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Peripheral blood inflammatory markers in patients with attention deficit/hyperactivity disorder (ADHD): A systematic review and meta-analysis

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ABSTRACT

It has been observed that subclinical inflammation might be involved in the pathophysiology of attention deficit/hyperactivity disorder (ADHD). However, studies investigating peripheral blood levels of immune-inflammatory markers have provided mixed findings. We performed a systematic review and meta-analysis of studies comparing unstimulated serum or plasma levels of C-reactive protein (CRP) and cytokines in subjects with ADHD and healthy controls (the PROSPERO registration number: CRD 42021276869). Online searches covered the publication period until 30th Sep 2021 and random-effects meta-analyses were carried out. Out of 1844 publication records identified, 10 studies were included. The levels of interleukin (IL)-6 were significantly higher in studies of participants up to the age of 18 years (k = 10, g = 0.70, 95%CI: 0.10–1.30, $p = 0.023$) and after including those above the age of 18 years (k = 10, g = 0.71, 95%CI: 0.12–1.31, $p = 0.019$). In turn, the levels of tumor necrosis factor-α (TNF-α) were significantly lower in subjects with ADHD compared to healthy controls (k = 7, g = −0.16, 95%CI: −0.30 - -0.03, $p = 0.020$). Individual studies had a high contribution to the overall effect, since the overall effect was no longer significant after removing single studies. No significant differences were found with respect to the levels of CRP, IL-1β, IL-10 and interferon-γ. The present findings indicate that individuals with ADHD tend to show elevated levels of IL-6 and reduced levels of TNF-α. Larger and longitudinal studies recording potential confounding factors and comorbid psychopathology are needed to confirm our findings.

1. Introduction

Attention deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder which affects about 5.2% of children and 2.6% of adults (Polanczyk et al., 2007, 2014; Song et al., 2021). Importantly, ADHD has a great impact on lives of affected individuals, leading to low educational and work attainments (Arnold et al., 2020; Kessler et al., 2005), risk-taking behaviors (Pollak et al., 2019) and unsatisfactory relationships (Moyá et al., 2014). Moreover, high comorbidity rates of ADHD and other mental disorders have been observed, especially with respect to mood disorders, anxiety disorders, substance and alcohol use disorders as well as autism spectrum disorders (Bartoli et al., 2022; Sandstrom et al., 2021; Schiweck et al., 2021). A recent meta-analysis also revealed that childhood ADHD is associated with higher risk of subsequent psychotic disorder (Nourredine et al., 2021). Current diagnostic criteria of ADHD require to document the presence and specific characteristics of symptoms related to impairment of attention and/or hyperactivity/impulsivity before the age of 12 years (Rigler et al., 2016). A recall bias during a diagnostic process initiated in adults may lead to underdiagnosing ADHD. Moreover, increasing awareness of ADHD may account for overdiagnosis if the diagnostic process is not carried out thoroughly (Dalrymple et al., 2020). While in depth diagnosis by a trained professional is crucial for diagnosing ADHD, additional biomarkers to improve treatment and/or potentially complement

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current diagnostic procedures would be an added value (Takahashi et al., 2021).

The etiology of ADHD is not yet fully understood and is likely attributable to complex interactions between genetic and environmental risk factors, although genetic factors play an important role considering heritability rates of 70–80% (Faraone et al., 2005). In addition to genetic factors, current evidence indicates that a number of environmental insults during the prenatal period increase the risk of ADHD in offspring. These include maternal pre-pregnancy obesity, hypertensive disorders during pregnancy, pre-eclampsia and maternal exposure to acetaminophen during pregnancy (Kim et al., 2020). These observations suggest that various factors acting on during pregnancy might play a role in the development of ADHD in offspring. Some studies have provided evidence supporting the role of maternal immune activation. For instance, Gustafsson et al. (2020) found that maternal inflammation during pregnancy, measured by plasma levels of interleukin (IL)-6, tumor necrosis factor-α (TNF-α) and monocyte chemoattractant protein-1, increases the risk of ADHD symptoms in children at the age of 4–6 years. However, another study that determined serum levels of C-reactive protein (CRP) in women during first and early second trimester of pregnancy failed to find a significant association between maternal inflammation and ADHD in offspring (Chudal et al., 2020). Finally, the role of immune activation in the etiology of ADHD is supported by studies showing that individuals with ADHD and their mothers have higher risk of developing chronic diseases with immune component (Hegvik et al., 2018; Instanes et al., 2017; Miyazaki et al., 2017). Interestingly, genome-wide association studies revealed that variations in genes encoding proteins involved in the inflammatory response, e.g., *ADAM23*, *YWHAZ*, *EIF2S2*, *IL6*, *EIF3H*, *ZBTB16* and *TRIM36* are associated with an increased risk of ADHD (De Jong et al., 2016; Zayats et al., 2015). One of these studies revealed that ADHD and depression share genetic backgrounds related to the immune-inflammatory responses (De Jong et al., 2016).

