appear to underlie the abnormalities of sustained attention that characterise both affective and non-affective psychotic disorders [287]. Moreover, there is sexual-dimorphism (both structural and functional) in the brain systems associated with psychosis, which may contribute to differences in treatment response across males and females [288].* Heterogeneity is even more pronounced in high-risk samples, with meta-analyses including help-seeking CHR-P individuals presenting symptoms consistent with the prodrome, through to members of the general population who present PLEs that are often benign and not distressing. Even within the CHR-P group there is considerable variation, where individuals presenting with BLIPS (which form only a small proportion of CHR-P individuals) have the highest liability for transition [38]. Thus, the probability of finding any mean difference in biomarkers in high-risk groups relative to controls is further reduced. Second, given the wealth of psychosocial stressors that increase psychosis risk, it is unsurprising that studies examining correspondence between stress exposure and neurobiological markers have failed show evidence of an association [161]. Such studies typically measure one, or a limited set, of psychosocial stressors and correlate these with biomarker levels. Yet, even if we assume that psychosocial stress contributes to illness onset among *all* individuals with psychosis (which is highly unlikely), as there is no stressor experience that is common to all individual with psychosis, the ability to detect associations with physiological parameters is greatly diminished. Adding to this complexity, these stressors operate throughout the lifespan, ranging from events in early childhood which may set the scene for emerging psychopathology, through to ‘triggering’ life events occurring proximal to illness onset. The fact that these stressors are commonly assessed retrospectively, with hypothesised biomarkers measured many years later, further reduces the ability to detect associations. Finally, the neurobiological systems that are relevant to our understanding of the impact of psychosocial stress extend far beyond the HPA axis. As noted, the HPA axis has reciprocal relationships with immuno-inflammatory processes and the gut-microbiome, and changes within these systems can influence brain structure and function. However, these neurobiological mechanisms are often examined in isolation, using a single biomarker and the external (e.g., environment, diet, infections, substance use, and medication) and internal factors (e.g., somatic disorders, biological sex, age) that influence these mechanisms are scarcely measured [10]. As such, our ability to identify

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3 physiological correlates of psychosocial stressors, even where these are robustly associated with illness onset in
4 a high proportion of individuals, is limited.
5

6 7 **6.1. Moving the translational field forward**

8 As we argue above, studies investigating isolated markers of single neurobiological systems, in small
9 samples of FEP or high-risk individuals will continue to generate conflicting, and sometimes, spurious findings.
10 We propose that a more useful strategy (see Figure 1) may be to ensure that large-scale, multisite studies
11 recruiting high-risk and FEP participants routinely collect data on stress exposure and a range of samples (blood,
12 saliva, and stool) that can be used to assess multiple, putative markers of stress neurobiology (i.e., HPA axis,
13 immuno-inflammatory, and gut-microbiome). In this way, we can determine the extent to which these data can
14 be used alongside precision psychiatry methods to detect at-risk individuals, predict illness trajectories and
15 psychosis onset, and stratify individuals to enable targeted interventions. Precision psychiatry tools provide
16 individualised risk estimates to inform clinical decisions and can incorporate data on stress to refine and
17 improve the accuracy of their predictions. Multivariable models combining clinical and/or sociodemographic
18 data with stress exposure [99, 289, 290] or stress biomarkers [156] have already been developed and appear to
19 have promise. However, most of them are not replicated and fail the implementation test [291-293], thus lacking
20 clinical relevance. Better representation of interactions between risk factors in a multivariable approach (e.g.,
21 combining information on momentary stress with trauma history and cortisol levels) is essential for future
22 research, particularly when considering multiple measures of stress, which will be highly correlated. Preliminary
23 work has been encouraging [294], for example using polyenvironmental risk scores [289, 290, 295] but large,
24 generalisable samples are needed to develop and validate these tools. External validation studies, where
25 independent datasets are used to replicate model performance, are rare in psychiatry [292] but are needed in
26 order to provide evidence that precision psychiatry tools can perform well in multiple settings and are viable for
27 use in real-world clinical care [296].
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38 **[Insert Figure 1 here]**
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40 41 **6.2. Conclusions**

42 We propose that among individuals who are at high-risk for psychosis, there will be a small proportion for
43 whom dysregulation within neurobiological stress systems is present, and within this group, some for whom this
44 dysregulation is relevant to illness onset and course (rather than epiphenomenal). The next step is to develop
45 methods to systematically identify these individuals and determine whether targeted interventions (e.g.,
46 supplementation with anti-inflammatory agents or gut-microbiome interventions) might be beneficial. The
47 establishment of several international consortiums throughout the world will enable the collection of biomarkers
48 to a much larger scale than we have seen previously. These efforts are needed to determine the translational
49 utility of stress biomarkers in vulnerable populations, as evidence to support this is currently lacking.
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LIST OF ABBREVIATIONS

