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Chapter 6

Immune dysregulation as an intermediate between social adversity and psychosis: a systematic review

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Submitted

Abstract

Social adversity during childhood increases risk for psychosis later in life. Multiple pathways are thought to play a role, one of these is immune dysregulation. We systematically review studies that examined the association between immune dysregulation and exposure to environmental risk factors (1) childhood trauma (2) ethnic minority status and (3) growing up in an urban environment in psychosis patients. There is extensive literature on the association between childhood trauma and low-grade inflammation in the general population. In psychosis patients, studies also find the association between low-grade inflammation and trauma (most commonly measured markers IL-6, CRP and TNF-α), but the evidence is less robust and lacks replication for individual markers. For ethnic minority status and urbanicity, the available literature in psychosis patients is very limited. Findings from the general populations support an association between race/ethnicity with low-grade inflammation and between neighborhood characteristics with low-grade inflammation. In this review, we further comment on mediators and moderators, including increased stress levels and obesity. Lastly, we hypothesize that immune activation in response to social adversity in childhood may be an adaptive response to adverse circumstances.

Introduction

Psychosis is a multifactorial condition characterized by hallucinations, delusions, disorganization and negative symptoms [1]. It is thought to arise from an interaction between genetic susceptibility and exposure to environmental risk factors. A growing body of evidence points to the importance of exposure to social adversity as one of the environmental risk factors [2,3]. Social stressors such as childhood trauma, densely populated urban environments and ethnic minority status are consistently associated with psychotic disorders. Furthermore, they are so in a dose-response manner and across varying designs, indicating a causal mechanism.

Social adversity is particularly detrimental when exposure occurs early in life, whereas disease onset is typically not until adolescence or early adulthood. Immune dysregulation has been proposed as a possible link between environmental risk factors and psychotic disorders. The immune system is intrinsically sensitive to modulation by environmental exposures, including psychosocial stressors [4]. Further, there is accumulating evidence for low-grade inflammation in patients with psychotic disorders. This includes aberrant levels of peripheral cytokines, numbers and functioning of immune cell populations and activation of microglia in psychosis patients [5]. It remains an open question whether these immune changes are the cause or consequence of psychosis. In support of a more causal role, immune dysregulation has an impact on brain function which could make the brain vulnerable for psychosis [6].

Here, we further explore immune dysregulation as an intermediate between exposure to social adversity in early life and psychotic disorders in later life. Several excellent reviews discuss links between immune dysregulation and psychotic disorders and potential underlying mechanisms [6–8], but the link between specific social stressors relevant to psychosis and low-grade inflammation is not yet reviewed. We therefore review the evidence of associations between exposure to social stressors and immune dysregulation in the context of psychosis. We focused on three social stressors most consistently linked to psychotic disorders, namely (1) childhood trauma, (2) ethnic minority status and (3) growing up in an urban environment (urbanicity). We have systematically reviewed studies that examined the association between exposure to one of these three stressors and immune dysregulation in psychosis patients. We also discuss findings in the general populations as well as other patient populations.

Methods

Pubmed, MEDLINE, EMBASE and PsycINFO were searched with the following key words: (1) inflammation, immunology, cytokine, C-reactive protein AND (2) psychosis, schizophrenia AND (3a) childhood trauma, child abuse, child maltreatment, early life adversity (3b) race/ethnicity, ethnic minority, immigrants, discrimination (3c) urbanicity, urbanization, urban environment, population density.

Inclusion criteria were as follows (a) published in English or Dutch (b) including patients with diagnosis of psychotic disorder or assessment of (subclinical) symptoms of psychotic disorder (c) quantitative data on inflammatory markers, including cytokines and immune cell populations (d) including childhood trauma or race/ethnicity or urbanicity as a predictor of inflammatory markers.

Exclusion criteria were as follows (a) genetic studies not quantifying inflammatory markers (b) studies reporting solely on infectious agents (c) studies reporting on prenatal (e.g. intrauterine) exposure only, including measurements in newborn blood spots (d) reviews and theoretical articles, case reports, editorials and conference abstracts.

The last search was conducted on July 1st 2020. The preliminary search retrieved 148 studies for childhood trauma, 58 for urbanicity and 817 for ethnic minority status. One additional study was retrieved by cross-referencing.

Titles and abstracts were analyzed for inclusion and exclusion criteria by two researchers (JC, MvB and WV) independently. Where necessarily, full-text papers were retrieved and assessed. Dissimilarities were discussed until consensus was reached.

Results

Our systematic literature research yielded nine papers for childhood trauma, six for ethnic minority status and one for urbanicity (Table 6.1). Below, we summarize these findings. For each stressor, we start with a short introduction of the stressor and we discuss findings in both general and high risk populations.

Childhood trauma

Introduction

The term childhood trauma includes a wide range of adverse experience during early life, including abuse (sexual, physical or emotional), neglect, peer victimization (bullying), parental loss or separation and exposure to war or natural disaster. Adversities may occur as single or repeated traumatic events or may even have a chronic character. Exposure to multiple types of adversity is common and exposure to one type of adversity increases the risk of exposure to another. Child maltreatment tends to cluster with other risk factors across the lifespan. Such problems of definition, varying measuring methods and potential confounders have long created controversy surrounding the increased incidence of trauma in psychosis. However, an accumulating number of methodologically sound studies, using varying experimental designs and accounting for potential confounders have consistently found a strong association between childhood trauma and psychotic disorders, with evidence for a dose-response relationship [28–33]. In a meta-analysis, childhood adversity and trauma increased the risk of psychosis with an odd-ratio of 2.8 [34].