Little is known about immune-inflammatory alterations in subjects with ADHD and studies in this field have provided mixed findings. The most recent meta-analysis found that youths with ADHD have significantly lower levels of TNF-α and unaltered levels of IL-1β, IL-6 and IL-10 in the peripheral blood (Chang et al., 2021). However, this meta-analysis was based on four studies and did not include adults with ADHD. Importantly, immune system responses in adults, compared to children or adolescents, are already developed, more stable and less influenced by hormones (Bereshchenko et al., 2018; Simon et al., 2015). Moreover, cytokines play important roles in neurodevelopmental processes as they impact the development of glial cells as well as neural and synaptic maturation (Ratnayake et al., 2013). The perspective of maturational processes and aging might be of importance for ADHD as this neurodevelopmental disorder continues to adulthood in up to half of diagnosed cases (Caye et al., 2016). Therefore, it might be expected that there are differences in immune-inflammatory factors between adults and children or adolescents with ADHD. Given that results of new studies in this field have been published, we aimed to perform an updated qualitative and quantitative synthesis of studies comparing unstimulated levels of CRP and cytokines in subjects with ADHD and healthy controls.

2. Materials and methods

2.1. Search strategy

Two reviewers (AW-K and BS) searched electronic databases (the MEDLINE, the ERIC, the CINAHL Complete, the International Pharmaceutical Abstracts as well as the Academic Search Ultimate and the Health Source: Nursing/Academic Edition) independently from their inception until 30th Sep 2021. The keywords were as follows: ((“ADHD” OR “attention-deficit/hyperactivity disorder”) AND (“cytokine” OR “interleukin” OR “crp” OR “c-reactive protein” OR “interferon” OR “chemokine” OR “tumor necrosis factor” OR “tumour necrosis factor” OR “immun*” OR “inflamm*”)). Disagreements regarding inclusion and exclusion of specific publication records were resolved through discussion with the third reviewer (BM). Online searches were performed and reported in agreement with the PRISMA guidelines (Page et al., 2021). The PRISMA checklist is shown in Supplementary Table 1. The protocol of this systematic review and meta-analysis was registered in the PROSPERO database (registration number: CRD 42021276869).

2.2. Eligibility criteria

The following inclusion criteria were applied: 1) publications had to report peripheral blood (serum or plasma) levels of cytokines and/or CRP; 2) case-control studies comparing the levels of CRP and/or cytokines between individuals with ADHD and healthy controls; 3) necessary data (mean or median and SD or range or interquartile range for the levels of CRP and/or cytokines as well as the number of individuals with ADHD and healthy controls) were available in the publication or upon request from the corresponding author and 4) English language full-text articles. Publication records were excluded in case of meeting at least one of the following criteria: 1) animal model studies; 2) non-original studies (e.g., reviews, commentaries and editorials); 3) publications without possibility to obtain the necessary data; 4) studies that did not include individuals with a diagnosis of ADHD according to DSM/ICD criteria or healthy controls; 5) studies of individuals with ADHD and comorbid neurological diseases and 6) studies measuring mRNA levels of cytokines. In case of a lack of necessary data, corresponding authors of eligible publications were contacted.

2.3. Data extraction

Data were extracted in duplicates by two independent reviewers (BM and BS), and included: 1) age; 2) sex; 3) body-mass index (BMI); 4) the number of individuals with ADHD and healthy controls; 5) medication status; 6) diagnostic criteria used to establish a diagnosis of ADHD and 7) serum or plasma levels of CRP and/or cytokines. Wherever possible, data were retrieved as mean and standard deviation (SD) or number of cases.

Conversion methods were used to calculate mean and SD in case data provided as median, range, interquartile range (IQR) and standard error (SE). The median was included as an approximation of the mean (Higgins and Green, 2011). In turn, SD was calculated using the following formulas: $SD = IQR/1.35$, $SD = SE \times \sqrt{N}$ or $SD = \text{maximum} - \text{minimum}/4$ (Higgins and Green, 2011; Hozo et al., 2005).

