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Review

Immune-inflammatory markers and psychosis risk: A systematic review and meta-analysis

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ABSTRACT

Subclinical inflammation has been associated with psychosis; however, it remains unknown whether this phenomenon appears also in the premorbid phase. Therefore, we performed a systematic review and meta-analysis of studies comparing peripheral blood levels of C-reactive protein (CRP) and cytokines between individuals at risk of psychosis and controls. Moreover, we tested the hypothesis that the levels of these markers may be different in high-risk converters versus non-converters. Two independent reviewers searched electronic databases until Dec 16th, 2020. After reviewing publication records, 16 studies (548 high-risk individuals and 559 controls) were included. Random-effects meta-analyses with Hedges' g as the effect size estimate were performed. Individuals at clinical risk of psychosis had significantly higher levels of interleukin-6 (IL-6) compared to controls (g = 0.33, 95%CI: 0.06–0.60, p = 0.018). Heterogeneity was not significant in this subgroup analysis. Changes in the levels of IL-6 in subjects at familial risk of psychosis were not significant (g = 0.04, 95%CI: −0.24 to 0.31, p = 0.798). The use of antidepressants was associated with significantly higher levels of IL-6 in high-risk individuals (Beta = 1.56, 95%CI: 0.60–2.53, p = 0.001). No significant differences in the levels of immune-inflammatory markers were found between high-risk converters and non-converters. Our findings suggest that individuals at clinical risk of psychosis show subclinical inflammation in terms of elevated IL-6 levels. This phenomenon might be related to the use of antidepressants. The present meta-analysis does not support the usefulness of single immune-inflammatory markers in predicting transition to psychosis.

1. Introduction

Psychotic disorders affect about 3% of the general population and are perceived as substantial causes of disability (Perala et al., 2007; Vigo et al., 2016). In recent years, considerable efforts have been made to conceptualize prodromal symptoms of psychosis that are increasingly being recognized as promising target for prevention of psychotic disorders. Indeed, the construct of at-risk mental state (ARMS), also known as ultra-high risk (UHR) or clinical high risk (CHR) state has been developed to capture the premorbid phase. Three diagnostic categories have been included in these constructs: (1) trait vulnerability group, also known as genetic risk and deterioration syndrome (GRDS) defined as schizotypal personality disorder or familial liability (first-degree relative with psychotic disorder), and decline in functioning or sustained low functioning; (2) attenuated psychotic symptoms (APS) defined by the presence of subthreshold psychotic symptoms and decline in functioning or sustained low functioning and (3) brief limited intermittent psychotic symptoms (BLIPS), transient but overt psychotic symptoms lasting less than 1 week with spontaneous remission and decline in functioning or sustained low functioning. However, not all individuals meeting these

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criteria transition to psychosis. Indeed, transition rates have been estimated at 36% in a 3-year observation (Fusar-Poli et al., 2012). A recent meta-analysis revealed that there are substantial differences between distinct categories of clinical risk with the highest risk in case of BLIPS, followed by APS and GRDS (Fusar-Poli et al., 2016). Although this meta-analysis revealed that GRDS poorly predicts the development of psychosis, familial liability has been shown to serve as a risk factor for the development of schizophrenia. For instance, having one first-degree relative with schizophrenia increases the risk eightfold (Lo et al., 2020).

Psychotic disorders are associated with multisystemic biological dysregulations that can be observed in the peripheral blood (Pillinger et al., 2018). It has been found that individuals with schizophrenia at various stages of illness show several immune-inflammatory alterations. These include elevated levels of C-reactive protein (CRP) (Fernandes et al., 2016), pro-inflammatory cytokines(Miller et al., 2011) and various antibodies (Ezeoke et al., 2013) as well as changes in the counts of specific subpopulations of peripheral blood leukocytes (Karpiński et al., 2018, 2016; Miller et al., 2013). Some of them can be detected at all stages of psychosis while others are present only in subjects with first-episode psychosis (FEP) or in those with an acute relapse of illness (Miller et al., 2013, 2011). In addition, subclinical inflammation in subjects with psychosis has been associated with treatment-resistance (Lin et al., 1998), deficit schizophrenia subtype (Goldsmith et al., 2018), greater neurostructural alterations (Quidé et al., 2020) and cognitive impairment (Misiak et al., 2018).