Childhood trauma and low-grade inflammation in general and other populations

Childhood trauma was shown to be associated with inflammatory markers, such as CRP, IL-1β, IL-6 and TNF-α in both the general population as well as in various patient populations. In large prospective studies, childhood maltreatment during the first decade of life was associated with markers of inflammation in adults [35]. A dose-response relation was found between severity of maltreatment and increased levels of C-Reactive Protein (CRP), fibrinogen and white blood cell count. In this cohort study, children exposed to maltreatment were also more likely to have a low birth weight and grow up under low socio-economic conditions. Furthermore, they were more likely to engage in health-damaging behaviors and experience high stress levels in adult life. Even after controlling for these variables related to maltreatment and for high cardiovascular risk profiles, the increase in inflammatory markers remained visible. This supports the idea that child maltreatment is indeed an independent risk factor for low-grade inflammation [35].

The effects of early life adversity on low-grade inflammation are apparent both during childhood and adolescence [36,37]. Furthermore, effects persist along the lifespan as evident in older adults giving care for a spouse with Alzheimer who were compared with non-caregiver older adults. Among both caregivers and non-caregivers, those who experienced maltreatment as children were more likely to have higher levels of IL-6 and TNF-α than those who did not. Strikingly, even the chronic and severe stress of caregiving for a spouse with dementia was offset by the long-lasting effect of maltreatment during early childhood [38].

Table 6.1. Results of systematic literature search of exposure to social adversity and low-grade inflammation in psychosis.

	Participants	Childhood Trauma (measure, prevalence)	Measures	Results
Corsi-Zuelli et al. (2020) [9]	- 114 first-episode psychosis patients (64 % male, age 30.8±12.5, BMI 24.8±5.1) - 57 unaffected siblings (32% male, age 30.7±10.5, BMI 24.9±4.9) - 251 community-based controls (51 % male, age 31.3±11.0, BMI 26.2±5.3)	- CTQ[1] dichotomized. - Childhood trauma was reported by 43.9% of patients and 22.7% of controls***. - EA**, PA**, EN*** and PN*, but not SA were reported more often by patients than controls. - Frequency of adverse life events in the last year was higher in controls than patients**.	IL-1β, IL-4, IL-6, IL-10, IFN-γ, TGF-β, TNF-α	- FEP had increased levels of IL-6***, TNF-α***, IL-10*** and TGF-β** compared to controls. - physical abuse was associated with higher levels of TGF-β in patients*, but with lower levels of TGF-β in controls*. - no other associations of trauma with cytokines. - controlled for age, gender, BMI, substance use, education and relationship status and recent stress.
Counotte et al. (2019) [10]	- 49 patients with high psychosis liability (38 recent onset psychosis patients + 11 patients at ultra-high risk for psychosis) (76% male, age 25.9±4.7, BMI 23.2±4.3) - 68 controls with low psychosis liability (29 non-affected siblings of psychosis patients + 39 healthy controls) (51% male, age25.2±4.8, BMI 23.1±3.4)	- CTQ[1] dichotomized. - Childhood trauma was reported by 16.2% in low liability group and 59.2% in high liability group***.	BDNF, CCL2, CRP, IFN-γ, IGFBP-2, IL-6, PDGF, SCF, TNF-α	- No statistically significant main or interaction effects of psychosis liability or childhood trauma on concentrations of cytokines or growth factors in peripheral blood were found. - neither in uncontrolled models nor models controlled for age, gender, BMI, smoking, cannabis use and oral contraceptive use.
Chase et al. (2019) [11]	- 20 patients with schizophrenia and 'present state psychosis' (50% male, age 37.9±12.4, BMI 34.9±7.6) - 20 healthy controls (50% male, age 38.2±13.5, BMI 27.9±6.5)	- ACE[2] questionnaire. - Schizophrenia patients had higher scores in total (5.70±2.11 vs. 3.45±2.95)** and for subscales abuse (2.50±0.76 vs. 1.45±1.47)** and dysfunction (1.90±0.91 vs. 1.20±1.51)* than controls.	Expression levels of *CXCL10*, *IFNG*, *IL6*, *IRF1*, *STAT1* and TLR4 mRNA in peripheral blood mononuclear cells	- In schizophrenia patients, *IL6*** expression was higher and *IFNG***, *CXCL10**, *IRF1**** and *STAT1** expression was lower than in controls. - TLR4 was not significantly different. - total ACE scores correlated positively with *IL6* mRNA in controls and patients and negatively with *IRF1* and *TLR4* mRNA in controls only. - No associations between ACE scores and *IFNG*, *CXCL10* and *STAT1* mRNA levels. - not controlled for BMI.
Quide et al. (2018) Psychological Medicine [12]	- 68 patients with psychotic disorder (42 schizophrenia and 26 schizoaffective disorder) (57% male, age 41.8±11.3) - 69 patients with bipolar 1 disorder with psychotic features (33% male, age 38.1±12.3) -72 healthy controls (53% male, age 36.2±11.6) - no data on BMI provided	- CTQ[1] total and subscale scores. - Patients with psychotic disorders had significantly higher scores compared to controls both for total CTQ score (48.5±16.8 vs. 37.6±11.9)*** as well for subscales EA (11.6 ±5.4 vs. 8.6±4.2)**, SA (8.3±4.6 vs. 6.0±2.6)**, EN (12.0±4.8 vs. 9.5±3.6)** and PN (8.5 ±3.3 vs. 6.9±2.6)**.	IL-6, TNF-α and CRP	- levels of IL-6**, TNF-α* and CRP* were increased in psychosis group compared to healthy controls. - Exposure to sexual abuse was associated with CRP-levels in the psychosis group*. - There were no associations between trauma exposure and cytokine levels in healthy controls (or bipolar patients). - controlled for age, sex, symptom severity and medication use.
Counotte et al. (2018) [13]	- 52 patients with high psychosis liability (38 recent onset psychosis patients + 14 patients at ultra-high risk for psychosis) (69% male, age 25.9±4.7, BMI 23.9±4.7) - 80 controls with low psychosis liability (34 non-affected siblings of psychosis patients + 46 healthy controls) (49% male, age 25.2±4.6, BMI 23.5±3.8)	- CTQ[1] dichotomized. - Childhood trauma was reported by 18.8% in low liability group and 57.7 % in high liability group***.	NK and Th1, Th2, Th17 and Treg populations. (flow cytometry)	- no significant main effect of psychosis liability or childhood trauma on Th1, Th2, T regulator, Th17 or NK cell populations. - significant interaction effect: In the high psychosis liability group, childhood trauma was associated with increased Th17 cell numbers*. - controlled for age, sex, ethnicity, education level and smoking.
Aas et al. (2017) [14]	- 148 patients with schizophrenia (59% male, age 28.6±9.3, BMI 26.3±5.5) - 123 patients with bipolar disorder (41% male, age 32.2±11.7, BMI 24.0±3.4) - 212 healthy controls (59% male, age 30.9±7.5, BMI 24.0±3.4)	- CTQ[1] abuse scales (PA, EA, SA) only were used. Total scores of these scales were used. Severity was defined as no, one, two or three types of abuse (dichotomized). - Total scores were higher for schizophrenia patients compared to controls (PA: 7.0±3.5 vs. 5.1±0.6*, SA 6.8± 3.4 vs. 5.1±0.6*, EA 11.4±5.2 vs. 6.3±2.1*). - Patients (BD+SZ): 0 (n=157),1 (n=54), 2 (n=32) or 3 (n=17) types of abuse - Controls: 0 (n=202) or 1 or more types of abuse (n=8)	CRP, gp130 (IL-6 antagonist), sTNFR-R1	- schizophrenia patients had increased levels of CRP, decreased gp130, higher BMI and reported more childhood trauma. - Severity of abuse was associated with elevated BMI*** and CRP**. - Combined effects of disease** and abuse* were found for CRP, but disappeared when BMI was added to the model.
Di Nicola et al. (2013) [15]	-24 first-episode psychosis patients (10 schizophrenia-like, 9 affective, 5 NOS) (67% males, age 28.1 ± 1.1) - 24 healthy controls (63% males, age 26.6 ± 0.9) - BMI was not significantly different (p=0.1) between groups due to matching, but no data on BMI was provided.	- Modified version of CECA[2] questionnaire. - No data on prevalence of childhood trauma among participants.	- serum levels of IL-1α, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, TNF-α, IFN-γ, VEGF, EGF, MCP-1 - leukocyte gene expression of *IL1A, IL1B, IL6, IL8, TNFA*	- Patients had significantly higher serum levels of IL-1α*, IL1-β**, IL-8** and TNF-α* - Patients had higher leukocyte mRNA levels of *IL1A**, *IL6*** and *TNFA****. - In HC, those with childhood trauma had significantly higher mRNA-levels of *IL1B**. In patients, those with childhood trauma had significantly higher serum level of TNF-α** and MCP-1** and lower serum levels of VEGF**. - No correlation between BMI or duration of antipsychotic treatment and cytokines.