2.4. Quality assessment

Quality of studies was scored in duplicates by two reviewers (BM and BS) using the Newcastle-Ottawa Scale (NOS) (Wells et al., 2000). The NOS was developed to evaluate three categories of quality: 1) the selection of study groups (the maximum score is 4 stars); 2) the comparability of study groups (the maximum score is 2 stars) and 3) the ascertainment of exposure or outcome of interest (the maximum score is 3 stars). The total NOS score ranges from 0 to 9 stars, where higher scores indicate better quality. Matching patients and healthy controls for age and sex was considered to score the comparability category.

2.5. Data analysis

Differences in blood levels of cytokines and/or CRP between individuals with ADHD and healthy controls were tested as main outcome measures. The I^2 statistics were analyzed as the measures of heterogeneity. Heterogeneity was considered moderate when I^2 ranges between 50% and 75%, and high when I^2 is greater than 75% (Higgins et al., 2003). Analyses were performed using random-effects models due to

expected between-study differences in sample size, recruitment procedures and methods used to determine the levels of inflammatory markers. Random-effects models should be used if eligible studies are characterized by heterogeneous methodology, and thus it is unreasonable to assume that they share a common effect (Tufanaru et al., 2015). Effect size estimates were calculated as the Hedges' g. The leave-one-out sensitivity analysis was performed to investigate if any single study accounted for heterogeneity. Meta-regression analyses were carried out in case of continuous moderators that were assessed by at least six studies (Fu et al., 2011). Subgroup analyses were performed to test the effects of medication status (studies with medicated patients vs. studies with unmedicated patients) and age of participants at blood sampling (studies with adult participants vs. studies with those under the age of 18 years). Publication bias was assessed using the Egger's test if the levels of specific inflammatory markers were determined by at least 10 studies (Sterne et al., 2008). Results of meta-analyses were considered significant if the *p*-value was <0.05. Data analysis was performed using the IBM SPSS software, version 28.

3. Results

3.1. General characteristics of eligible studies

Online searches identified 1844 publication records and 10 studies (Chang et al., 2020; Corominas-Roso et al., 2017; Darwish et al., 2019; Dursun et al., 2021; Elsadek et al., 2020; Leffa et al., 2021; Mahmoud et al., 2020; Oades et al., 2010; Puzino et al., 2021; Verlaet et al., 2019) were finally included in the systematic review and meta-analysis according to the pre-specified in- and exclusion criteria (Supplementary Fig. 1). General characteristics of these studies are presented in Table 1. There was one register-based study that assessed the levels of inflammatory markers at the age of 18 years and 22 years (Leffa et al., 2021). Children and youths were recruited by the majority of studies, except two studies that were based on adult participants (Corominas-Roso et al., 2017; Leffa et al., 2021). In two studies, approximately 40% of patients with ADHD were medicated (Oades et al., 2010; Puzino et al., 2021). Medication status was not specified in two eligible publications (Elsadek et al., 2020; Leffa et al., 2021). In other studies, individuals with ADHD were unmedicated (Chang et al., 2020; Corominas-Roso et al., 2017; Darwish et al., 2019; Dursun et al., 2021; Mahmoud et al., 2020; Verlaet et al., 2019). Notably, one study assessed the levels of immune-inflammatory markers (CRP and IL-6) at two timepoints (at the age of 18 and 22 years) (Leffa et al., 2021). The NOS score ranged between 4 and 8. There were no significant differences between patients with ADHD and healthy controls with respect to age and sex, except for one study (Puzino et al., 2021) which was based on significantly more males among individuals with ADHD compared to controls.

The following immune-inflammatory markers were determined in the eligible studies: CRP, IL-1β, IL-6, IL-10, TNF-α and IFN-γ. Results of pooled and subgroup analyses are summarized in Table 2.

3.2. CRP

The levels of CRP were assessed by three studies (Chang et al., 2020; Leffa et al., 2021; Puzino et al., 2021). There were no significant differences in the levels of CRP between patients with ADHD and healthy controls [with participants from the study by Leffa et al., 2021 assessed at the age of 18 years: k = 3, g = 0.28, 95% CI: −0.17–0.73, $p = 0.218$, $I^2 = 88\%$; with participants from the study by Leffa et al., 2021 assessed at the age of 22 years: k = 3, g = 0.26, 95%CI: −0.23–0.75, $p = 0.305$, $I^2 = 90\%$; Supplementary Fig. 2]. Similarly, no significant difference in CRP levels was found when the analysis was limited to studies based on participants below the age of 18 years (k = 2, g = 0.43, 95%CI: −0.32–1.18, $p = 0.258$, $I^2 = 87\%$). The difference in CRP levels between patients with ADHD and healthy controls remained not significant after removing any single study in the sensitivity analysis (Supplementary Table 3).

