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Association between inflammatory cytokines and ADHD symptoms in children and adolescents with obesity: A pilot study

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ABSTRACT

Whilst the association between Attention-Deficit/Hyperactivity Disorder (ADHD) and obesity is supported by meta-analytic evidence, the mechanisms underpinning this link need to be further elucidated. Inflammatory processes may increase the risk of ADHD symptoms in individuals with obesity. This pilot study set out to start testing this hypothesis by assessing the correlation between serum levels of inflammatory cytokines and ADHD symptoms severity in a sample of children and adolescents with obesity. We measured ADHD symptoms severity in 52 children/adolescents with obesity (BMI > 95th centile) with the Conners questionnaire, revised, short version, parent (CPRS-R:S) and teacher (CTRS-R:S) versions. Additionally, a categorical diagnosis of ADHD was established using the Kiddie-SADS-PL. Serum levels of IL-6, Il-10, and TNF-alpha were also obtained. The prevalence of ADHD was 9.6%. We found a significant correlation between IL-6, as well as TNF-alpha, and hyperactivity/impulsivity subscores of the CPRS-R:S and CTRS-R:S, that held even after controlling for BMI and oppositional symptoms. This study provides a rationale for larger, longitudinal studies to gain insight into inflammatory processes underpinning the link between obesity and ADHD. This line of research has the potential to lead to novel, pathophysiologically-based management strategies for individuals with obesity and ADHD.

1. Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) (American Psychiatric Association, 2013) is characterized by age-inappropriate and impairing levels of inattention and/or hyperactivity/impulsivity. It is estimated to affect around 3–5% of school-age children worldwide (Polanczyk et al., 2014; Polanczyk et al., 2015). ADHD is often comorbid with a number of neuropsychiatric conditions, including oppositional defiant disorder, conduct disorder, mood and anxiety disorders, and sleep disturbances (Cortese et al., 2008; Faraone et al., 2015).

Whilst the association between ADHD and neuropsychiatric conditions is established, in recent years there has been an increasing body of research focusing on somatic disorders possibly related to ADHD. The link between ADHD and obesity has received particular attention due to its possible clinical and public health implications (Cortese and Vincenzi, 2012). Indeed, given the high worldwide prevalence of obesity, estimated at around 37% in adults and 13% in children (Ng et al., 2014), individuals affected by the burden of both obesity and ADHD represent a sizable portion of the population in need of integrated physical and mental health care.

To date, two meta-analyses have supported a significant association between ADHD and obesity, albeit with partially different conclusions. The first one (Cortese et al., 2016) found a significant association between obesity and ADHD for both children and adults. Compared to individuals without ADHD, the pooled prevalence of obesity was increased by about 70% and 40%, in adults and children with ADHD, respectively. The second meta-analysis (Nigg et al., 2016) confirmed a significant association between ADHD and obesity, highlighting however a larger association in adults than in youth. Furthermore, in the Nigg et al. meta-analysis, the association was significant in females, but

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not in males.

The link between ADHD and obesity has relevant treatment implications, since it has been shown that treating comorbid ADHD reduced obesity rates in individuals with a history of weight loss failure, possibly due to a sustained decrease in impulsivity and improvement in organizational skills, which may lead to better adherence to obesity treatment (Cortese and Castellanos, 2014). This is highly relevant as there are no curative treatments for the majority of cases of obesity and, despite efforts to implement weight-loss programmes, patients and practitioners are frequently disappointed by the long-term results of weight control efforts (Anderson and Wadden, 1999). As such, to increase the chances of success, it is crucial to understand the factors and mechanisms that increase the risk of ADHD in individuals with obesity and to intervene on them.