Dennison et al. (2012) [16]	- 40 patients (34 schizophrenia and 6 schizoaffective disorder) (60% male, age 38.33±1.7, BMI 27.94±0.85) - 40 healthy controls (33% male, age 36.2±1.76, BMI 23±0.83)	- Self-report presence of psychological trauma in childhood, namely (1) death of a family member or close friend in childhood (2) parental separation (3) exposure to physical abuse (4) exposure to sexual abuse (5) exposure to violence - 60% of patients and 20% of controls reported psychological trauma in childhood. Patients reported on average more childhood traumatic events than controls (1.75±0.24 vs. 0.67±0.15***)	IL-1β, IL-6, IL-8, TNF-α	- IL-1β and IL-8 not different between 3 groups: schizophrenia patients with childhood trauma (SCZ+), schizophrenia patients without childhood trauma (SCZ-) controls without childhood trauma (CON-). - IL-6 significant higher in SCZ+ compared to CON-* (difference with SCZ- not significant) - TNF-α significantly higher in SCZ+ compared to SCZ-* and CON-***. - TNF-α significantly associated with number of traumatic events*. - Patients had significantly higher BMI**. There was no significant difference in cytokines between obese and non-obese patients.
Hepgul et al. (2012) [17]	- 37 first-episode psychosis patients (24 schizophrenia-like, 7 affective psychosis, 1 delusional disorder, 5 NOS) (65% male, age 28.5±1.1, BMI 25.5±1.2) - 49 healthy controls (74% male, age 26.3±0.6, BMI 23.4±0.5)	- Modified version CECA[3] questionnaire (incl. loss of parents, separation from parents, physical abuse and sexual abuse) - mean no of childhood trauma: patients 1.0±0.2, controls: 0.7±0.1 (p=0.1)	CRP	- CRP was higher in patients compared to controls*. - Trend for difference between three groups patients with any trauma, patients without any trauma and controls (p = 0.089). - Patients with severe sexual abuse had higher CRP levels than patients without sexual abuse*** and controls***. - CRP was correlated with BMI in patients* but not controls. - BMI was higher in patients with sexual abuse than in patients without sexual abuse (p=0.055) and controls**.