3.3. IL-1β

The levels of IL-1β were analyzed by four studies (Chang et al., 2020; Dursun et al., 2021; Oades et al., 2010; Verlaet et al., 2019). No significant between-group differences in IL-1β levels were found (k = 4, g = −0.06, 95%CI: −0.31–0.18, $p = 0.606$, $I^2 = 0\%$, Supplementary Fig. 3). Similarly, the difference in IL-1β was not significant when the analysis was limited to studies of unmedicated individuals with ADHD (k = 3, g = −0.08, 95%CI: −0.34–0.17, $p = 0.524$, $I^2 = 0\%$). This difference remained not significant in the sensitivity analysis (Supplementary Table 3).

3.4. IL-6

All eligible studies investigated the levels of IL-6. Pooled analyses demonstrated significantly higher levels of IL-6 in subjects with ADHD compared to healthy controls [with participants from the study by Leffa et al., 2021 assessed at the age of 18 years: k = 10, g = 0.70, 95%CI: 0.10–1.30, $p = 0.023$, $I^2 = 96\%$; with participants from the study by Leffa et al., 2021 assessed at the age of 21 years: k = 10, g = 0.71, 0.12–1.31, $p = 0.019$, $I^2 = 96\%$; Fig. 1]. However, after removing single studies (Darwish et al., 2019; Elsadek et al., 2020; Mahmoud et al., 2020) in the sensitivity analysis, the difference in IL-6 levels appeared to be not significant (Supplementary Table 3). Results of the Egger's test were not significant, indicating no evidence of publication bias [with participants from the study by Leffa et al., 2021 assessed at the age of 18 years: coefficient = 4.50, 95%CI: −5.14–14.14, $p = 0.313$; with participants from the study by Leffa et al., 2021 assessed at the age of 22 years: coefficient = 4.17, 95%CI: −5.61–13.96, $p = 0.354$]. Interestingly, subgroup analysis revealed that the difference between groups was significant when the analysis was limited to studies based on participants under the age of 18 years (k = 8, g = 0.87, 95%CI: 0.16–1.58, $p = 0.017$, $I^2 = 96\%$) and not significant when the analysis was based on

Table 1
General characteristics of studies included in the meta-analysis.

Study	ADHD			Controls			%medicated	Inflammatory markers	NOS
	n	Age (yrs), mean (SD)	%males	n	Age (yrs), mean (SD)	%males			
Chang et al. (2020)	98	9.32 (3.05)	86.0	21	9.19 (3.0)	71.0	0	CRP, IL-1β, IL-6, TNF-α, IL-10	5
Corominas-Roso et al. (2017)	108	35.6 (9.6)	59.0	27	32.0 (8.6)	52.0	0	IL-6, TNF-α	6
Darwish et al. (2019)	60	8.4 (1.3)	83.3	60	8.7 (1.9)	68.3	0	IL-6	4
Dursun et al. (2021)	60	8.0 (2.75)	85.0	20	9.0 (2.25)	80.0	0	IL-1β, IL-6, TNF-α	4
Elsadek et al. (2020)	80	8.7 (2.3)	68.75	80	8.2 (2.7)	63.75	NS	IL-6, TNF-α	4
Leffa et al. (2021)	474	18.0 and 22.0	50.0	2807	18.0 and 22.0	46.3	NS	CRP, IL-6	8
Mahmoud et al. (2020)	20	8.4 (2.3)	85.0	20	9.0 (1.8)	65.0	0	IL-6	4
Oades et al. (2010)	35	10.4 (2.5)	74.3	21	11.0 (1.5)	95.2	40.0	IL-1β, IL-6, IL-10, TNF-α, IFN-γ	5
Puzino et al. (2021)	54	15.8 (2.0)	66.7	208	16.1 (2.2)	39.9	40.7	CRP, IL-6, TNF-α	5
Verlaet et al. (2019)	57	8.98 (1.75)	71.9	69	8.37 (1.7)	65.2	0	IL-1β, IL-6, IL-10, TNF-α, IFN-γ	4

Abbreviations: CRP, C-reactive protein; IFN-γ, interferon-γ; IL, interleukin, NOS, the Newcastle Ottawa Scale, NS, not specified; TNF-α, tumor necrosis factor-α.

Table 2
Results of pooled and subgroup analyses.