Following the association between psychotic disorders and subclinical inflammation, several studies have explored whether immune-inflammatory alterations appear in individuals at risk of psychosis. A recent meta-analysis of studies in this field demonstrated significantly higher levels of interleukin(IL)−6 and lower levels of IL-1β in subjects at risk of psychosis. This meta-analysis also showed higher levels of IL-12 in converters compared to non-converters; however, this association did not reach statistical significance. It should be noted that this meta-analysis was based on a limited number of studies (n = 8) and did not investigate whether distinct categories of psychosis risk (e.g., clinical risk versus familial risk) differ with respect to the association with immune-inflammatory alterations. To support the rationale of dissecting the familial risk group, two important lines of evidence should be highlighted. Firstly, genome-wide association studies revealed that schizophrenia risk is related to variation in genes encoding major histocompatibility complex on chromosome 6 (Ripke et al., 2014). Secondly, the polygenic risk score for schizophrenia has been associated with the levels of immune-inflammatory markers (Maj et al., 2019) and risk of immune disorders (Stringer et al., 2014). In this regard, we aimed to perform an updated systematic review and meta-analysis of studies comparing peripheral blood levels of CRP and cytokines in subjects with distinct categories of psychosis risk (unaffected first-degree relatives of individuals with schizophrenia and individuals at clinical risk) with healthy controls. Moreover, we aimed to investigate whether specific altered levels of CRP and cytokines might predict transition to psychosis in this population.

2. Material and methods

2.1. Search strategy

The following databases of publication records were accessed by two independent reviewers (BS and AG): MEDLINE, ERIC, CINAHL Complete, International Pharmaceutical Abstracts as well as the Academic Search Ultimate and the Health Source: Nursing/Academic Edition. These databases were searched using the following keywords: “risk” OR “siblings” OR “relatives” OR “offspring” AND “psychosis” OR “schizophr*” AND “inflamm*” OR “immun*” OR “interleukin” OR “cytokine” OR “crp” OR “chemokine” OR “interferon” OR “tum* necrosis factor” from their inception until Dec 16th, 2020. In addition, references of eligible publications were checked. All disagreements regarding inclusion or exclusion of specific studies were resolved through the consultation with the third reviewer (BM). The search strategy was based on the PRISMA guidelines (see the PRISMA checklist in Table S1) (Moher et al., 2009). The protocol of this systematic review and meta-analysis was registered in the PROSPERO database (CRD 42020221571).

2.2. Eligibility criteria

Inclusion criteria were as follows: (1) studies comparing serum or plasma levels of CRP and/or cytokines in individuals at risk of psychosis, including CHR or UHR or ARMS individuals or unaffected first-degree relatives of individuals with schizophrenia and healthy controls; (2) studies comparing serum or plasma levels of CRP and/or cytokines in high risk converters and non-converters; (3) necessary data (sample size, mean and SD for the levels of CRP and cytokines) were available in the manuscript or upon request (if needed the corresponding authors were contacted to obtain relevant data) and (4) records published in English. In case of overlapping samples, we included the study with the largest sample size reported. Excluded publication records involved studies measuring the mRNA levels of immune-inflammatory markers, animal model studies, case reports, non-original studies (e.g., reviews, editorials and commentaries) and studies that did not provide necessary data to perform meta-analysis.

2.3. Data extraction

Extracted data were as follows: (1) age; (2) sex; (3) body-mass index (BMI); (4) the levels of CRP and/or cytokines; (5) information regarding the use of psychotropic medications and (6) duration of observation period in case of studies comparing the levels of immune-inflammatory factors between converters and non-converters. In case of data expressed as median and interquartile range (IQR), relevant conversion methods were applied. The median was recorded as the approximation of the mean (Higgins and Green, 2011). In turn, IQR was divided by 1.35 to obtain SD (Hozo et al., 2005). To perform quality assessment, between-group differences with respect to age and sex across specific studies were analyzed (Bartoli et al., 2018). Studies were classified as meeting the comparability criterion if there were no significant differences in age and sex between high-risk individuals and healthy controls or between high-risk converters and non-converters ($p > 0.05$).