	Participants	Ethnicity	Measures	Results
Stubbs (2015) [18]	- U.K. - 250 patients with established psychosis (60.8% male, age 48.2 ± 10.2)	54.4% white 33.6% black British 12.0% other non-white (Self-report ethnicity)	CRP levels dichotomized into high or normal (cut-off 5.0 mg/µl)	- 36.4% of participants had high CRP levels. - Non-white ethnicity predicted high CRP-levels**
Mahendran et al. (2004) [19]	- Singapore - 30 patients with schizophrenia (all male, age range 20-69) - 10 healthy Chinese controls males (age range 20-49, all male)	Patients: 16 Chinese, 9 Malays, 4 Indians and 1 Mixed parentage (Chinese/Indian) Controls: all Chinese	IL-2 production after in vitro stimulation with Phytohaemagglutinin (5 mL/mL for 48 hrs)	- IL-2 levels were lower in patients than controls*** - No differences in IL-2 Levels across the different ethnic groups
Rapaport et al. (1994) [20]	- U.S.A.: - 37 schizophrenia patients (51% male, age 36 ± 2.7) - 37 controls (age 31.6 ± 7.9, 51% male) Korea:(samples were air-shipped to U.S.A.) - 61 schizophrenic patients from chronic psychiatric hospital ward (84% male, age 30.6 ± 7.3) - 35 controls (76% male, age 29.8 ± 5.2)	All participants from U.S.A. were Caucasian. All participants from Korea were Korean.	Soluble interleuk-2 receptor (sIL-2R)	- Caucasian patients had higher sIL-2R levels than Caucasian controls** and Korean patients*** - Korean patients had higher levels than Korean controls***
Ganguli et al. (1994) [21]	- 128 schizophrenia patients (55% male, age 34.5 ± 10.0) - 110 controls (55% male, age 31.7 ± 10.5)	Patients: 57 white, 55 black Controls: 64 white, 34 black	IL-6	- Mean IL-6 concentration was significantly higher in patients** - African-American patients had higher IL-6 levels than Caucasian patients*. - Among controls, there was no significant difference in IL-6 levels between Caucasians and African-Americans.
Ganguli et al. (1992) [22]	- 122 patients with schizophrenia (56% male, age 33.9 ±11.6) - 98 controls (44% male, age 30.5 ± 8.8)	Patients: 65 black, 57 white Controls: 34 black, 64 white	IL-2 production in vitro after PHA stimulation (1o ng/ml) measured indirectly by thymidine proliferation assay of IL-2 dependent murine cytotoxic T cells.	- Black subjects produced significantly lower IL-2 than white subjects. - After correction for race, patients had lower IL-2 production than controls*.
Strahilevitz et al. (1976) [23]	- 19 schizophrenia patients presenting to emergency room with psychotic symptoms (47% male, age 34 ± 11.47) - 31 controls (48% male, age 30.8 ± 11.1)	Schizophrenia patients: 11 black, 8 white Controls: 14 black, 17 white	Immunoglobulin G, A, M and D (radial immunodiffusion in agar gels), defined as high (above median) or low (at of below median)	- IgA was higher in schizophrenia blacks than in either schizophrenia whites* or black controls**. - IgD was higher in schizophrenia blacks than in schizophrenia whites*.

	Participants	Urbanicity	Measures	Results
Pulkkinen (1977) [24]	76 clinically admitted schizophrenia patients (50% male, average age 34.8)	Residential environment (rural–urban). Definitions unclear	Serum IgA, IgG and IgM	Place of birth (rural–urban) was negatively correlated with IgA concentration**.

Age is mean ± SD unless stated otherwise
All measures were taken from peripheral blood.
[1]CTQ = Child Trauma Questionnaire: a retrospective self-report questionnaire, including five subscales: emotional abuse (EA), emotional neglect (EN), physical abuse (PA), physical neglect (PN) and sexual abuse (SA). Subscale scores as well as total scores are yielded. Furthermore, norm scores are available to classify each subscale as none/minimal, low/moderate, moderate/severe or severe/extreme [25], which is commonly dichotomized intro presence (yes/no) of moderate/severe trauma.
[2]ACE = Adverse Childhood Experiences. A ten-item questionnaire is used to (binary) assess experiences occurring prior to the age of 18 related to (1) abuse (emotional, physical and sexual) (2) neglect (emotional and physical) and (3) household dysfunction (parental separation/divorce, violence against mother, household substance abuse and incarceration of household member) [26].
[3]CECA = Childhood Experience of Care and Abuse questionnaire: a self-report questionnaire to determine absence of presence of adverse experiences during childhood, namely parental loss, parental care (neglect and antipathy), physical abuse and sexual abuse. Cut-off points are published to dichotomize responses into severe and non-severe categories [27].
*p <0.05, **p<0.01, ***p<0.001.