Marker	Analysis	k	g	95%CI	p	I^2
CRP	Pooled analysis with participants from the study by Leffa et al., 2021 assessed at the age of 18 years	3	0.28	−0.17–0.73	0.218	88%
	Pooled analysis with participants from the study by Leffa et al. (2021) assessed at the age of 22 years	3	0.26	−0.23–0.75	0.305	90%
	Subgroup analysis of participants aged <18 years	2	0.43	−0.32–1.18	0.258	87%
IL-1β	Pooled analysis	4	−0.06	−0.31–0.18	0.606	0%
	Subgroup analysis of unmedicated individuals with ADHD	3	−0.08	−0.34–0.17	0.524	0%
IL-6	Pooled analysis with participants from the study by Leffa et al. (2021) assessed at the age of 18 years	10	0.70	0.10–1.30	**0.023**	96%
	Pooled analysis with participants from the study by Leffa et al. (2021) assessed at the age of 22 years	10	0.71	0.12–1.31	**0.019**	96%
	Subgroup analysis of participants aged <18 years	8	0.87	0.16–1.58	**0.017**	96%
	Subgroup analysis of participants aged ≥18 years (with participants from the study by Leffa et al. (2021) assessed at the age of 18 years)	2	0.11	−0.07–0.29	0.221	0%
	Subgroup analysis of participants aged ≥18 years (with participants from the study by Leffa et al. (2021) assessed at the age of 22 years)	2	0.36	−0.18–0.50	0.356	57%
	Subgroup analysis of unmedicated individuals with ADHD	6	0.73	0.00–1.45	**0.049**	93%
IL-10	Pooled analysis	3	−0.01	−0.26–0.25	0.965	0%
	Subgroup analysis of unmedicated individuals with ADHD	2	0.06	−0.31–0.42	0.753	31%
TNF-α	Pooled analysis	7	−0.16	−0.30 - -0.03	**0.020**	0%
	Subgroup analysis of participants aged <18 years	6	−0.17	−0.32 - -0.03	**0.018**	0%
	Subgroup analysis of unmedicated individuals with ADHD	4	−0.23	−0.45 - -0.01	**0.036**	0%
IFN-γ	Pooled analysis	2	−0.03	−0.33–0.27	0.847	0%

k refers to the number of effect size estimates.
Abbreviations: CRP, C-reactive protein; IFN-γ, interferon-γ; IL, interleukin; TNF-α, tumor necrosis factor-α.
Significant differences ($p < 0.05$) were marked with bold characters.

studies with older participants. Moreover, the levels of IL-6 were significantly higher in unmedicated individuals with ADHD compared to healthy controls (k = 6, g = 0.73, 95%CI: 0.00–1.45, $p = 0.049$). Meta-regression analyses demonstrated that between-group differences in age and sex as well as the NOS scores were not significantly associated with effect size estimates for IL-6 (Supplementary Table 4).

3.5. IL-10

The levels of IL-10 were assessed by three studies (Chang et al., 2020; Oades et al., 2010; Verlaet et al., 2019). No significant differences in the levels of IL-10 between individuals with ADHD and healthy controls were found in pooled analysis (k = 3, g = −0.01, 95%CI: −0.26–0.25, $p = 0.965$, $I^2 = 0\%$, Supplementary Fig. 4) and subgroup analysis of unmedicated individuals with ADHD (k = 2, g = 0.06, 95%CI: −0.31–0.42, $p = 0.753$, $I^2 = 31\%$). This difference remained not significant in sensitivity analysis (Supplementary Table 3).

3.6. TNF-α

The levels of TNF-α were determined by seven studies (Chang et al., 2020; Corominas-Roso et al., 2017; Dursun et al., 2021; Elsadek et al., 2020; Puzino et al., 2021; Verlaet et al., 2019). The levels of TNF-α were significantly lower in subjects with ADHD compared to healthy controls (k = 7, g = −0.16, 95%CI: −0.30 - -0.03, $p = 0.020$, $I^2 = 0\%$, Fig. 2). This difference was significant in subgroup analyses of studies with participants aged below 18 years (k = 6, g = −0.17, 95%CI: −0.32 - -0.03, $p = 0.018$, $I^2 = 0\%$) and studies with unmedicated individuals with ADHD (k = 4, g = −0.23, 95%CI: −0.45–0.01, $p = 0.036$, $I^2 = 0\%$). However, sensitivity analysis (Supplementary Table 3) revealed that the difference in TNF-α appeared to be not significant after removing any of two studies (Chang et al., 2020; Puzino et al., 2021). Meta-regression analyses demonstrated that between-group differences in age and sex as well as the NOS scores were not significantly associated with effect size estimates for TNF-α (Supplementary Table 4).