2.4. Data analysis

Data analysis was limited to markers assessed by at least two studies. The Cochran Q and the I^2 statistics were used to assess heterogeneity. Standardized mean difference (SMD) was calculated as the Hedges’ g using the random-effects models. A leave-one-out sensitivity analysis was performed to investigate whether any single study accounted for heterogeneity. Subgroup analyses were carried out to explore whether the association with immune-inflammatory alterations would differ between unaffected first-degree relatives of individuals with schizophrenia (hereinafter referred to as “familial risk”) and CHR or UHR or ARMS individuals (hereinafter referred to as “clinical risk”). Potential moderators were assessed using the meta-regression analyses if they were reported by at least six studies.(Fu et al., 2011) Publication bias was tested by the Egger’s test in case of markers tested by at least ten studies.(Sterne et al., 2008) Results of data analysis were considered statistically significant if the p-value was less than 0.05. All analyses were carried out using the STATISTICA software, version 12.5.

3. Results

3.1. General characteristics of eligible studies

The initial screening phase of online searches identified 6550

publication records (Table S1). After screening, 16 studies (548 subjects at risk of psychosis and 559 controls) were included in systematic review and meta-analysis (Chouinard et al., 2019; Counotte et al., 2019; Delaney et al., 2019; Föcking et al., 2016; Gaughran et al., 2002; Karanikas et al., 2017; Kelsven et al., 2020; Labad et al., 2015; Lizano et al., 2016; Martorell et al., 2019; Nunes et al., 2006; Piotrowski et al., 2019; Rebouças et al., 2019; Stojanovic et al., 2014; Zeni-Graiff et al., 2016). Tables 1 and 2 present general characteristics of these studies. There were 15 studies comparing the levels of CRP and/or cytokines in subjects at risk of psychosis and controls (Table 1). In turn, 4 studies compared the levels of CRP and/or cytokines between high-risk converters and non-converters (Table 2). Individuals at clinical risk of psychosis were assessed by 10 studies (Counotte et al., 2019; Delaney et al., 2019; Föcking et al., 2016; Karanikas et al., 2017; Kelsven et al., 2020; Labad et al., 2015; Martorell et al., 2019; Perkins et al., 2015; Stojanovic et al., 2014; Zeni-Graiff et al., 2016), while individuals at familial risk of psychosis were included in 7 studies (Chouinard et al., 2019; Counotte et al., 2019; Gaughran et al., 2002; Lizano et al., 2016; Nunes et al., 2006; Piotrowski et al., 2019; Rebouças et al., 2019). A total of 11 studies met the comparability criterion (Chouinard et al., 2019; Counotte et al., 2019; Delaney et al., 2019; Föcking et al., 2016; Karanikas et al., 2017; Kelsven et al., 2020; Labad et al., 2015; Nunes et al., 2006; Perkins et al., 2015; Rebouças et al., 2019; Zeni-Graiff et al., 2016). The following diagnostic constructs were included in the clinical risk: (1) CHR of psychosis (Delaney et al., 2019; Kelsven et al., 2020; Perkins et al., 2015); (2) UHR of psychosis (Counotte et al., 2019; Karanikas et al., 2017; Zeni-Graiff et al., 2016) and (3) ARMS (Föcking et al., 2016; Labad et al., 2015; Martorell et al., 2019; Stojanovic et al., 2014).

3.2. Meta-analysis of immune-inflammatory markers levels

Meta-analyses were performed for the following immune-inflammatory markers: CRP (10 studies), IL-1β (5 studies), IL-4 (2 studies), IL-5 (2 studies), IL-6 (12 studies), IL-7 (2 studies), IL-8 (5 studies), IL-10 (4 studies), IL-15 (2 studies), IFN-γ (6 studies), TNF-α (9 studies), IL-12p70 (3 studies), IL-12p40 (2 studies), MCP-1 (3 studies) and eotaxin-1 (3 studies). Forrest plots are presented in the Supplementary Material.

Analyses that pooled together both categories of psychosis risk (clinical and familial risk) revealed no significant differences in the levels of immune-inflammatory markers between individuals at risk of psychosis and controls (Table 3, Fig. 1). However, subgroup analyses demonstrated significantly higher levels of IL-6 in subjects at clinical risk of psychosis compared to controls ($g = 0.33$, 95%CI: 0.06 – 0.60, $p = 0.018$, small-to-medium effect size estimate). Heterogeneity was not significant in this subgroup analysis. A leave-one-out sensitivity analysis revealed that after removing the largest study by Perkins et al. (2015), individuals at clinical risk of psychosis had higher levels of IL-6 at the trend level significance ($g = 0.30$, 95%CI: −0.04 to 0.65, $p = 0.088$). This difference remained significant after excluding other studies. Results of the Egger's test for studies comparing the levels of IL-6 between high-risk individuals and controls were not significant (regression intercept = 1.32, 95%CI: −2.26 to 4.90, $p = 0.432$), indicating no publication bias. No significant differences in the levels of immune-inflammatory markers between high-risk converters and non-converters were found (Table 4).