It has been proposed that inflammatory alterations related to obesity contribute to ADHD symptoms in individuals with obesity (Cortese and Tessari, 2017). Indeed, obesity is currently conceptualized as a low grade, chronic inflammatory disease (Stolarczyk, 2017) and alterations in inflammatory peripheral cytokines have been related to ADHD symptoms severity (Anand et al., 2017). However, the hypothesis of obesity-related inflammatory alterations leading to ADHD symptoms has not been empirically tested yet. The present pilot study set out to preliminarily test this hypothesis. More specifically, we aimed to assess the correlation between peripheral (blood) circulating inflammatory cytokines levels and severity of ADHD core symptoms (i.e., inattention, hyperactivity, and impulsivity) in a sample of children and adolescents with obesity. We adopted a dimensional approach (i.e., focusing on ADHD symptoms severity) rather than a categorical one (i.e., comparing inflammatory cytokines levels in individuals with and without ADHD) to assess the possible link between cytokines and specific ADHD dimensions (i.e., inattention, hyperactivity, impulsivity). We expected a significant correlation between levels of inflammatory cytokines and severity of ADHD symptoms. Given the exploratory nature of the study, we did not formulate any *a priori* hypothesis as to which specific cytokines would be significantly related to ADHD severity symptoms.

2. Methods

2.1. Participants

In total, $n = 52$ Caucasian children were included in the study. Participants were children and adolescents with obesity, and their parents, who had been consecutively referred to the outpatient clinic of the Pediatric Diabetes and Metabolic Disorders Unit, at the University Hospital in Verona, Italy. Inclusion criteria were: age range: 6–18 years; obesity [Body Mass Index, BMI higher than the 95th percentile of BMI for age and gender reported in the reference tables developed in the same geographical area of recruitment (Luciano et al., 1997)]; children/adolescents and their parents able to provide the requested information and fill out the questionnaires used in this study. Exclusion criterion was the presence of obesity secondary to organic causes, which would potentially alter brain functions thus biasing study estimates of ADHD symptoms.

The children/adolescents and their parents gave their informed consent to the study. The investigation was carried out in accordance with the latest version of the Declaration of Helsinki. The protocol was approved by the Institutional Ethics Committee of Verona, Italy.

2.2. Measures

2.2.1. Demographic and clinical information

Demographic (age, race) and clinical (e.g., medication status, other diseases) data were obtained from the subjects and their parents during an initial consultation.

2.2.2. Anthropometric measures

Each child underwent a physical examination. Height and weight were measured at the first visit. Height was measured to the nearest 0.5 cm on a standardized height board. Weight was rounded to the nearest 0.1 kg on a standard physician's beam scale, with the subject dressed only in light underwear and no shoes. The BMI was calculated as weight (kilograms) divided by height (meters) squared. Since BMI changes physiologically with age in childhood in both genders, we considered standardized BMI (BMI-z scores) using age-(to the nearest month) and sex-specific median, SD, and power of the Box-Cox transformation (LMS method) based on national norms (Luciano et al., 1997).

2.2.3. Psychopathological assessment

The severity of ADHD symptoms was assessed with the Italian version of the Conners questionnaire, revised, short version, parent (CPRS-R:S) and teacher (CTRS-R:S) versions (Nobile et al., 2007). Each version includes the following three subscales: oppositional (Opp), cognitive problems/inattention (Inatt), and hyperactivity/impulsivity (H/I), plus the ADHD index (overall score).

Although the main study aim focused on ADHD symptoms severity, we also assessed the categorical diagnosis of ADHD, to estimate to which extent our sample was representative of other samples of children with obesity and ADHD reported in previous studies. The diagnosis of ADHD was confirmed using the Italian version (Kaufman et al., 2004) of the semi-structured diagnostic interview Kiddie-SADS-PL(Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version) (Kaufman et al., 1997).

2.2.4. Measurement of cytokines

IL-6, IL-10, and TNF-alpha were measured by a multiplex sandwich ELISA (Aushon BiosSystem, Billerica, MA) according to the manufacturer's instructions. Venous blood samples were obtained from the antecubital vein in suitable vacutainers at 0800 h of the interview day after 12-h overnight fasting conditions (Del Mar Bibioni et al., 2013). Serum samples were separated as soon as possible, coded, frozen and stored at –80 1 °C. The reported limits of detection of these assays were 0.2 pg/ml, 0.2 pg/ml, and 0.8 pg/ml for IL-6, IL-10, and TNF-alpha, respectively. These cytokines were selected as they have been the most commonly investigated in ADHD (Anand et al., 2017) and obesity (Stolarczyk, 2017). We note that some of the so-called inflammatory cytokines are indeed anti-inflammatory (e.g., IL-10). Other cytokines, such as IL-6, are both anti and pro-inflammatory, depending on the context (Siegert and Luther, 2012). In this paper, for convenience, we use the term “inflammatory” to indicate cytokines that are involved in inflammatory processes, regardless of their role as pro-inflammatory, anti-inflammatory, or both.