3.7. IFN-γ

The levels of IFN-γ were assessed by two studies. No significant differences in IFN-γ between individuals with ADHD and healthy controls were found (k = 2, g = −0.03, 95%CI: −0.33–0.27, $p = 0.847$, $I^2 = 0\%$, Supplementary Fig. 5). Due to low number of studies, potential moderators were not tested and sensitivity analysis was not performed.

4. Discussion

Overall, the present meta-analysis demonstrated significantly higher unstimulated levels of peripherally measured IL-6 and lower levels of TNF-α in subjects with ADHD compared to healthy controls. Heterogeneity was high for studies that measured levels of IL-6 and low across studies that determined levels of TNF-α. Importantly, differences in the levels of both cytokines were significant when the analyses were limited to studies of unmedicated individuals with ADHD or to children or adolescents. The difference in IL-6 levels was not significant in studies of adult participants. However, this subgroup analysis was based on a low number of studies. Moreover, sensitivity analyses showed that between-group differences in IL-6 and TNF-α levels were no longer significant after removing several single studies, indicating that the effect is not very stable.

It should be noted that IL-6 is a pleiotropic cytokine that is secreted by various cells, including lymphocytes, macrophages, osteoblasts, smooth muscle cells, neurons, microglia and astrocytes. It exerts a number of activities within the central nervous system that might be relevant for neurodevelopmental disorders. Indeed, IL-6 has been shown to regulate expression of neurotrophins, circadian rhythm and food intake as well as learning and memory processes (Borovcanin et al., 2017). Peripheral inflammation might be related to neurofunctional alterations that are observed in ADHD and include reduced dopamine levels as well as impaired noradrenergic neurotransmission (Anand et al., 2017). Experimental studies in rodents showed that