Meta-regression analysis was performed for studies comparing the

Table 1
General characteristics of studies comparing the levels of inflammatory markers in individuals at risk of psychosis and healthy controls.

Study	N		Age		% males		Definition of high psychosis risk	Inflammatory markers	Comparability *
	Psychosis risk	Healthy controls	Psychosis risk	Healthy controls	Psychosis risk	Healthy controls			
Chouinard et al. (2019)	22	15	24.2 ± 5.6	22.5 ± 3.5	36.4	41.2	Siblings of patients with SZ	CRP, IL-6 and TNF-α	Yes
Counotte et al. (2019)	40	38	25.1 ± 6.5	24 ± 3.7	55.0	84.2	UHR and siblings of patients with SZ	CRP, IL-6, IFN-γ, TNF-α and MCP-1	Yes
Delaney et al. (2019)	17	33	22.8 ± 3.7	25.3 ± 4.75	64.7	42.4	CHR	CRP and IL-6	Yes
Gaughran et al. (2002)	51	126	33.5 ± 19.6	44.2 ± 32.5	41.2	UK	Unaffected 1st degree relatives of patients with SZ	sIL-2R	No
Karanikas et al. (2017)	12	23	24.5 ± 3.1	27.0 ± 2.9	100	100	UHR	IL-1β, IL-4, IL-5, IL-8, IL-10, IL-12p70, IFN-γ and TNF-α	Yes
Kelsven et al. (2020)	11	7	18.5 ± 4.7	20.4 ± 4.9	63.6	71.4	CHR	IL-1β, IL-6, IL-8, IL-10, IL-12p70, IFN-γ, TNF-α, MCP-1 and eotaxin-1	Yes
Labad et al. (2015)	39	44	22.3 ± 4.6	23.2 ± 4.4	69.2	65.9	ARMS	CRP	Yes
Lizano et al. (2016)	35	39	16.5 ± 0.6	25.1 ± 1.0	42.8	64.1	1st and 2nd degree relatives	IL-1β, IL-6, IL-8, IL-10, IL-12p70 and TNF-α	No
Martorell et al. (2019)	14	21	22.0 ± 3.0	29.0 ± 3.0	71.4	33.3	ARMS	CRP and IL-6	No
Nunes et al. (2006)	41	48	UK	UK	UK	UK	Unaffected relatives of patients with SZ	IL-6	Yes
Perkins et al. (2015)	72	35	19.4 ± 4.2	20.0 ± 4.5	66.1	65.0	CHR	CRP, IL-1β, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12p40, TNF-α and eotaxin-1	Yes
Piotrowski et al. (2019)	37	42	36.9 ± 11.0	27.8 ± 8.4	32.4	38.1	Unaffected offspring of patients with SZ	CRP	No
Rebouças et al. (2019)	36	47	40.5 ± 19.0	41.0 ± 26.0	41.7	44.7	Unaffected siblings of patients with SZ	CRP and IL-6	Yes
Stojanovic et al. (2014)	17	25	21.4 ± 2.4	27.3 ± 4.2	70.6	40.8	ARMS	CRP and IL-6	No
Zeni-Graiff et al. (2016)	12	16	17.0 ± 3.0	19.0 ± 3.7	75.0	68.75	UHR	IL-6 and IFN-γ	Yes

Abbreviations: ARMS – at-risk mental state; CHR – clinical high risk; CRP – C-reactive protein; IFN-γ – interferon-γ; IL - interleukin; MCP-1 – monocyte chemoattractant protein-1; sIL-2R – soluble receptor for interleukin-2; SZ – schizophrenia; TNF-α – tumor necrosis factor-α; UHR – ultra high risk; UK – unknown

* The comparability criterion was met if individuals at risk of psychosis and controls were matched for age and sex.

Table 2
General characteristics of studies comparing the levels of inflammatory markers in at risk converters and non-converters.