1		
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6	ACTH	Adrenocorticotrophic hormone
7		
8	AUC	Area under the curve
9		
10	BDNF	Brain-derived neurotrophic factor
11		
12	CAR	Cortisol awakening response
13		
14	CHR-P	Clinical high-risk for psychosis
15		
16	CI	Confidence interval
17		
18	CRH	Corticotrophin-releasing hormone
19		
20	CRP	C-reactive protein
21		
22	DHEAs	Sulphate dehydroepiandrosterone
23		
24	EMA	Ecological momentary assessment
25		
26	ESM	Experience sampling methods
27		
28	FEP	First-episode psychosis
29		
30	FHR	Familial high-risk
31		
32	GFM	Germ-free mice
33		
34	GRs	Glucocorticoid receptors
35		
36	HPA	Hypothalamic-pituitary-adrenal axis
37		
38	IFN	Interferon
39		
40	IL	Interleukin
41		
42	MIA	Maternal immune activation
43		
44	mRNA	Messenger ribonucleic acid
45		
46	MRs	Mineralocorticoid receptors
47		
48	NICE	National Institute for Health and Care Excellence
49		
50	NMDA	N-methyl-D-aspartate
51		
52	OR	Odds ratio
53		
54	PLEs	Psychotic-like experiences
55		
56	PTSD	Post-traumatic stress disorder
57		
58	<i>r</i>	Pearson's correlation coefficient
59		
60	rCBF	Resting cerebral blood flow
	RCT	Randomised controlled trial

rs-FC	Resting-state functional brain connectivity
SPD	Schizotypal personality disorder
TGF	Transforming growth factor
TNF	Tumor necrosis factor

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

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Figure 1 caption: Proposed strategy for moving the translational field forward

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Table 1. Meta-analyses examining hypothalamic-pituitary-adrenal (HPA) axis markers in established psychosis and high-risk populations

Author	Population	Measure	Findings
Berger et al. (2016)	Schizophrenia, FEP, CHR-P	Cortisol awakening response	Pooled analysis of all patient groups [schizophrenia, FEP, CHR-P] showed significantly lower CAR in patients relative to healthy controls [k = 11, g = -0.426 (95% CI: -0.585 to -0.267) $p < 0.001$]. However, subgroup analyses indicated no differences in the CAR between CHR-P individuals and controls [k = 3, g = -0.170 (95% CI: -0.435 to 0.095) $p = 0.207$].
Ciufolini et al. (2014)	Schizophrenia	Cortisol response to psychosocial stressor tasks	Compared to controls, individuals with schizophrenia demonstrated significantly lower cortisol levels during the anticipatory phase of the psychosocial stressor task [k = 3, g = -0.39, (95% CI: -0.74 to -0.03), $p = 0.032$] and in response to the stressor [k = 3, g = -0.66, (95% CI: -1.20 to -0.12) $p = 0.016$]; however, no significant differences in cortisol levels were observed during the recovery phase [k = 3, g = -0.34 (95% CI: -1.03 to 0.35) $p = 0.33$].
Chaumette et al. (2016)	FEP, CHR-P	Basal salivary cortisol	Basal salivary cortisol observed to be significantly increased in CHR-P individuals relative to healthy controls [k = 8, g = 0.59 (95% CI not reported) $p = 0.004$]. Subgroup analysis showed no differences between CHR-P individuals who subsequently transitioned and those who did not [k = 4, g = not reported (95% CI not reported) $p = 0.90$]. No significant differences in basal salivary cortisol in comparisons between FEP patients and healthy controls [k = 6, g not reported (95% CI not reported), $p = 0.56$].
Cullen et al. (2020)	Schizophrenia, FEP, CHR-P, FHR, SPD, PLEs	Stressor-cortisol concordance	When pooled across all populations (established psychosis, high-risk, healthy controls) only a weak, positive association observed between naturally occurring stressors and cortisol [k = 134, $r = 0.05$ (95% CI: -0.00 to 0.10) $p = 0.059$]. Meta-regression analyses showed no significant effect of either established psychosis status [$r = 0.01$ (95% CI: -0.01 to 0.16) $p = 0.838$] or high-risk status [$r = 0.02$ (95% CI: -0.05 to 0.10), $p = 0.477$] on effect sizes, indicating that the degree of concordance in these groups did not differ from healthy controls.
Girshkin et al. (2014)	Schizophrenia	Morning cortisol	Morning cortisol levels significantly increased in schizophrenia patients relative to controls [k = 44, g = 0.387, (95% CI: 0.154 to 0.619) $p = 0.001$]. Sub-analyses restricted to patients free from antipsychotic medication showed more pronounced increases of morning cortisol relative to controls [k = 16, g = 0.468 (95% CI: 0.242 to 0.693) $p < 0.001$].
Hubbard & Miller (2019)	First-episode psychosis	Blood cortisol	Blood cortisol levels significantly increased in FEP relative to controls [k = 27, SMD = 0.37 (95% CI: 0.16 to 0.57) $p < 0.001$], with larger effect sizes when restricted to antipsychotic naïve samples [k = 18, SMD = 0.46 (95% CI 0.20: to 0.73) $p = 0.001$].
Misiak et al. (2021a)	FEP, CHR-P, FHR,	Blood and salivary cortisol	Compared to healthy controls, FEP group showed significantly higher levels of unstimulated blood cortisol levels [k=22, g = 0.48, (95% CI = 0.25 to 0.70) $p < 0.001$], a lower CAR [k = 4, g = -0.40 (95% CI = -0.68 to -0.12) $p = 0.006$] but no differences in unstimulated salivary cortisol levels [k = 7, g = 0.09 (95% CI: -0.09 to 0.26) $p = 0.331$]. In contrast, no differences between high-risk individuals and healthy controls were observed for unstimulated blood cortisol [k = 7, g = 0.39 (95% CI: - 0.42 to 1.21) $p = 0.342$], unstimulated salivary cortisol [k = 10, g = 0.15 (95% CI: -0.01 to 0.31) $p = 0.062$], or the CAR [k = 5, g = -0.13 (95% CI: -0.44 to 0.19) $p = 0.433$]. Unstimulated salivary cortisol levels did not differ between CHR-P converters and non-converters [k = 4, g = -0.13 (95% CI: -0.50 to 0.24) $p = 0.500$].
Nordholm et al. (2013)	Schizophrenia, FEP, CHR-P, SPD,	Pituitary volume	No significant differences in pituitary volume observed in comparisons between all high-risk individuals [CHR-P and SPD] and healthy controls [k = 3, SMD = 0.25 (95% CI: -0.17 to 0.66), $p = 0.24$] or when CHR-P individuals who transitioned to psychosis were compared with healthy controls [k = 2, SMD = 0.37 (95% CI: 0.00 to 0.75) $p = 0.05$]. Similarly, no significant differences in pituitary volume observed when all patients with established psychosis (schizophrenia and FEP) were compared with controls [k = 9, SMD = 0.10 (95% CI: -0.20 to 0.40) $p = 0.52$] or when restricted to patients with FEP [n = 4, SMD = 0.39 (95% CI: -0.05 to 0.84) $p = 0.09$].