Furthermore, childhood trauma was associated with higher levels of inflammatory markers in the context of diverse pathology, including depression [39–42], post-traumatic stress disorder [39,43], breast cancer [44] and migraine [45]. A raise in CRP was the most robust finding among the various markers measured [46]. A transdiagnostic meta-analysis across various psychiatric and non-psychiatric conditions confirmed the association between childhood trauma and increased inflammatory markers in adulthood, which largest effects sizes of trauma exposure on IL-1β, IL-6, TNF-α and CRP [47].

Systematic review of childhood trauma and low-grade inflammation in psychosis patients

Our literature search revealed nine research papers reporting on the relation between childhood trauma and inflammatory markers in psychosis patients (Table 6.1). Seven papers measured inflammatory markers, two measured expression levels (mRNA) of inflammatory markers and one measured immune cell populations. All measures were taken from peripheral blood. Comparing and interpreting findings is challenging as the specific set of markers, the patient populations and the statistical analysis methods varied between studies. Some (especially earlier) studies use sensitivity analysis of subgroups with and without childhood trauma, whereas others have more formally tested independent and combined effects of disease state and childhood trauma on inflammatory markers.

The most commonly examined markers are CRP, IL-6 and TNF-α. The first reports found that CRP [17], IL-6 and TNF-α [16] were raised only in the subset of psychosis patients that had been exposed to childhood trauma. Moreover, TNF-α levels correlated with the extent of the trauma [16]. The increase in CRP levels appeared specific for patients who had experienced sexual abuse [17]. These early findings were partially replicated by later studies. Quide et al. (2018) also found that sexual abuse was associated with CRP in psychosis patients – but not in a combined psychosis/bipolar group, bipolar group or in healthy controls [12]. A large study by Aas et al. (2017) [14] also found significant effects of both disease state and severity of childhood trauma on CRP levels. When BMI was added to the model in mediation analysis, the relationship between childhood trauma and CRP levels became non-significant [48]. In our own sample of recent onset psychosis patients with relatively low BMI, we did not find an association of childhood trauma with CRP [10]. Chase et found that adverse childhood experiences were correlated positively with *IL6* mRNA in controls and patients. Others did not confirm associations between childhood trauma and IL-6 levels in psychosis patients [9,10,12]. Associations between trauma and TNF-α in psychosis patients were not found by three other studies [9,10,12]. Di Nicola et al.

(2013) found that childhood trauma was associated with increased TNF-α levels in psychosis patients only [15].

As summarized in Table 6.1, there are more reports of childhood trauma and single inflammatory markers. In multiple studies, these associations are different for psychosis patients and healthy controls. For example, childhood trauma was associated with decreased MCP-1 and VEGF levels in psychosis patients and with higher mRNA levels of IL-1β in healthy controls. Childhood trauma was associated with increased Th17 cell numbers in a high psychosis liability group only [13]. Physical abuse was associated with higher levels of TGF-β in first episode psychosis patients, but lower levels of TGF-β in controls [9]. Adverse childhood experiences were correlated negatively with *IRF1* and *TLR4* mRNA in controls only [11]. Possibly, childhood trauma affects inflammatory pathways differently in patients with genetic susceptibility for psychosis. However, these are all single reports, without replication and in most studies, it is unclear if they correct for multiple testing, which is concerning because multiple markers and sometimes multiple types of childhood trauma were analyzed.

Summary

There is a large body of evidence for an association between childhood trauma and low-grade inflammation in the general population and in the context of diverse psychiatric and somatic morbidity. Nine papers have investigated the association between childhood trauma and inflammatory markers in psychosis patients specifically. The largest study to date found an association between CRP and childhood trauma that was explained by BMI and our own group reported a negative study. The other studies reported associations between childhood trauma and specific markers of inflammation in psychosis patients, but none of these results were replicated and the magnitude of the effect in IL-6, CRP and TNF-α was variable between studies. In addition, most studies were unable to control for BMI and other variables.

Ethnic minority status

Rates of psychotic disorders are increased among immigrant populations. A meta-analysis of over 40 individual studies yielded a relative risk of 2.13 for non-affective psychosis [49]. The risk varies greatly and is far greater for specific ethnic minority groups [50]. Both first and second generation migrants are affected, indicating ethnic minority position is relevant rather than personal migration history [49]. Rates vary greatly depending on the social context [50]. Strikingly, rates are highest among immigrants living in neighborhoods where their own ethnic group comprised a smaller proportion of the population (low ethnic density) [51,52]. Also, higher rates are reported among groups that are more visually apparent, with a darker skin color in Northern Europe [49]. It is thought that exposure to discrimination and threat are primary determinants of increased risk [50].

Systematic review of ethnic minority status and low-grade inflammation in psychosis patients

Research on associations between ethnic minority status and low-grade inflammation in psychosis patients is limited to papers exploring the role of ethnicity/race as a potential confounder. Only six papers reported data on associations between ethnicity/race and inflammatory makers in psychosis patients (Table 6.1). Among 19 schizophrenia patients presenting to emergency room with psychotic symptoms, IgA and IgD levels where higher in black patients than in white patients [23]. Rapaport compared soluble interleukin-2 receptor levels in Caucasian and Koreans psychosis patients and controls. SIL-2R levels were significantly higher for patients compared to controls and significantly higher for Caucasians compared to Koreans. However, this concerned Koreans residing in Korea and Caucasians in the U.S.A. and therefore not an ethnic minority populations [20]. Ethnicity was shown to correlate with IL-6 levels and PHA-stimulated IL-2 production in Caucasian and African-Americans [21,22]. However, the latter was not confirmed in a – very small - Singaporean population of 16 Chinese, 9 Malay, 4 Indian and 1 mixed Chinese/Indian schizophrenia patients [19]. In a multi-ethnic sample of 250 psychosis patients in England, non-white ethnicity predicted high CRP levels (> 5.0 mg/µl) [18].