Study	N Converters	Non-converters	Age Converters	Non-converters	% males Converters	Non-converters	Definition of high psychosis risk	Inflammatory markers	Follow-up time	Comparability *
Föcking et al. (2016)	11	28	15.9 ± 0.3	16.2 ± 0.3	36.4	28.6	ARMS	CRP, IL-6, IL-7, IL-8, IL-10, IL-15, IFN-γ, TNF-α, IL-12p40 and eotaxin-1	12 months	Yes
Labad et al. (2015)	10	29	20.4 ± 3.1	23.0 ± 4.9	50.0	75.9	ARMS	CRP	At least 12 months	Yes
Lizano et al. (2016)	3	32	UK	UK	UK	UK	FHR	IL-1β, IL-6, IL-8, IL-10, IL-12p70 and TNF-α	36 months	No
Perkins et al. (2015)	32	40	19.2 ± 3.7	19.5 ± 4.6	69.7	62.5	CHR	CRP, IL-1β, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12p40, TNF-α and eotaxin-1	24 months	Yes

Abbreviations: ARMS – at-risk mental state; CHR – clinical high risk; CRP – C-reactive protein; FHR – familial high risk; IFN-γ – interferon-γ; IL - interleukin; MCP-1 – monocyte chemoattractant protein-1; sIL-2R – soluble receptor for interleukin-2; TNF-α – tumor necrosis factor-α; UK – unknown
* The comparability criterion was met if individuals at risk of psychosis and controls were matched for age and sex.

Table 3
Main and subgroup analyses of inflammatory markers in individuals at risk of psychosis.

Marker	Analysis	k	Meta-analysis			Heterogeneity analysis		
			g	95%CI	p	I^2	Q	p (Q)
CRP	FHR, ARMS, CHR and UHR	9	0.08	−0.12–0.28	0.448	6.4%	8.55	0.381
	ARMS, CHR and UHR	6	0.09	−0.13–0.30	0.431	0%	0.16	0.999
	FHR	3	0.01	−0.57–0.60	0.960	73.5%	7.56	**0.023**
IL-1β	CHR, FHR and UHR	4	0.13	−0.13–0.40	0.323	0%	0.96	0.811
	CHR and UHR	3	0.09	−0.23–0.42	0.576	0%	0.78	0.676
IL-4	CHR and UHR	2	1.50	−0.52–3.51	0.145	92.4%	13.17	**< 0.001**
IL-5	CHR and UHR	2	-0.17	−0.51–0.18	0.349	0%	0.03	0.868
IL-6	FHR, ARMS, CHR and UHR	12	0.18	−0.02–0.39	0.082	40.1%	18.36	0.073
	ARMS, CHR and UHR	7	0.33	0.06–0.60	**0.018**	25.3%	8.03	0.236
	FHR	5	0.04	−0.24–0.31	0.798	41.7%	6.86	0.144
IL-8	FHR, CHR and UHR	4	0.35	−0.23–0.93	0.242	74.4%	11.72	**0.008**
	CHR and UHR	3	0.58	−0.22–1.37	0.155	75.4%	8.12	**0.017**
IL-10	FHR, CHR and UHR	3	0.27	−0.16–0.70	0.222	25.2%	2.67	0.263
	CHR and UHR	2	0.03	−0.54–0.61	0.916	8.1%	1.08	0.297
IFN-γ	FHR, CHR and UHR	7	0.08	−0.25–0.41	0.625	35.9%	7.80	0.167
	CHR and UHR	5	0.16	−0.42–0.74	0.589	57.3%	7.03	0.071
	FHR	2	0.01	−0.35–0.35	0.982	0%	0.52	0.472
TNF-α	FHR, CHR and UHR	8	0.10	−0.19–0.39	0.506	51.1%	14.32	**0.046**
	CHR and UHR	4	0.19	−0.29–0.67	0.442	53.8%	6.49	0.090
	FHR	4	0.05	−0.36–0.47	0.811	61.2%	7.72	0.052
IL-12p70	FHR, CHR and UHR	3	0.17	−0.19–0.53	0.363	4.1%	2.08	0.352
	CHR and UHR	2	-0.04	−0.61–0.52	0.881	4.8%	1.05	0.306
MCP-1	FHR and UHR	3	0.55	−0.43–1.53	0.273	82.5%	11.43	**0.003**
	UHR	2	0.89	−1.26–3.04	0.418	90.9%	10.96	**< 0.001**
Eotaxin-1	CHR	2	0.76	−0.47–2.00	0.226	80.6%	5.14	**0.023**