2.2.5. Statistical analysis

Descriptive data were presented as mean (or percentage) and standard deviation (SD). The correlation between inflammatory cytokines and ADHD symptoms severity was assessed using the bivariate correlations (Pearson coefficient). Our power calculation indicated that $n = 50$ participants would allow us to detect a correlation $r \geq 0.4$ with alpha = 0.05 and beta = 0.2. To test the robustness of the findings, we ran multiple regression analyses (Enter model) considering CPRS-R:S/CTRS-R:S H/I subscale scores as dependent variable and cytokines significantly associated with CPRS-R:S/CTRS-R:S H/I in the bivariate correlation (independently) as well as CPRS-R:S/CTRS-R:S Opp and BMI as independent variables. We also conducted a sensitivity analysis removing BMI from the model. These independent variables were chosen considering the results of the bivariate correlation and the need to minimise co-linearity in the model. A probability level of $p < 0.05$ was used to indicate statistical significance. Statistical analyses were performed using SPSS v15.0 (SPSS, Inc., Chicago, IL, USA).

Table 1
Sample demographic and clinical characteristics (n = 52).

Variable	N or mean (SD)
Age (years)	10.5 (1.9)
Sex (males/females)	37/15
Race: Caucasian	52/52
BMI z score	2.1 (0.3)
CPRS-R:S Opp	53.4 (10.9)
CPRS-R:S Inatt	57.7 (12.7)
CPRS-R:S H/I	54.1 (12.3)
CPRS-R:S Index	57.4 (11.5)
CTRS-R:S Opp	55.6 (11.9)
CTRS-R:S Inatt	55.5 (12.7)
CTRS-R:S H/I	55.9 (11.3)
CTRS-R:S Index	58.4 (10.7)
IL-6 (pg/ml)	5.3 (42.5)
IL-10 (pg/ml	5.05 (9.7)
TNF-alpha (pg/ml)	11.1 (52.1)

CPRS-R:S: scores on the Conners parent rating scale, revised, short version.
CTRS-R:S: scores on the Conners teacher rating scale, revised, short version.
Opp: Oppositional sub scale; H/I: Hyperactive/Impulsive subscale; Inatt: Inattentive subscale.

3. Results

The demographic and clinical characteristics of the sample are reported in Table 1. The prevalence of ADHD was 9.6%. We found a significant correlation between IL-10 levels and the scores on the CPRS-R:S H/I subscale (r = 0.417, p = 0.003) well as of the CTRS-R:S H/I subscale (r = 0.406, p = 0.008). We also found a significant correlation between TNF-alpha levels and the scores on the CPRS-R:S H/I subscale (r = 0.426, p = 0.002) well as on the CTRS-R:S H/I subscale (r = 0.318, p = 0.043). The significant association between IL-10, as well as TNF-alpha, and CPRS-R:S/CTRS-R:S H/I subscales remained significant in the regression models controlling for BMI and CPRS-R:S/CTRS-R:S Opp subscale scores (Table 2). The sensitivity analysis removing BMI from the model provided similar results (i.e., the association between IL-10, as well as TNF-alpha, and CPRS-R:S/CTRS-R:S H/I subscales remained significant) (Table 3).

4. Discussion

To our knowledge, this is the first study that assessed the relationship between peripheral inflammatory cytokines levels and severity of ADHD core symptoms. Pending replication in larger studies controlling for additional potential confounding factors, our pilot study provides support to a possible implication of inflammatory mechanisms underpinning the link between ADHD and obesity.

To date, six studies (Donfrancesco et al., 2016; O'Shea et al., 2014a; Hariri et al., 2012; Oades et al., 2010b; Oades et al., 2010a; Oades, 2011) have assessed the correlation between peripheral inflammatory cytokines levels and childhood ADHD. The results on individual peripheral cytokines levels are mixed, but overall they suggest a low-grade inflammation in patients with ADHD (Anand et al., 2017).