Saunders et al. (2019)	CHR-P, FHR, SPD, PLEs	Pituitary volume	Significant increase in pituitary volume observed in the primary analysis comparing all high-risk groups (CHR-P, FHR, SPD, PLEs) and healthy controls [k = 11, g = 0.16 (95% CI: 0.00 to 0.32) $p = 0.04$]. Pituitary volumes larger among high-risk individuals who later transitioned to psychosis when compared to controls [k = 4, g = 0.55 (95% CI: 0.06 to 1.04), $p = 0.028$]. No significant differences observed in individual subgroup analyses comparing healthy controls with CHR-P individuals [k = 4, g = 0.17 (95% CI: -0.12 to 0.45) $p = 0.25$], or FHR groups [k = 4, g = 0.20 (95% CI: -0.03 to 0.43) $p = 0.09$].
Zorn et al. (2017)	Schizophrenia	Cortisol response to psychosocial stressor tasks	Individuals with schizophrenia showed diminished increase (AUCi) in cortisol levels [k = 4, SMD = -0.594 (95% CI: -1.150 to -0.037) $p = 0.04$] and lower overall cortisol levels (AUCg) during the stressor task [k = 4, SMD = -0.543 (95% CI: -0.968 to -0.118) $p = 0.01$] relative to healthy controls.

Note. FEP: first-episode psychosis; CHR-P: clinical high-risk; FHR: familial high-risk; SPD: schizotypal personality disorder; PLEs: psychotic-like experiences; CAR: cortisol awakening response; k: number of effect sizes included in analysis; g: Hedges g effect size; SMD: standardised mean difference; r : correlation coefficient; CI: confidence interval; AUCi: area under the curve with respect to increase; AUCg: area under the curve with respect to ground.

Table 2. Meta-analyses examining immuno-inflammatory markers in established psychosis and high-risk populations