Ethnic minority status and low-grade inflammation in other populations

Associations between race/ethnicity and inflammatory markers have been studied in several large cohort studies of the general population designed to identify risk factors for morbidity and mortality. In this context, low-grade inflammation is considered a risk factor and is most commonly assessed by CRP levels. In Western societies, CRP levels are higher in individuals with African, Latin American or South Asian ancestry compared to those with an European background [53]. In the US National Health and Nutrition Examination Study (NHANES), mean CRP levels were higher in the non-Hispanic black group (n=1978) and the Mexican American group (n=2260) compared to the white (n=4858) and other Hispanic groups (n=1053) [54]. In the community based multi-ethnic Dallas Heart Study (740 black men, 1018 black women, 475 white men and 516 white women), female gender and black race were both associated with higher CRP levels, before and after adjustment for traditional cardiovascular risk factors including age, lipids, BMI, estrogen and statin use [55]. In the Netherlands, CRP levels were higher among Turkish immigrants and Moroccan woman in Amsterdam compared to native Dutch. While traditional cardiovascular risk factors including BMI attenuated the ethnic differences in high CRP levels in men, they did not in woman [56].

It is interesting to speculate if these ethnic differences in levels of inflammatory markers are due to social stress associated with ethnic minority status. Some studies have addressed discrimination as a relevant exposure. In the Dallas Heart Study, CRP levels were not significantly different between subjects that did or did not report discrimination in any group [57]. Discrimination was defined dichotomously based on a single question if participants had "ever been discriminated against due to race/ethnic background" and as such reported by 48.9% of blacks, 22.0% of Hispanics and 13.6% of whites, which may have been an underestimation. In the Coronary Artery Risk Development in Young Adults (CARDIA) study, a similar, essentially dichotomous question was used to asses discrimination [58]. However, it was asked across seven domains (e.g. school, work, public setting), which revealed a complicated association. For white woman a positive association was found between reported discrimination and CRP levels, whereas no such association was found for white men. For black woman, those who reported discrimination for one or two domains had higher serum levels of CRP than woman not reporting any discrimination or woman reporting discrimination across three domains or more. In contrast, for black men, a negative linear association was found between self-reported experiences of discrimination and CRP levels.

Positive associations with CRP levels were found with "everyday discrimination" in 296 older blacks [59]. Everyday discrimination was defined as a chronic stressor of fairly minor day-to-day forms of interpersonal mistreatment. This does not mention race/ethnicity explicitly and includes discrimination based on e.g. gender or sexuality. Furthermore, higher perceived everyday discrimination was associated with higher CRP levels over a 7 year period in non-obese middle-aged woman from different racial/ethnic groups [60]. For obese (BMI > 30) woman there was no such association. Interestingly, the relationship did not vary across the various groups, including white women.

In a study of 151 Brazilian migrants in the US, those with a longer residence in a neighborhood with lower ethnic density were more likely to have high CRP levels, although this did not reach significance in a multivariate analysis in this small sample size. Non-authorized status, increased neighborhood disorder and decreased social capital were significantly associated with higher CRP levels. There was no white or native control group.

Summary

Ethnicity/race has been associated with low-grade inflammation especially in large population studies. There is some data to support that this association is at least in part dependent on social stressors associated with ethnicity minority status, e.g. discrimination. In psychosis patients, available data does support an association between ethnic minority status and inflammatory markers, but is too limited to draw definite conclusions.

Urbanicity

Introduction

Urban environments are associated with an increased incidence of psychotic disorders [61]. Psychosis risk is higher with increasing degree of urbanization [62]. The highest rates were found for people born in urban environments, regardless of urban residence around disease onset. There is a dose-response relationship between cumulative exposure to urbanicity during upbringing and schizophrenia risk. This renders selective migration of people with (prodromal) psychotic symptoms to urban environments unlikely to account for the findings. Urban environments are characterized by increased incidence of cannabis use, migrant status and other risk factors for psychosis. However, the association between urbanicity and psychosis persists after controlling for these and other confounders. Interestingly, neighborhood characteristics appear critical to the increased risk of psychosis and interact with individual level characteristics. Furthermore, not the individual level characteristics per se, but the degree to which they are exceptional compared to the community are relevant for psychosis risk. Therefore, it is thought that social exclusion may be the underlying pathogenic exposure in the etiology of psychosis.

Systematic review of urbanicity and low-grade inflammation in psychosis patients

Our systematic literature research yielded only one early report on IgA, IgG and IgM titers in schizophrenia patients that included place of residency as a covariate. Urban place of birth was positively correlated to IgA concentration [24].