Significant results ($p < 0.05$) were marked with bold characters. k refers to the number of comparisons. ARMS – at-risk mental state; CHR – clinical high risk; CRP – C-reactive protein; FHR – familial high risk; IFN-γ – interferon-γ; IL - interleukin; MCP-1 – monocyte chemoattractant protein-1; sIL-2R – soluble receptor for interleukin-2; TNF-α – tumour necrosis factor-α; UHR – ultra high risk

levels of CRP, IL-6, IFN-γ and TNF-α between high-risk individuals and healthy controls (Table S2). The following potential moderators were tested: between-group differences in age, sex, BMI and cigarette smoking rates as well as the rates of using antipsychotics, antidepressants and mood stabilizers in subjects at clinical risk of psychosis. There was a significant positive correlation between the percentage of high-risk individuals receiving antidepressants and the effect size estimates for differences in the levels of IL-6 ($\beta = 1.56$, 95%CI: 0.60 – 2.53, $p = 0.001$). Effects of other potential moderators were not significant.

4. Discussion

In the present meta-analysis, we found significantly higher levels of IL-6 in individuals at clinical risk of psychosis but not in those at familial risk. Although genetic backgrounds of schizophrenia have been associated with immune-inflammatory processes (Maj et al., 2019; Ripke et al., 2014; Stringer et al., 2014), the GRDS construct poorly predicts psychosis risk when compared to other categories of clinical risk with no significant differences in transition rates when compared to controls in a 48-month observation (Fusar-Poli et al., 2016). In this regard, we may assume that the familial risk group of unaffected first-degree relatives of individuals with schizophrenia would have even lower risk of transition to psychosis than the GRDS individuals. It is also important to note that our results with respect to IL-6 were relatively consistent across studies (between-study heterogeneity was not significant). However, after removing a single study (Perkins et al., 2015) in sensitivity analysis, IL-6 levels were higher in individuals at clinical risk of psychosis compared to controls at the trend-level significance. It should be noted that it was the largest study included in our meta-analysis (weight estimated at 25.31%), and both groups from this study were comparable not only of age and sex but also other sociodemographic characteristics.