On the one hand, our results of a significant correlation between IL-10 and ADHD symptoms are in line with findings from a previous study (Donfrancesco et al., 2016) showing significantly higher levels of IL-10 in children with vs. those without ADHD. Our dimensional approach extends the finding from this previous study highlighting that IL-10 levels may be specifically associated with hyperactivity-impulsivity rather than with the ADHD core symptoms triad (hyperactivity, impulsivity and inattention). Of note IL-10 is anti-inflammatory cytokine that increases in individuals with chronic inflammation and, as highlighted by Donfrancesco et al. (2016), it may have a protective role during inflammation.

Additionally, the significant correlation we found between TNF-alpha and hyperactive-impulsive symptoms is supported by the previous finding (O'Shea et al., 2014) of significantly higher levels of TNF-R1 (the receptor for TNF-alpha) in children with compared to those without ADHD. On the other hand, we did not find a significant correlation between ADHD symptoms and IL-6, which was found as significantly higher in ADHD vs. controls in two previous studies in children (Donfrancesco et al., 2016; O'Shea et al., 2014) and one in adults (Corominas-Roso et al., 2017). It is possible that our relatively small sample size did not allow us to detect smaller albeit statistically significant correlations.

Of note, our results remained significant also after controlling for BMI and CPRS-S:R /CTRS-S:R Opp subscale (and even in the sensitivity analysis excluding BMI). This is relevant considering that oppositional/conduct disorders have been linked to inflammatory processes. For instance, conduct disorder has been shown to be significantly associated with atopic dermatitis (Yaghmaie et al., 2013). Furthermore, oppositional behaviors are significantly associated with ADHD (Faraone et al., 2015). As such, oppositional symptoms may represent a possible confounding factor in the relationship between cytokines levels and ADHD symptoms.

It is important to highlight that our results based on cross-sectional correlation do not allow us to infer any causal direction between increase in cytokines levels and ADHD symptoms severity. However, our study provides a rationale to conduct further longitudinal studies aimed to elucidate the cause-effect relationship between inflammatory cytokines and ADHD symptoms in individuals with obesity. The hypothesis of an increase in cytokines, reflecting a pro inflammatory status, contributing to ADHD symptoms is plausible considering that high levels of cytokines can influence synaptic plasticity and neurogenesis (McAfoose and Baune, 2009), which may contribute to ADHD symptoms. Additionally, cytokines can influence cognitive processes, including reaction time and working memory, which are often deficit in ADHD (McAfoose and Baune, 2009; Nakanishi, 2003).

However, two alternative hypotheses are also possible: 1) ADHD symptoms (more specifically, hyperactive impulsive symptoms) increases stress-related biomarkers (Vogel et al., 2017) which in turn are related to and contribute to inflammatory process of obesity (Liu et al., 2017); 2) Both ADHD and obesity stem from a chronic inflammatory process.

Our findings should be considered in the light of study strengths and limitations. Among the strengths, it is worthy to note that the prevalence of ADHD was 9.6%, which is very similar to the pooled prevalence (10.3%) of ADHD rates in samples of children with obesity calculated by Cortese et al. (2016) in their meta-analysis. As such, the present sample is comparable to previous ones, indicating that important selection bias was unlikely. Another strength is the fact that participants were ADHD medication naïve. This is relevant as a previous study (Oades et al., 2010a) found that ADHD pharmacological treatment could lead to a decrease in the levels of inflammatory cytokines. An additional strength is that we used standardized tools for the assessment of ADHD symptoms. As for the study limitations, the relatively small sample size did not allow us to detect moderate-to-small significant correlations. Furthermore, whilst we could control for the possible confounding effect of BMI and oppositional symptoms, we did not collect data on other possible confounders, such as mood disorders or other psychopathological conditions that are associated both with ADHD and inflammatory markers. Finally, since this was designed as a pilot, cross-sectional study, it did not aim to assess causality patterns between inflammatory markers and ADHD symptoms in children with obesity.