Urbanicity and low-grade inflammation in other populations

In the general population, there is evidence for an association between neighborhood characteristics and low-grade inflammation. Most studies have focused on socio-economic status (SES) of the neighborhood. While SES explains part of the concept of urbanicity at best, these findings supports the hypothesis that characteristics of the living environment can affect markers of inflammation. Both community and individual-level socioeconomic status were shown to be inversely associated with inflammatory markers [63,64]. In the sample of Pollit et al (2007), area-level SES had a stronger impact on CRP than individual-level SES. Petersen found that community SES remained a significant predictor of IL-6 – but not CRP - after full adjustment for both lifestyle factors and individual SES in a sample of 851 middle-aged adults. In contrast, the association between individual-level SES and inflammatory markers disappeared after adjustment for lifestyle factors. Both

these samples there were multi-ethnic and the strength of associations was dependent on ethnicity. Modulation of the relation between SES level and low-grade inflammation by ethnicity might explain negative findings in a smaller and more homogenous sample of Mexican-American women from San Diego. In this sample, neighborhood SES did not have an additional significant effect on CRP, IL-6 or s-ICAM1 after accounting for individual SES [65]. Individual level SES was significantly associated with lower levels of CRP, IL-6 and sICAM-1. This effect was attenuated to non-significant levels after accounting for obesity and behavioral measures (diet, exercise) [65].

Urban environments differ from rural environments in many aspects besides SES level. In a large study of 8249 adults from 216 urban, suburban and rural Chinese communities, urbanization was defined using a 12-point index capturing community-level physical, social, cultural and economic environments. The composite score of 12 levels of urbanization was associated with higher probability of elevated CRP levels [66]. The association of different components of urbanization was most strongly associated with low-grade inflammation in younger men and middle-aged women and remained significant after correction for individual-level risk sociodemographic, obesogenic and pathogenic risk factors in both these groups for housing conditions, economic activity and access to modern markets. In general, the relation between increasing urbanicity on different components and elevated CRP levels was less pronounced or even reversed in older men and younger women. As China has undergone rapid urbanization and the study was cross-sectional in nature, exposure to urbanization was not necessarily during early childhood.

Some aspects of urbanization may be protective while others are pathogenic. Neighborhood disorder (whether respondents or their neighbors had experienced personal violence, their homes broken in to, property damage or stolen property) was associated with an increased probability of having high CRP levels in a sample of Brazilian migrants in US [67]. In contrast, social capital (neighborhood safe at night, neighbors know each other, share similar value and are willing to help each other) was associated with a decreased probability of high CRP levels in the same sample.

The protective effect of social cohesion was not confirmed in a sample of 5370 participants of the Multi Ethnic Study of Atherosclerosis (MESA) [68]. In this sample, greater levels of neighborhood problems were associated with higher levels of fibrinogen and lower levels of neighborhood safety were associated with higher levels of fibrinogen and IL-6 after adjustment for race/ethnicity and individual level SES. However, neighborhood social cohesion was not consistently associated with inflammatory markers (fibrinogen, IL-6 and CRP) [68].

Another potential protective factor is "walkable urban form", a composite measure including residential density, street connectivity and land use mix. Increased walkability is thought to promote physical activity (walking) and may reduce obesity and low-grade inflammation. After controlling for individual sociodemographic measures, residential density was associated with increased CRP-levels, whereas land mix use is inversely related and thus potentially protective [69].

The balance between pathogenic and protective aspects of urban environment may differ across the world. Surprisingly, in the study of Holmes and Marcelli (2012) [67], migrants born in an urban (Brazilian) environment were less likely to have higher CRP levels. The authors argue that this contradictory finding might be explained by higher levels of urbanization in Brazil being home to greater social and material resources and less exposure to a variety of infectious and other inflammatory exposures in childhood.

Furthermore, the characteristics that constitute pathogenic or protective aspects may differ for sociodemographic groups. Browning (2012) examined changes in burglary rates to levels of CRP in the Dallas Heart Study. They found an association between short-term spikes in burglary rates and CRP levels in men. In woman, short-term increases in burglary was not associated with CRP, but overall prior-year burglary rate change was.

Summary

There is evidence for associations between neighborhood characteristics with inflammatory markers in the general population that cannot be explained by individual-level characteristics of people living in the community. Some aspects of urban environments are protective, while other aspects are pathogenic. The evaluation may differ both on the broader social and geographical setting of the urban environment as well as on the sociodemographic characteristics of the population. Most studies suggest a complex interaction between neighborhood characteristics and individual-level characteristics, including age, ethnicity and gender. The studies have been mostly limited to CRP and IL-6. The determinants for low-grade inflammation and psychosis may partly overlap or differ. While exposure during early life is most critical for psychosis risk, the age and duration of exposure to urbanicity in relation to low-grade inflammation has received very little attention.

Discussion

We hypothesized immune dysregulation is an intermediate between exposure to social adversity in early life and increased risk of psychotic disorders later in life. We reviewed associations between psychosis risk factors (childhood trauma, ethnic minority status and urbanicity) and low-grade inflammation in psychosis. Overall, the evidence we reviewed is limited, but supportive of our hypothesis. There is extensive literature on an association between childhood trauma and low-grade inflammation in the general population. In psychosis patients, studies also find the association between low-grade inflammation and trauma (most commonly measured markers IL-6, CRP and TNF-α), but the evidence is less robust and lacks replication for individual markers. For ethnic minority status and urbanicity, the available literature in psychosis patients is very limited and overall quite dated. Findings from the general population support an association between race/ethnicity with low-grade inflammation and between neighborhood characteristics with low-grade inflammation.

Important methodological limitations need to be considered when drawing conclusions. The included papers were mostly cross-sectional. Exposure to social adversity was assessed retrospectively and measures of inflammation were taken decades after the critical time frame for exposure to social adversity. The main research question of the papers often differed from our own research question, especially for urbanicity and ethnicity. The definition of 'race/ethnicity' and 'urban environments' was in general wider and more varied than common in psychosis research. While the aspect of psychosocial stress is thought to be most relevant for psychosis risk, the association with low-grade inflammation may be (partly) explained by other aspects. For example, urban dwellers are likely to be exposed to different pathogens than farmers in rural areas. Migrants from low-income countries are more likely to have been exposed to helminth infections, which tends to stimulate a regulatory immune response [70]. Deficiency of vitamin D, an immunoregulator, is more likely in migrants with darker skin and in urban environments.