Author	Population	Measure	Findings
Miller et al. (2011)	Schizophrenia and FEP	Cytokines measured in blood	In acutely relapsed patients compared with controls, IL-10 levels were significantly decreased [k = 2, g = -0.57 (95% CI: -0.98 to -0.17) $p = 0.006$], levels of IL-6 [k = 6, g = 0.96 (95% CI: 0.74 to 1.18) $p < 0.001$], IL-8 [k = 2, g = 0.59 (95% CI: 0.18 to 1.00) $p = 0.004$], TNF- α [k = 4, g = 0.73 (95% CI: 0.46 to 0.99) $p = 0.001$], IFN- γ [k = 2, g = 0.49 (95% CI: 0.18 to 0.80) $p = 0.002$], TGF- β [k = 2, g = 0.53 (95% CI: 0.26 to 0.79) $p < 0.001$], and IL-1RA [k = 2, g = 0.49 (95% CI: 0.07 to 0.90) $p = 0.02$] were significantly increased, whilst IL-2 [k = 2, g = -0.26 (95% CI: -0.60 to 0.08) $p = 0.13$] and sIL-2R [k = 2, g = 0.27 (95% CI: -0.13 to 0.68) $p = 0.19$] were not significantly different compared to controls. In medication naive FEP patients vs controls, IL-1 β [k = 3, g = 0.60 (95% CI: 0.37 to 0.84) $p < 0.001$], IL-6 [k = 4, g = 1.40 (95% CI: 1.14 to 1.65) $p < 0.001$], IL-12 [k = 2, g = 0.98 (95% CI: 0.61 to 1.35) $p < 0.001$], IFN- γ [k = 2, g = 0.57 (95% CI: 0.24 to 0.90) $p = 0.001$], TNF- α [k = 4, g = 0.81 (95% CI: 0.61 to 1.01) $p < 0.001$], TGF- β [k = 2, g = 0.48 (95% CI: 0.22 to 0.74) $p < 0.001$], and sIL-2R [k = 3, g = 1.03 (95% CI: 0.55 to 1.52) $p < 0.001$] levels were significantly decreased relative to controls, with no differences in IL-2 [k = 4, g = -0.09 (95% CI: -0.32 to 0.14) $p = 0.44$].
Miller et al. (2013)	Schizophrenia and FEP	Lymphocytes	Relative to controls, acutely relapsed patients showed increased total WBC [k = 2, g = 0.54 (95% CI: 0.08 to 1.00) $p = 0.02$], CD4% [k = 5, g = 0.26 (95% CI: 0.02 to 0.50) $p = 0.04$], and CD56% [k = 2, g = 0.83 (95% CI: 0.41 to 1.25) $p < 0.01$], but no differences in total lymphocyte count [k = 6, g = -0.04 (95% CI: -0.29 to 0.20) $p = 0.72$], CD3 [k = 5, g = 0.04 (95% CI: -0.19 to 0.27) $p = 0.74$], CD3% [k = 5, g = -0.12 (95% CI: -0.36 to 0.11) $p = 0.31$], CD4 [k = 4, g = 0.05 (95% CI: -0.20 to 0.30) $p = 0.70$], CD8 [k = 4, g = -0.16 (95% CI: -0.40 to 0.09) $p = 0.22$], CD8% [k = 5, g = 0.07 (95% CI: -0.17 to 0.31) $p = 0.57$], CD4/CD8 [k = 6, g = 0.15 (95% CI: -0.07 to 0.36) $p = 0.19$], CD19 [k = 4, g = 0.17 (95% CI: -0.08 to 0.42) $p = 0.18$], CD19% [k = 3, g = 0.0 (95% CI: -0.32 to 0.33) $p = 0.98$], CD25% [k = 2, g = -0.05 (95% CI: -0.45 to 0.36) $p = 0.81$], or CD56 [k = 3, g = 0.26 (95% CI: -0.06 to 0.57) $p = 0.11$]. Medication-naive FEP patients showed significantly increased total lymphocyte count [k = 2, g = 0.77 (95% CI: 0.25 to 1.29) $p < 0.01$], CD3 [k = 2, g = 0.72 (95% CI: 0.20 to 1.24) $p < 0.01$], CD4 [k = 2, g = 0.86 (95% CI: 0.33 to 1.38) $p < 0.01$], and CD4/CD8 [k = 2, g = 0.56 (95% CI: 0.04 to 1.07) $p = 0.03$] levels relative to controls, but no differences in CD3% [k = 3, g = -0.31 (95% CI: -0.63 to 0.00) $p = 0.05$], CD4% [k = 3, g = 0.02 (95% CI: -0.29 to 0.33) $p = 0.90$], CD8 [k = 2, g = 0.44 (95% CI: -0.08 to 0.95) $p = 0.10$], CD8% [k = 3, g = -0.03 (95% CI: -0.34 to 0.29) $p = 0.88$], or CD19 [k = 2, g = 0.30 (95% CI: -0.09 to 0.69) $p = 0.13$].
Misiak et al. (202b)	FHR, CHR-P	Immuno-inflammatory markers	In analyses including all available high-risk groups (CHR-P and FHR) no significant differences observed in levels of CRP [k = 9, g = 0.08 (95% CI: -0.12 to 0.28) $p = 0.448$], IL-1 β [k = 4, g = 0.13 (95% CI: -0.13 to 0.40) $p = 0.323$], IL-4 [k = 2, g = 1.50 (95% CI: -0.52 to 3.51) $p = 0.145$], IL-5 [k = 2, g = -0.17 (95% CI: -0.51 to 0.18) $p = 0.349$], IL-6 [k = 12, g = 0.18 (95% CI: -0.02 to 0.39) $p = 0.082$], IL-8 [k = 4, g = 0.35 (95% CI: -0.23 to 0.93) $p = 0.242$], IL-10 [k = 3, g = 0.27 (95% CI: -0.16 to 0.70) $p = 0.222$], IFN- γ [k = 7, g = 0.08 (95% CI: -0.25 to 0.41) $p = 0.625$], TNF- α [k = 8, g = 0.10 (95% CI: -0.19 to 0.39) $p = 0.506$], IL-12p70 [k = 3, g = 0.17 (95% CI: -0.19 to 0.53) $p = 0.363$], MCP-1 [k = 3, g = 0.55 (95% CI: -0.43 to 1.53) $p = 0.273$], or eotaxin-1 [k = 2, g = 0.76 (95% CI: -0.47 to 2.00) $p = 0.226$] when compared with healthy controls. In subgroup analyses, significantly higher levels of IL-6 were observed in CHR-P individuals relative to controls [k = 7, g = 0.33 (95% CI: 0.06 to 0.60) $p = 0.018$].
Pillinger et al. (2019)	FEP	Immuno-inflammatory markers	Compared to healthy controls, antipsychotic naive FEP patients showed significantly higher levels of IFN- γ [k = 9, g = 0.32 (95% CI = 0.11–0.53) $p = 0.003$], IL-17 [k = 7, g = 0.48 (95% CI = 0.06–0.89) $p = 0.03$], IL-6 [k = 15, g = 0.62 (95% CI = 0.32–0.92) $p < .0001$], TGF- β [k = 3, g = 0.53 (95% CI = 0.18–0.88) $p = .003$], and TNF- α [k = 11, g = 0.56 (95% CI = 0.22–0.90) $p = 0.001$], but no differences in CRP [k = 5, g = 0.66 (95% CI = -0.03 to 1.34) $p = 0.06$], total lymphocyte count [k = 3, g = 0.31 (95% CI = -0.13 to 0.76) $p = 0.17$], IL-10 [k = 9, g = 0.24 (95% CI = -0.13 to 0.62) $p = 0.20$], IL-1 β [k = 7, g = 0.49 (95% CI = -0.13 to 1.11) $p = 0.12$],

IL-2 [k = 9, g = -0.07; (95% CI = -0.53 to 0.39) $p = 0.77$], IL-4 [k = 7, g = 0.23 (95% CI = -0.05 to 0.51) $p = 0.10$], IL-8 [k = 5, g = 0.04 (95% CI = -0.62 to 0.70) $p = 0.90$], or sIL-2R [k = 4, g = 2.66 (95% CI = -0.03 to 5.34) $p = 0.05$].