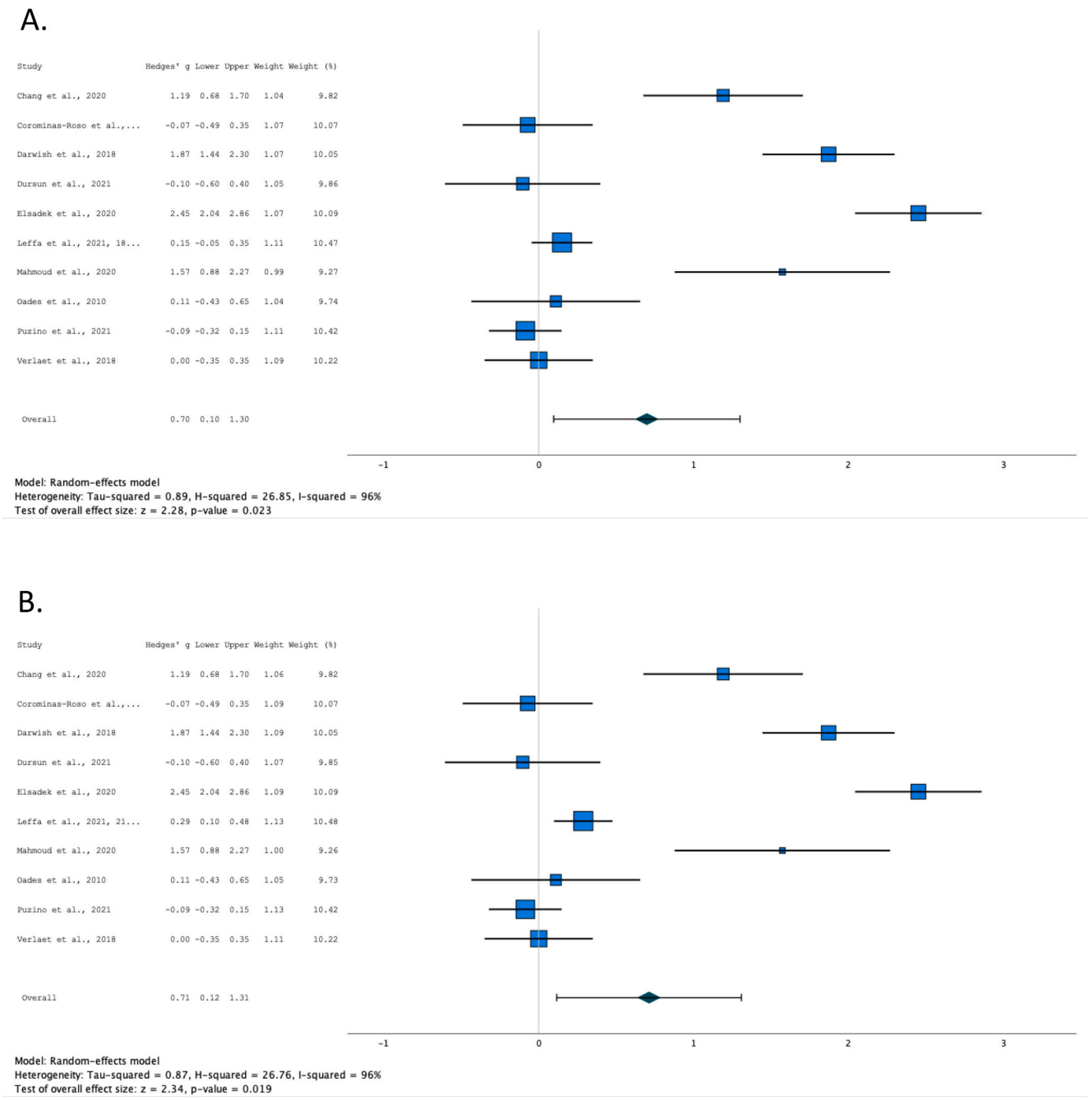

Fig. 1. Forrest plot for the analysis of interleukin-6 levels (A. with participants up to the age of 18 years; B. after including participants aged >18 years).

administration of IL-6 decreases the level of dopamine in the brain (Zalcman et al., 1994). Moreover, elevated levels of IL-6 together with lowered volume of medial prefrontal cortex and up-regulation of dopamine D2 receptors have been observed in spontaneously hypertensive rats (animal model of ADHD) (Kozłowska et al., 2019). Nevertheless, other mental disorders, including schizophrenia, bipolar disorder and major depression have also been associated with elevated IL-6 levels (Goldsmith et al., 2016). Additionally, elevated levels of IL-6 have been observed in psychosis risk states (Misiak et al., 2021). Notably, high rates of comorbidity with mood disorders have been documented in subjects with ADHD (Sandstrom et al., 2021; Schiweck et al., 2021), and it has been found that childhood ADHD increases a risk of subsequent psychosis (Nourredine et al., 2021). Therefore, it cannot be ruled out that our findings simply reflect the effect of comorbid mental disorders that were not assessed by studies included in the present meta-analysis or common underlying mechanisms.

The observation that the levels of TNF-α are reduced in subjects with ADHD seems to be interesting in light of opposite findings reported in other mental disorders (Goldsmith et al., 2016). However, the exact mechanisms underlying these differences remain unclear. These findings confirm those from the meta-analysis performed by Chang et al. (2021). Moreover, decreased levels of TNF-α have been observed in the prefrontal cortex, hippocampus and striatum of spontaneously hypertensive rats, being the animal model of ADHD (Leffa et al., 2017). On the other site, the TNF-α knockout mice have been found to show impairment of learning and poor retention in the novel object test (Baune et al., 2008).