With the limited number of immune markers taken at single time-points it is not possible to fully capture the complexity and dynamics of the immune system. Furthermore, the immune system has reciprocal links with obesity that warrant more exploration than the data of the studies can support. Adipose tissue has endocrinological and immunological activity, with excessive nutrient accumulation and obesity resulting in low-grade inflammation [71,72]. Increased levels of e.g. IL-6 and CRP are observed in obesity [73]. Obesity rates are higher in psychosis patients [74] and all three social stressors are associated with obesity. Obesity rates are higher in migrants [75,76] and groups exposed to childhood trauma [77]. For urbanization, the direction of association is dependent on sociogeographical characteristics of the country [78]. Thus, obesity is important to take into account when considering links between social adversity, immune dysregulation and psychosis. However, not all studies included in this review reported on BMI. For other studies, BMI was reported but sample size restricted opportunities for interaction analyses. Where BMI was reported, it was on average higher in psychosis patients than controls. A notable exception to this rule was a study from our own research group, which was also characterized by an absence of main effects of childhood trauma or psychosis liability on immune cell populations. Other studies found that BMI was associated with both low-grade inflammation and childhood trauma, especially sexual abuse. Only [12] performed a mediation analysis with BMI and found that association between childhood trauma and low-grade inflammation was no longer significant afterwards. As these associations do not tell us anything about causality, it is both possible that obesity is a confounder or an essential mediator of the relation between social adversity, immune dysregulation and psychosis.

Studies discussed in this review all report on measures from peripheral blood. Peripheral inflammation has been shown to have direct and indirect communication links to the brain (see e.g. [79,80]). Firstly, some cytokines can pass the blood brain barrier by diffusion or active transport. Inflammation is thought to make the blood-brain barrier more permeable [81]. Secondly, IL-6 and other pro-inflammatory cytokines activate indoleamine 2,3-dioxygenase (IDO). IDO is an enzyme involved in tryptophan metabolism and activation results in increased levels of quinolinic acid and kynurenic acid. Both are involved in glutamatergic neurotransmission and quinolinic acid is also neurotoxic [82]. Thirdly, peripheral inflammation has been linked to decreased levels of brain-derived neurotrophic factor (BDNF) [83]. BDNF is a growth factor essential for neurodevelopment and plasticity. Reduced BDNF levels have been reported in schizophrenia [84]. Findings by Mondelli et al. suggest by IL-6 is a mediator of the effects of childhood trauma on reduced BDNF expression in patients with psychosis [85]. Fourthly, peripheral inflammation is thought to modulate or mirror microglia function. Microglia are resident immune cells of the brain. Under non-inflammatory conditions, they are important for brain development and homeostasis [86,87]. Post-mortem immunohistochemistry as well as in vivo imaging studies suggest that microglia are abnormally activated in psychosis [88], hindering their role in brain homeostasis.

These are all potential mechanisms for effects of immune activation on brain development and function. While the focus has been on damaging and pathological effects, this is likely to be an oversimplification. In fact, immune activation may be

necessary for normal development and adaptive responses to stress. For example, Th17 cells are traditionally viewed as "pro-inflammatory" and brain destructive. However, recent neuroscience literature shows that under non-inflammatory conditions Th17 cells are essential for hippocampal growth, myelin-related frontal-hippocampal connectivity, stress coping and beneficial mood regulation [89–93]. We should therefore consider the option that immune activation in response to social adversity in childhood may be an adaptive response to adverse circumstances, promoting neurogenesis and white matter integrity to dampen excessive stress responses in the individuals prone to psychosis. The concept of immune activation as an adaptive response is supported by findings of effects of social adversity on immune function independent of disease state. While the focus is often on pathology, it would be interesting to examine resilient groups in more detail, to find out if similar pathways are activated, but result in different outcomes (and why) or if activated pathways somehow differ. Potentially this could lead to discovery of pathways that could be strengthened to promote resilience.

We focused this review specifically on psychosis and three social stressors in particular. However, the underlying mechanisms are likely to be involved in other exposures and outcomes. Other stressors, both genetic and environmental and both psychological and biological in nature have effects on the immune system. Dysregulation of the immune system is likely to predispose to multiple (adverse) outcomes, ranging from autoimmune disorders to cardiovascular disease and psychiatric symptoms. This implicates that psychotic disorders should be regarded not just as a cluster of psychological symptoms arising from brain dysfunction, but seen as a systemic disease or risk state. Also, it raises important questions what other genetic or environmental conditions are necessarily for the development of psychotic symptoms in particular.

Several randomized controlled trials have been conducted with anti-inflammatory agents as add-on treatments for psychosis and others are being conducted [94]. Our findings suggest that the use of such agents could also be considered in earlier stages, possibly preventing or limiting adverse effects of social stressors on immune dysregulation. Also, it would be interesting to examine what effects of nonpharmacological therapies, e.g. psychosocial interventions for improving coping skills and stress management, are on immune function. This review again highlights effects of social adversity on (mental) health. Importantly, the social stressors we discussed are potentially preventable or modifiable.

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