Note. CHR-P: clinical high-risk; FHR: familial high-risk; FEP: first-episode psychosis; k: number of effect sizes included in analysis; g: Hedges g effect size; SMD: standardised mean difference; CI: confidence interval; CRP: C-reactive protein; IL: interleukin; IFN: interferon; TNF: tumour necrosis factor; TGF: transforming growth factor; MCP-1: monocyte chemoattractant protein-1; WBC: white blood cell count.

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Table 3. Meta-analyses examining associations between childhood trauma and neuroimaging measures in clinical and non-clinical populations

Author	Population	Measure	Findings
Heany et al. (2018)	Adults (clinical and non-clinical)	fMRI responses to socioaffective cues and childhood trauma	Across all studies reporting positive associations ($k = 9$), CTQ scores positively associated with brain activation in the left superior frontal gyrus extending into the medial frontal gyrus. Across all studies reporting negative associations ($k = 6$), brain activation in a cluster within the left superior parietal lobule was negatively associated with CTQ scores.
Paquola et al. (2016)	Adults (clinical and non-clinical)	Grey matter volume and childhood trauma	In the analysis of hippocampal volume, across all study samples (including clinical and non-clinical populations: $k = 17$) childhood trauma was associated with a significant reduction in left ($g = -0.642, p = 0.001$), right ($g = -0.616, p < 0.001$) and combined hippocampal volume ($g = -0.517, p < 0.001$). When stratified by disorder group (healthy controls, PTSD, BPD, mood disorder), reductions were significantly greater in the BPD cohort relative to controls and this was the only group to show reductions in left, right, and combined hippocampal volume. For amygdala volume, across all studies (including clinical and non-clinical populations: $k = 13$) childhood trauma was associated with a significant reduction in left ($g = -0.482, p = 0.006$), right ($g = -0.668, p = 0.002$) and combined amygdala volume ($g = -0.559, p < 0.001$), effect sizes more pronounced when restricted to psychiatric cohorts for left ($g = -0.926, p < 0.001$), right ($g = -1.234, p < 0.001$) and combined amygdala volume ($g = -1.020, p < 0.001$) In the analysis of WBV derived from VBM, analysis of all samples ($k = 19$) indicated that childhood trauma was associated with significantly reduced grey matter in three clusters: right dorsolateral prefrontal cortex ($SMD = -1.897, p < 0.001$), right hippocampus ($SMD = -1.718, p < 0.001$), and right postcentral gyrus ($SMD = -1.582, p = 0.002$).

Note. fMRI: functional magnetic resonance imaging; CTQ: childhood trauma questionnaire; k: number of effect sizes included in analysis; PTSD: post-traumatic stress disorder; BPD: borderline personality disorder; g: Hedges g effect size; SMD: standardised mean difference; WBV: whole brain volume; VBM: voxel based morphometry.

Table 4. Meta-analyses examining associations of cortisol and immune markers with cognitive function in clinical populations