Our findings point to the involvement of IL-6 in the pathophysiology

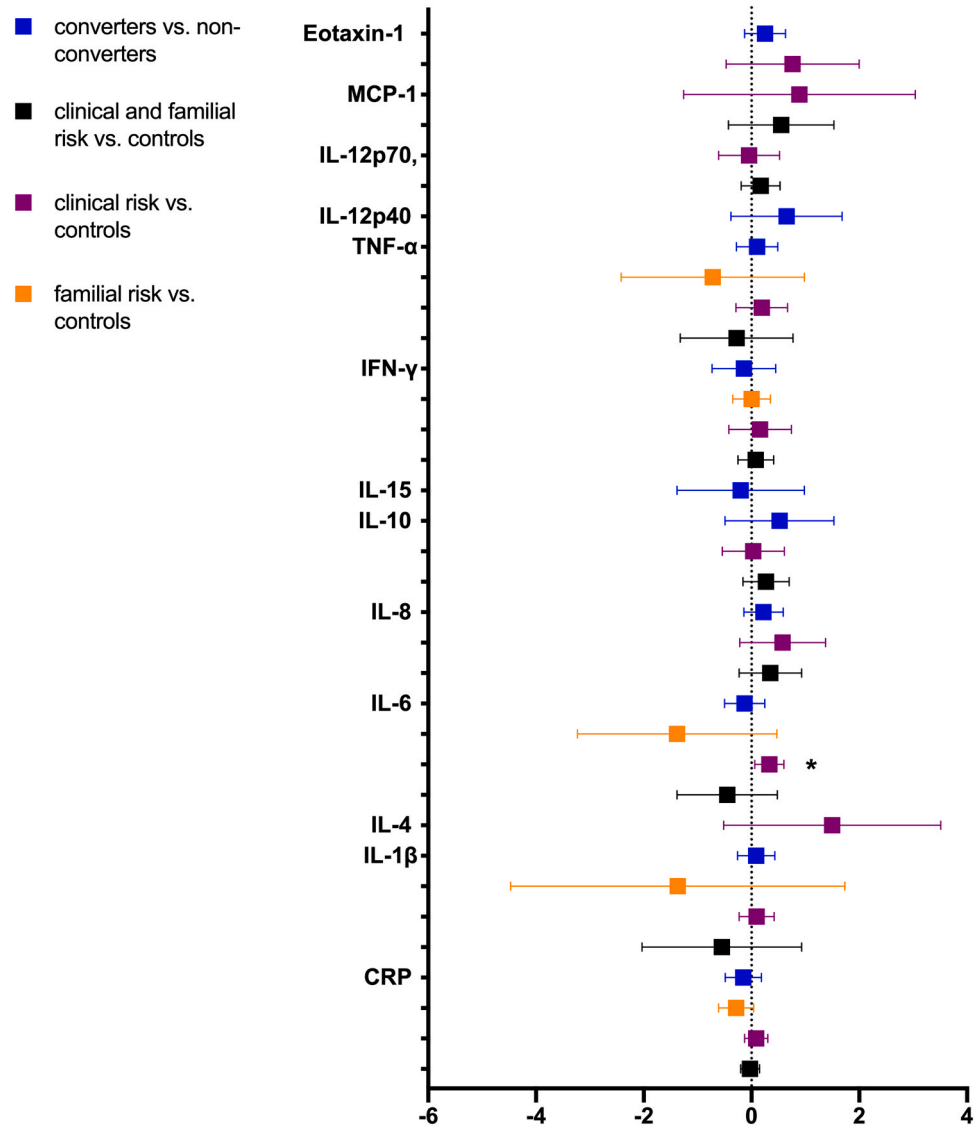

Fig. 1. Summary of effect size estimates for differences in the levels of immune-inflammatory markers. Error bars refer to 95%CI. Abbreviations: CRP – C-reactive protein; IFN-γ – interferon-γ; IL – interleukin; MCP-1 – monocyte chemoattractant protein-1; TNF-α – tumor necrosis factor-α. *p < 0.05.

Table 4
Analysis of studies comparing the levels of inflammatory in at risk converters and non-converters.

Marker	k	Meta-analysis			Heterogeneity analysis		
		g	95%CI	p	I^2	Q	p (Q)
CRP	3	−0.15	−0.49–0.18	0.371	0%	1.48	0.476
IL-1β	3	0.09	−0.26–0.43	0.629	0%	0.80	0.670
IL-6	3	−0.13	−0.50–0.25	0.504	2.9%	2.06	0.357
IL-7	2	−0.01	−0.66–0.64	0.968	60.1%	2.51	0.113
IL-8	3	0.22	−0.14–0.59	0.228	0%	1.66	0.436
IL-10	2	0.52	−0.49–1.53	0.313	56.0%	2.27	0.132
IL-15	2	−0.20	−1.38–0.98	0.740	87.2%	7.81	0.005
IFN-γ	2	−0.14	−0.73–0.45	0.642	0%	0.39	0.534
TNF-α	2	0.10	−0.28–0.49	0.595	0%	< 0.01	0.988
IL-12p40	2	0.65	−0.38–1.68	0.214	82.2%	5.63	0.018
Eotaxin-1	2	0.25	−0.13–0.63	0.204	0%	0.30	0.585

Significant results (p < 0.05) were marked with bold characters. k refers to the number of comparisons. CRP – C-reactive protein; IFN-γ – interferon-γ; IL – interleukin; MCP-1 – monocyte chemoattractant protein-1; sIL-2R – soluble receptor for interleukin-2; TNF-α – tumour necrosis factor-α; UHR – ultra high risk.

of psychosis. Apart from the role in immune-inflammatory processes, IL-6 exerts a number of pleiotropic activities that might be relevant to the pathophysiology of psychosis. These activities include, i.e.: (1) boosting effects on the secretion of neurotrophins in the brain; (2) regulation of body weight, food intake and energy expenditure; (3) effects on circadian rhythms and emotional reactivity; (4) involvement in learning and memory processes and (5) up-regulation of dopamine and serotonin turnover in the hippocampus and frontal cortex (Borovcanin et al., 2017). There is consistent evidence originating from meta-analyses that individuals with FEP and established diagnosis of schizophrenia show elevated levels of IL-6 in the peripheral blood (Capuzzi et al., 2017; Fraguas et al., 2017; Miller et al., 2011; Upthegrove et al., 2014) and cerebrospinal fluid (Gallego et al., 2018). Moreover, reduced variability of IL-6 levels in subjects with psychosis has been reported, disproving the hypothesis of an immune subgroup within the psychosis spectrum (Pillinger et al., 2019). However, it has also been demonstrated that the level of IL-6 tends to decrease following the treatment with antipsychotics, and thus it can be perceived as one of state markers (Capuzzi et al., 2017; Miller et al., 2011). To date, a number of clinical correlates of elevated IL-6 levels have been reported in psychotic disorders. Higher IL-6 levels have been associated with treatment resistance (Mondelli