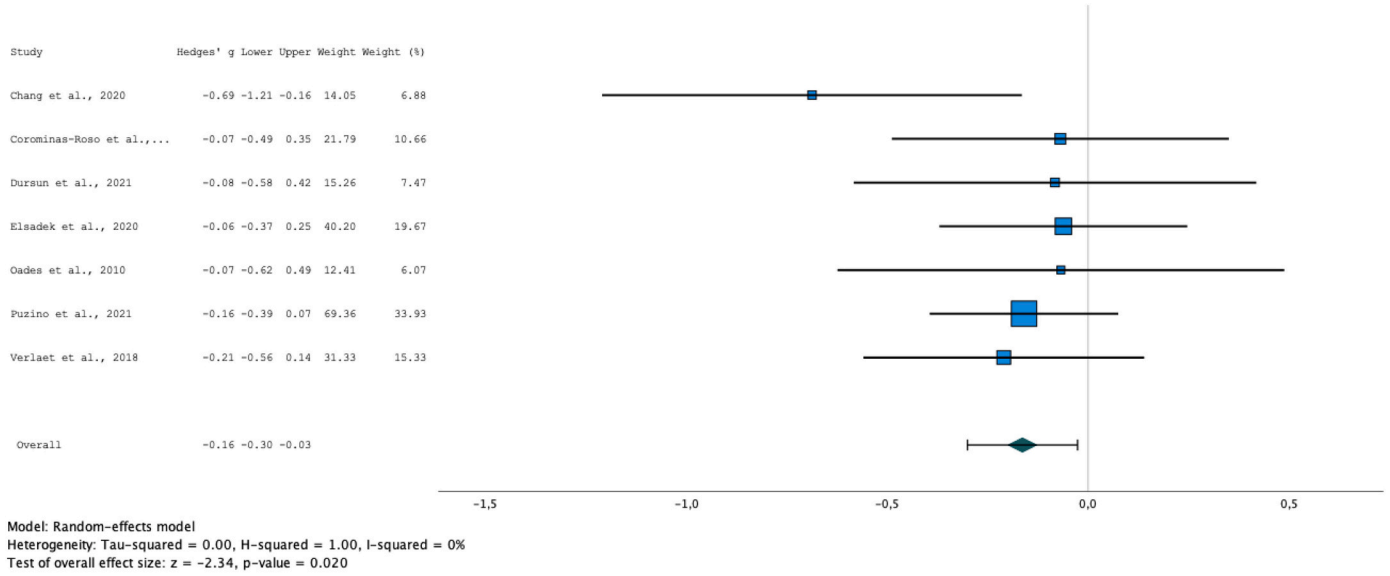

Fig. 2. Forrest plot for the analysis of tumor necrosis factor-α levels.

Human studies also show that TNF-α might be involved in cognitive processes (Bourgognon and Cavanagh, 2020). For instance, Beste et al. (2010) showed that the TNF-α rs1800629 polymorphism affect attention and action selection mechanisms in healthy participants. Also, one study included in the present meta-analysis demonstrated that lower TNF-α levels are associated with greater variability of reaction time in the continuous performance test that measures inattention (Oades et al., 2010).

The present meta-analysis is characterized by certain limitations. The main limitation is that it was based on a relatively low number of studies, and most of them had a low sample size. Nevertheless, it confirms and extends findings from the previous meta-analysis that included only four studies (Chang et al., 2021). We were also unable to control for the effects of potential confounding factors related to dietary habits, physical activity, substance use, the effects of comorbid mental disorders and somatic health impairments or simply stress imposed on the patients as a result of the disease. Moreover, only four studies included in the present meta-analysis recorded BMI (Corominas-Roso et al., 2017; Dursun et al., 2021; Oades et al., 2010; Puzino et al., 2021). At this point, it is important to note that various cytokines might be involved in the pathophysiology of obesity (Moghbeli et al., 2021). In turn, individuals with ADHD tend to develop obesity (Li et al., 2020) and share risk gene variants with patients suffering from obesity (Demontis et al., 2019). Therefore, it cannot be excluded that elevated levels of IL- 6 reported in our meta-analysis simply reflect the effects of overweight or obesity. Similarly, the impact of comorbid mental disorders or at least psychopathological symptoms should be taken into consideration. Therefore, it is likely that the effects of potential confounding factors not recorded by eligible studies account for high heterogeneity in analyses of IL-6 and CRP levels as well as not significant results after excluding some studies in sensitivity analyses of IL-6 and TNF-α. Moreover, it cannot be ruled out that only a certain subgroup of individuals with ADHD shows subclinical inflammation. Indeed, this observation has been made in patients with depression (Pariante, 2017). At this point, it should be noted that we did not perform subgroup analyses with respect to subtypes of ADHD (inattentive, hyperactive-impulsive and combined subtypes) as this information was not consistently reported by eligible studies. Similarly, sex differences were not exhaustively investigated due to a lack of consistent comparison of immune-inflammatory markers between male and female individuals with ADHD and controls. Indeed, we only performed meta-regression analyses for the association of differences in the percentage of males with effect size estimates of IL-6 and TNF-α. Another limitation is that significant findings of our meta-analysis could appear by chance due to multiplicity of analyzed markers. Finally, causal associations between inflammatory markers and ADHD cannot be established due to a lack of longitudinal and interventional studies in the present meta-analysis.

In conclusion, findings from this meta-analysis indicate that individuals with ADHD might show subclinical immune-inflammatory alterations in terms of elevated levels of IL-6 and reduced levels of TNF-α. However, larger studies recording potential confounding factors and comorbid mental disorders are needed to provide more insights into the role of inflammation in the pathophysiology of ADHD. Moreover, longitudinal and interventional studies are warranted to disentangle whether altered immune-inflammatory responses are causally associated with the development of ADHD.

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Declaration of Competing Interest

The authors declare that they have no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pnpbp.2022.110581.

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