Author	Population	Measure	Findings
Morrens et al. (2022)	Psychotic and mood disorders	Immune markers and cognitive dysfunction	In analysis including all psychotic and mood disorders patients, proinflammatory markers were negatively correlated with global cognitive performance [k = 53, r = -0.076 (95% CI: -0.126 to -0.027) $p = 0.003$], verbal memory [k = 36, r = -0.089 (95% CI: -0.148 to -0.029) $p = 0.004$], visual memory [k = 15, r = -0.036 (95% CI: -0.049 to -0.023) $p < 0.001$], working memory [k = 23, r = -0.065 (95% CI: -0.118 to -0.011) $p = 0.018$], and processing speed [k = 20, r = -0.082 (95% CI: -0.151 to -0.012) $p = 0.022$] but were not significantly associated with attention [k = 27, r = -0.027 (95% CI: -0.091 to 0.037) $p = 0.412$], reasoning [k = 37, r = -0.025 (95% CI: -0.096 to 0.045) $p = 0.378$], or language [k = 21, r = -0.052 (95% CI: -0.144 to 0.041) $p = 0.271$]. Anti-inflammatory markers were not significantly associated with global cognitive performance [k = 5, r = 0.067 (95% CI: -0.069 to 0.201) $p = 0.334$], verbal memory [k = 3, r = -0.074 (95% CI: -0.240 to 0.097) $p = 0.398$], processing speed [k = 4, r = 0.125 (95% CI: -0.030 to 0.275) $p = 0.113$], or reasoning [k = 4, r = -0.002 (95% CI: -0.245 to 0.241) $p = 0.985$]. In analyses restricted to patients with schizophrenia, proinflammatory markers were negatively correlated with visual memory [k = 9, r = -0.142 (95% CI: -0.241 to -0.040) $p = 0.006$] with no significant associations observed with global cognitive performance [k = 27, r = -0.036 (95% CI: -0.113 to 0.042) $p = 0.370$], verbal memory [k = 22, r = -0.072 (95% CI: -0.172 to 0.030) $p = 0.168$], working memory [k = 16, r = 0.002 (95% CI: -0.071 to 0.076) $p = 0.947$], attention [k = 16, r = -0.071 (95% CI: -0.164 to 0.022) $p = 0.135$], Processing speed [k = 12, r = -0.080 (95% CI: -0.171 to 0.013) $p = 0.090$], reasoning [k = 18, r = -0.026 (95% CI: -0.096 to 0.045) $p = 0.476$], or language [k = 16, r = -0.033 (95% CI: -0.137 to 0.072) $p = 0.538$].
Reddi Patlola et al. (2023)	Schizophrenia	Inflammatory biomarkers and cognitive dysfunction	IL-6 was significantly associated with attention and processing speed [k = 7, $\mu = -0.173$, (95% CI: -0.302 to -0.045) $p = 0.008$], executive functioning [k = 8, $\mu = -0.181$, (95% CI: -0.266 to -0.097) $p < 0.001$], verbal learning and memory [k = 7, $\mu = -0.169$, (95% CI: -0.307 to -0.032) $p = 0.016$], and working memory [k = 6, $\mu = -0.136$, (95% CI: -0.270 to -0.003) $p = 0.046$], but not with visual learning and memory [k = 4, $\mu = -0.08$, (95% CI: -0.227 to 0.065) $p = 0.279$]. TNF- α levels were significantly associated with attention and processing speed [k = 9, $\mu = -0.198$, (95% CI: -0.341 to -0.055) $p = 0.007$], executive functioning [k = 9, $\mu = -0.188$, (95% CI: -0.324 to -0.052) $p = 0.007$], and visual learning and memory [k = 4, $\mu = -0.38$, (95% CI: -0.538 to -0.222) $p < 0.001$] but not with verbal learning and memory [k = 7, $\mu = -0.118$, (95% CI: -0.324 to 0.089) $p = 0.610$] or working memory [k = 6, $\mu = -0.15$, (95% CI: -0.367 to 0.067) $p = 0.175$]. IL-1 β levels significantly associated with attention and processing speed [k = 4, $\mu = -0.372$, (95% CI: -0.619 to -0.125) $p = 0.003$], visual learning and memory [k = 3, $\mu = -0.454$, (95% CI: -0.627 to -0.282) $p < 0.001$], and working memory [k = 3, $\mu = -0.476$, (95% CI: -0.649 to -0.303) $p < 0.001$]. CRP levels significantly associated with attention and processing speed [k = 9, $\mu = -0.299$, (95% CI: -0.494 to -0.103) $p = 0.003$], verbal learning and memory [k = 7, $\mu = -0.278$, (95% CI: -0.356 to -0.20) $p < 0.001$], visual learning and memory [k = 5, $\mu = -0.311$, (95% CI: -0.538 to -0.084) $p = 0.007$], working memory [k = 6, $\mu = -0.168$, (95% CI: -0.315 to -0.022) $p = 0.024$], but not executive functioning [k = 5, $\mu = -0.159$, (95% CI: -0.502 to 0.184) $p = 0.364$].
Zheng et al. (2020)	Alzheimer's disease and controls	Cortisol secretion and cognitive decline	Compared to cognitively-normal controls, Alzheimer's disease patients showed significantly increased morning cortisol levels when measured in blood [k = 38, g = 0.422 (95% CI: 0.289 to 0.556) $p < 0.001$], saliva [k = 5, g = 0.540, (95% CI: 0.276 to 0.804) $p < 0.001$] and CSF [k = 5, g = 0.565 (95% CI: 0.198 to 0.931) $p = 0.003$]. In contrast, MCI patients showed no differences in cortisol levels when measured in blood [k = 5, g = 0.002 (95% CI: -0.162 to 0.167) $p = 0.978$] or saliva [k = 10, g = 0.106 (95% CI: -0.047 to 0.258) $p = 0.174$] when compared to cognitively-normal controls but showed elevations in CSF cortisol [k = 4, g = 0.309 (95% CI: 0.125 to 0.492) $p = 0.001$].

Note. k: number of effect sizes included in analysis; g: Hedges g effect size; SMD: standardised mean difference; CI: confidence interval; CRP: C-reactive protein; IL: interleukin; IFN: interferon; TNF: tumour necrosis factor; CSF: cerebrospinal fluid; MCI: mild cognitive impairment.

Table 5. Meta-analyses examining associations between childhood trauma and neuroimaging measures in clinical and non-clinical populations