Notwithstanding these limitations, this pilot study provides preliminary evidence supporting well designed larger longitudinal studies aimed to gain insight into the role of inflammatory processes underpinning the link between obesity and ADHD, with the ultimate goal to support novel, pathophysiologically-based management strategies for individuals with obesity and ADHD.

Table 2
Multiple regression models.

Dependent variable: CPRS-R:S H/I					
Model		Unstandardized coefficients	Standardized coefficients	t	Sig.
1		B	Std. error	Beta	
	(Constant)	33.96	8.325	4.079	0
	BMI	−5.807	3.46	−0.2	−1.678	0.102
	CPRS-R:S Opp	0.555	0.118	0.548	4.684	0
	Il-10	0.567	0.118	0.548	4.791	0
Dependent variable: CTRS-R:S H/I					
Model		Unstandardized coefficients		Standardized coefficients	t	Sig.
1		B	Std. error	Beta		
	(Constant)	28.007	12.424	2.254	0.032
	CTRS-R:S Opp	0.546	0.137	0.547	3.994	0
	BMI	−2.029	4.369	−0.065	−0.464	0.646
	Il-10	0.482	0.141	0.478	3.406	0.002
Dependent variable: CPRS-R:S H/I					
Model		Unstandardized coefficients		Standardized coefficients	t	Sig.
1		B	Std. error	Beta		
	(Constant)	35.754	8.614	4.151	0
	CPRS-R:S Opp	0.523	0.122	0.517	4.292	0
	BMI	−5.223	3.547	−0.18	−1.473	0.15
	TNF-alpha	0.099	0.022	0.52	4.424	0
Dependent variable: CTRS-R:S H/I					
Model		Unstandardized coefficients		Standardized coefficients	t	Sig.
1		B	Std. error	Beta		
	(Constant)	25.901	12.783	2.026	0.052
	CTRS-R:S Opp	0.576	0.143	0.577	4.044	0
	BMI	−1.241	4.46	−0.04	−0.278	0.783
	TNF-alpha	0.081	0.027	0.443	3.047	0.005

CPRS-R:S: scores on the Conners parent rating scale, revised, short version.
CTRS-R:S: scores on the Conners teacher rating scale, revised, short version.
Opp: Oppositional sub scale; H/I: Hyperactive/Impulsive subscale.

Table 3
Multiple regression models: sensitivity analysis removing BMI.

Dependent variable: CPRS-R:S H/I					
Model		Unstandardized coefficients		Standardized coefficients	t	Sig.
1		B	Std. error	Beta		
	(Constant)	19.22	6.535	2.9401	0.005
	CPRS-R:S Opp	0.616	0.119	0.550	5.156	0
	Il-10	0.505	0.131	0.410	3.838	0
Dependent variable: CTRS-R:S H/I					
Model		Unstandardized coefficients		Standardized coefficients	t	Sig.
1		B	Std. error	Beta		
	(Constant)	28.007	12.424	2.254	0.032
	CTRS-R:S Opp	0.518	0.114	0.544	4.534	0
	Il-10	0.478	0.126	0.456	3.803	0.001
Dependent variable: CPRS-R:S H/I					
Model		Unstandardized coefficients	Standardized coefficients	t	Sig.
1		B	Std. error	Beta		
	(Constant)	21.199	6.594	3.215	0.02
	CPRS-R:S Opp	0.597	0.121	0.533	4.933	0
	TNF-alpha	0.090	0.025	0.395	3.658	0.001
Dependent variable: CTRS-R:S H/I					
Model		Unstandardized coefficients		Standardized coefficients	t	Sig.
1		B	Std. error	Beta		
	(Constant)	24.293	6.855	3.544	0.001
	CTRS-R:S Opp	0.549	0.119	0.575	4.594	0
	TNF-alpha	0.081	0.024	0.419	3.345	0.002

CPRS-R:S: scores on the Conners parent rating scale, revised, short version.
CTRS-R:S: scores on the Conners teacher rating scale, revised, short version.
Opp: Oppositional sub scale; H/I: Hyperactive/Impulsive subscale.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2019.05.030.

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