et al., 2015; Zhang et al., 2005), chronic schizophrenia course with deterioration (Frydecka et al., 2015), reduced volumes at certain brain regions (Miller et al., 2020; Quidé et al., 2020), cognitive impairment (Misiak et al., 2018) and a history of childhood trauma (Dennison et al., 2012). Goldsmith et al. (2019) also found that IL-6 levels may predict the development of depressive and negative symptoms in subjects at clinical risk of psychosis.

In our meta-analysis, the levels of IL-6 or other markers did not predict transition to psychosis. However, there were only four studies in this analysis with clinically heterogeneous samples that differed with respect to follow-up duration. At this point it is also important to discuss specificity of our findings with respect to IL-6 levels. Indeed, elevated IL-6 levels appear also in subjects with other mental disorders, including euthymic bipolar disorder and major depression (Goldsmith et al., 2016). This observation is in agreement with a variety of diagnostic outcomes in subjects at clinical risk of psychosis. It has been demonstrated that 73% of them develop schizophrenia spectrum disorders (Fusar-Poli et al., 2013). Others convert to mood disorders with psychotic symptoms (about 11% of cases) and other psychotic disorders (about 17% of cases).

Importantly, we found that a higher percentage of high-risk individuals receiving antidepressants was associated with significantly higher effect size estimates for IL-6. As mentioned above, elevated IL-6 levels have been reported in subjects with major depression (Goldsmith et al., 2016). It is likely that our observation rather reflects the association between depressive symptoms and elevated IL-6 levels as antidepressants have been shown to decrease the levels of this cytokine (Więdłocha et al., 2018). Moreover, decreases in the levels of IL-6 were associated with improvement of depressive symptomatology in the observational study of individuals with FEP (Ventura et al., 2020). According to some studies performed in subjects with schizophrenia, depressive symptoms might be associated with subclinical inflammation (Fond et al., 2016). Finally, elevated levels of IL-6 at age of 9 years were associated with higher risk of psychotic-like experiences and depression at the age of 18 years in a population-based study (Khandaker et al., 2014). These observations, together with our findings suggest that there is a transdiagnostic association between depressive symptoms and inflammatory response. However, other reasons for taking antidepressants, e.g., anxiety, and negative symptoms that might resemble depressive symptomatology, should also be considered.

There are some important limitations of this meta-analysis that require further consideration. First, our meta-analysis was based on limited number of studies, especially with respect to those comparing the levels of immune-inflammatory markers in high-risk converters and non-converters. Second, there was a considerable heterogeneity in the criteria used to define clinical risk of psychosis. At this point, it should be noted that we were not able to examine the levels of cytokines in specific subgroups of individuals at clinical risk of psychosis (BLIPS, APS and GRDS). Furthermore, there are various potential moderators that were not tested. These include a severity of specific psychopathological symptoms, medication effects, comorbid physical health impairments, cigarette smoking or dietary habits. It should also be noted that it remains unknown whether there is a strong rationale behind studying single markers instead of more composite measures of inflammation. Indeed, it has been shown that the development of more comprehensive indices, e.g., proteomic prediction models may better predict transition to psychosis in CHR individuals (Mongan et al., 2020). Finally, due to multiplicity of markers analysed in the present study, it cannot be ruled out that significant results on IL-6 appeared by chance.

In conclusion, results of the present systematic review and meta-analysis imply that individuals at clinical risk of psychosis may present with subclinical inflammation in terms of elevated IL-6 levels. This observation might be associated with depressive symptoms. However, our findings do not support the association between familial liability to psychosis and subclinical inflammation. Moreover, existing evidence does not indicate the utility of immune-inflammatory markers in predicting transition to psychosis in subjects at clinical risk. Additional studies in this field are needed to determine characteristics and extent of subclinical inflammation in subjects at risk of psychosis. There is also a necessity of longitudinal studies addressing the usefulness of immune-inflammatory markers in predicting outcomes of psychosis risk.

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Conflict of interest

None to declare.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.psyneuen.2021.105200.

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