Author	Population	Measure	Findings
Nikolova et al. (2021)	Psychiatric disorders	Gut microbiota alterations across psychiatric disorders	<p>Analysis of alpha diversity showed a significant decrease in richness (number of species) across all observed species compared to controls for pooled analysis of all psychiatric disorders [k = 20, SMD = -0.26 (95% CI: -0.47 to -0.06) <i>p</i> = 0.01] and for sub-analyses examining bipolar disorder [k = 3, SMD = -0.61 (95% CI: -1.19 to -0.03)], but no significant differences in sub-analyses comparing patients with MDD [k = 6, SMD = -0.16 (95% CI: -0.58 to 0.27)] or schizophrenia and psychosis [k = 4, SMD = -0.04 (95% CI: -0.31 to 0.24)] with controls.</p> <p>Studies examining Chao1 showed a significant decrease relative to controls when data were pooled across all psychiatric disorders [k = 26, SMD = -0.5 (95% CI: -0.79 to -0.21) <i>p</i> = .001], and significant decreases for bipolar disorder [k = 4, SMD = -0.53 (95% CI: -1.01 to -0.05)] and anorexia nervosa [k = 4, SMD = -0.86 (95% CI: -1.52 to -0.21)]. No significant differences were observed for sub-analyses comparing controls with MDD [k = 6, SMD = -0.34 (95% CI: -1.08 to 0.40)] or schizophrenia and psychosis patients [k = 7, SMD = -0.58 (95% CI: -1.29 to 0.12)],</p> <p>Compared to controls, no significant differences in the Shannon index were observed across all psychiatric disorders [k = 29, SMD = -0.12 (95% CI: -0.27 to 0.03) <i>p</i> = .11], MDD [k = 11, SMD = -0.28 (95% CI: -0.62 to 0.06)], bipolar disorder [k = 4, SMD = 0.09 (95% CI: -0.43 to 0.62)], or schizophrenia and psychosis [k = 8, SMD = -0.02 (95% CI: -0.20 to 0.17)]. No differences compared to controls in the Simpson index were observed across all psychiatric disorders [k = 11, SMD = 0.04 (95% CI, -0.13 to 0.21) <i>p</i> = .66] MDD [k = 5, SMD = 0.14 (95% CI: -0.14 to 0.43)], or bipolar disorder [k = 3, SMD = -0.03 (95% CI: -0.34 to 0.28)].</p> <p>Phylogenetic diversity was significantly reduced when data from all psychiatric patients were compared with controls [k = 10, SMD = -0.24 (95% CI, -0.47 to -0.0012) <i>p</i> = .049], but not in sub-analyses examining MDD [k = 4, SMD = -0.42 (95% CI: -0.96 to 0.13)] or schizophrenia and psychosis [k = 3, SMD = -0.01 (95% CI: -0.22 to 0.20)].</p>
Safadi et al. (2022)	Severe mental illness	Biomarkers of gut dysbiosis differences in severe mental illness	<p>A combined analysis of BPD and MDD samples showed significant increases in zonulin [k = 4, SMD = 0.97 (95%CI: 0.10 to 1.85) <i>p</i> = 0.03] relative to controls. Antibodies to endotoxins were significantly elevated in BPD [k = 2, SMD = 0.72 (95% CI: 0.54 to 0.90)], MDD [k = 2, SMD = 0.77 (95% CI: 0.43 to 1.12)], but not schizophrenia [k = 3, SMD = 1.16 (95% CI: -0.48 to 2.81)]. Soluble CD14: significantly elevated relative to controls in BPD [k = 3, SMD = 0.61 (95% CI: 0.15 to 1.07)] but not schizophrenia [k = 3, SMD = 0.29 (95% CI: -0.24 to 0.82)]. Alpha-1-antitrypsin was significantly elevated in MDD [k = 3, SMD = 0.94 (95% CI: 0.35 to 1.53)] and schizophrenia [k = 3, SMD = 1.79 (95% CI: 1.16 to 2.42)] relative to controls. Intestinal fatty-acid binding protein showed no significant differences in comparisons between MDD and controls [k = 3, SMD = 0.30 (95% CI: -0.21 to 0.82)].</p>

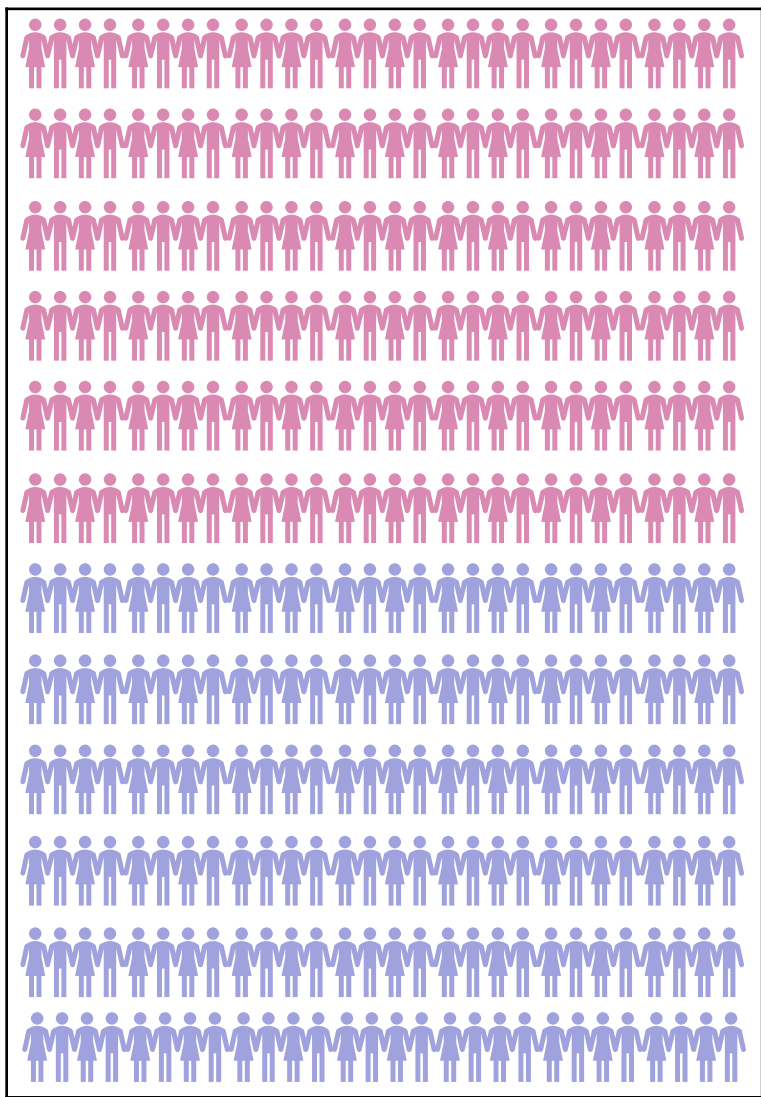
Note. k: number of effect sizes included in analysis; SMD: standardised mean difference; CI: confidence interval; *r*: correlation coefficient; MDD: major depressive disorder; BPD: bipolar disorder.

Table 6. Meta-analyses examining treatment effects

Author	Population	Measure	Findings
Capuzzi et al (2017)	Medication-naïve FEP	Cytokines levels following 4 weeks of antipsychotic treatment	Among medication-naïve FEP patients, levels of IL-2 [k = 2, SMD = -0.47 (95% CI: -0.87 to -0.07) $p = 0.023$] and IL-6 [k = 4, SMD = -0.51 (95% CI: -0.92 to -0.11) $p = 0.012$] were significantly reduced following 4 weeks of antipsychotic treatment. No differences observed in levels of IL-1 β [k = 4, SMD = -0.19 (95% CI: -0.66 to 0.28) $p = 0.437$], IL-17 [k = 2, SMD = -0.57 (95% CI: -1.22 to 0.09) $p = 0.088$], IFN- γ [k = 2, SMD = -0.42 (95% CI: -0.87 to 0.03) $p = 0.068$] or TNF- α [k = 4, SMD = 0.03 (95% CI: -0.16 to 0.22) $p = 0.745$] were observed.
Jeppesen et al (2020)	Schizophrenia and other psychotic disorders	Response to immunomodulating medications	Treatment with antipsychotics and anti-inflammatory treatment was associated with a significant improvement in total psychopathology [k = 55, SMD = -0.29 (95% CI: -0.40 to -0.19) $p < 0.001$], positive psychotic symptoms [k = 56, SMD = -0.13 (95% CI: -0.21 to -0.05) $p = 0.002$], negative symptoms [k = 55, SMD = -0.23 (95% CI: -0.35 to -0.12) $p < 0.001$], general psychopathology [k = 44, SMD = -0.16 (95% CI: -0.26 to -0.06) $p = 0.002$], and symptom severity [k = 13, SMD = -0.22 (95% CI: -0.40 to -0.03) $p = 0.024$] compared to antipsychotic medication and placebo, but was not associated with a significant improvement in functioning [k = 7, SMD = 0.14 (95% CI: -0.13 to 0.42) $p = 0.312$].
Lombardo et al (2019)	Mood disorders (major depression with and without psychotic features and bipolar)	Baseline cortisol levels and response to anti-glucocorticoid treatment	In combined analysis of antiglucocorticoid treatments combined, treatment responders showed no differences in baseline cortisol levels compared to non-responders [k = 16, SMD = -0.025 (95% CI: -0.173 to 0.124), $p = 0.747$]. In sub-analyses examining cortisol synthesis inhibitors, responders showed significantly higher peripheral baseline cortisol levels compared with non-responders [k = 4, SMD = 0.421 (95% CI: 0.010, 0.833), $p = 0.045$]. In sub-analyses examining GR antagonists, no differences in cortisol levels were observed in comparisons between responders and non-responders [k = 12, SMD = -0.092 (95% CI: -0.251, 0.068) $p = 0.261$].
Minichino et al (2021)	Schizophrenia and other psychotic disorders	Response to gut-microbiome targeted interventions	Compared to placebo, adjunctive treatment with sodium benzoate was associated with significant improvement in negative symptoms [k = 2, SMD = -0.63 (95% CI: -1.03 to -0.23) $p < 0.001$], positive symptoms [k = 2, SMD = -0.94 (95% CI: -1.35 to -0.53) $p < 0.001$], and total symptoms [k = 2, SMD = -0.68 (95% CI: -1.08 to -0.28) $p = 0.001$]. Analyses for negative symptoms showed that neither D-cycloserine [k = 10, SMD = -0.16 (95% CI: -0.40 to 0.08) $p = 0.20$] nor minocycline [k = 7, SMD = -0.35 (95% CI: -0.70 to 0.00) $p = 0.05$] were not significantly superior to placebo.

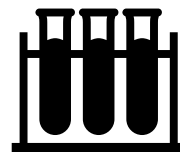
Note. FEP: first-episode psychosis; k: number of effect sizes included in analysis; SMD: standardised mean difference; CI: confidence interval; CRP: C-reactive protein; IL: interleukin; IFN: interferon; TNF: tumour necrosis factor; GR: glucocorticoid receptor.

PROSPECTIVE COHORTS



Large-scale, multisite, prospective studies recruiting high-risk individuals and first-episode psychosis patients whose outcomes are unknown

DATA



Collection of multiple measures of psychosocial stress exposure, putative stress biomarkers (HPA axis, immuno-inflammatory, gut-microbiome), and brain structure/function

MULTIVARIABLE PREDICTION MODELS

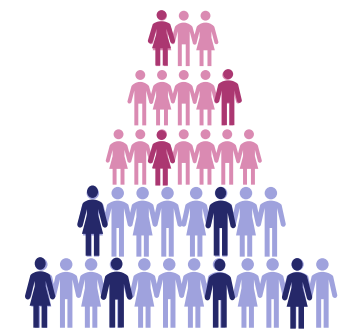
Psychosis onset

Poor disorder trajectory

Brain structure/function

Multivariable models combining psychosocial stress and putative stress biomarkers with clinical and demographic measures to predict clinical outcomes and changes in brain structure and function

EXTERNAL VALIDATION



TRANSLATIONAL IMPACT