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Decreased serum levels of adiponectin in adult attention deficit hyperactivity disorder

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ABSTRACT

The main aim of this study was to investigate serum levels of adiponectin in adult patients with attention deficit hyperactivity disorder (ADHD). The second objective was to examine the effects of rare missense mutations in T-cadherin, an adiponectin receptor encoded by the ADHD candidate gene *CDH13*, on serum adiponectin levels. Total and high molecular weight (HMW) adiponectin levels were measured by an enzyme-linked immunosorbent assay in 44 patients and 29 controls. We found decreased serum adiponectin levels in ADHD patients. In a logistic regression model, adjusting for confounding by age, body mass index, and gender, HMW adiponectin and its ratio to total adiponectin were significantly associated with ADHD. In partial correlations, HMW adiponectin and its ratio to total adiponectin were significantly inversely correlated with self-reported psychiatric symptomatology. A non significant trend for higher levels of total adiponectin was observed in patients carrying *CDH13* missense mutations compared to patients with wild type *CDH13*. The association of *CDH13* mutations with adiponectin levels should be investigated in larger studies. This study shows that ADHD patients have decreased serum adiponectin levels, which are inversely correlated to psychiatric symptoms, suggesting a possible involvement of adiponectin, in particular the HMW form, in the pathophysiology of ADHD.

1. Introduction

Attention deficit hyperactivity disorder (ADHD) is a common childhood neurodevelopmental disorder with worldwide prevalence estimates of around 5–10% (Faraone et al., 2003; Polanczyk et al., 2007). ADHD often persists into adulthood with a prevalence of around 3–5% in young adults (Fayyad et al., 2007; Simon et al., 2009). Although around 75% of the variability in childhood ADHD symptomatology is accounted for by genetic factors (Faraone and Doyle, 2001), unequivocal genetic associations with ADHD have not been identified yet (Faraone et al., 2005; Franke et al., 2012). Research in ADHD etiology has revealed several biological and psychosocial risk factors for this disorder, such as maternal smoking (Langley et al., 2005) and alcohol consumption during pregnancy (Banerjee et al., 2007), pre-term birth and low birth weight (Halmoy et al., 2012), maternal stress, environmental toxin exposure, and childhood adversity (Biederman, 2005). Still, the biological mechanisms mediating these risk factors have not yet been identified and few biomarkers have shown consistent associations with ADHD (Scassellati et al., 2012).

An increased prevalence of obesity, cardiovascular disease and diabetes mellitus has been reported in disorders like major depression, bipolar disorder, and schizophrenia (Bai et al., 2013; Stanley and Laugharne, 2012; Stanley et al., 2013). Likewise, recent studies have shown co-occurrence of obesity and ADHD in children (Agranat-Meged et al., 2005; Halfon et al., 2013) and adults (Fleming et al., 2005). Moreover, there is evidence that obesity genes such as the *FTO* gene, which codes for the enzyme alpha-ketoglutarate-dependent dioxygenase, may affect ADHD risk (Choudhry et al., 2013) and that obesity and ADHD may share common risk alleles (Albayrak et al., 2013). Thus, these co-morbidities may reflect a common etiology or the involvement of common pathways, as well as a cross-talk between adipose tissue and the central nervous system (Schulz et al., 2010).

In line with these findings, abnormal circulating levels of hormones secreted by adipose tissue, such as the adipocytokine adiponectin, have been detected in obesity (Arita et al., 1999; Ryo et al., 2004), type II diabetes and insulin resistance (Kadowaki et al., 2006; Yatagai et al., 2003), but also in patients with psychiatric disorders such as major depression (Leo et al., 2006), schizophrenia (Cohn et al., 2006), panic disorder (Unsal et al., 2012) and bipolar disorder (Barbosa et al., 2012). Adiponectin is an

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adipokine hormone that has insulin-sensitizing (Shehzad et al., 2012) and anti-inflammatory effects (Wolf et al., 2004), stimulates fatty acid oxidation (Yamauchi et al., 2001), and its expression is regulated by insulin (Scherer et al., 1995), testosterone (Nishizawa et al., 2002), and glucocorticoids (Sukumaran et al., 2012). Adiponectin molecules circulate in the blood mainly as trimers of 30 kDa subunits and multimers composed of combinations of trimers and hexamers (Kadowaki and Yamauchi, 2005; Tsao et al., 2003). The diverse functions of adiponectin are mediated by the AdipoR1 and AdipoR2 receptors that show predominant expression in muscle and liver, respectively, (Yamauchi et al., 2003) but are also expressed in the brain (Thundyil et al., 2012). A third adiponectin receptor, T-cadherin, selectively binds the hexameric and high molecular weight forms (HMW) of adiponectin and is abundantly expressed in the cardiovascular system and the brain (Hug et al., 2004). Several genome wide association (GWA) studies have detected associations between single nucleotide polymorphisms (SNPs) in the region of the *CDH13* gene, which codes for T-cadherin, and ADHD (Lasky-Su et al., 2008; Lesch et al., 2008). Moreover GWA studies have shown a strong association of *CDH13* polymorphisms with serum levels of adiponectin (Morisaki et al., 2012; Wu et al., 2010). Based on these findings, we wanted to examine serum adiponectin levels in ADHD and the effects of missense mutations in *CDH13* on serum adiponectin levels.

The main aim of this study was to compare serum adiponectin levels, and adiponectin multimer distribution, in a sample of ADHD patients and population derived controls. The second aim was to investigate the effects of missense heterozygous *CDH13* mutations, previously identified in our sample (Mavroconstanti et al., 2013) on the serum levels of adiponectin by comparing two subgroups of adult ADHD patients: (1) carriers of wild type *CDH13* and (2) carriers of either one of seven rare *CDH13* mutations.

2. Methods

2.1. Subjects and measures

The present study is part of a large multidisciplinary study of ADHD at the University of Bergen, Norway. Most of the patients in the study were recruited from a national registry of adults (> 18 years) diagnosed with ADHD between 1997 and 2005. Additionally, adult patients diagnosed after 2005 were recruited from outpatients clinics nationwide (Halmoy et al., 2009). The inclusion criteria was a formal diagnosis of ADHD or hyperkinetic disorder made by a clinician (psychiatrist or psychologist) according to ICD-10 or DSM-IV criteria, before entering the study (Johansson et al., 2008). The Medical Birth Registry of Norway was used to randomly recruit controls from the general population in the same range of age (Halmoy et al., 2009). There were no formal exclusion criteria. Blood was obtained between 9 am–4 pm and serum was subsequently collected and stored at −80 °C. All the study participants completed self-report questionnaires with a total of 110 questions relating to different comorbidities, psychiatric symptoms and treatment history, including (1) the adult ADHD self-report scale (ASRS) rating current symptoms of ADHD (Kessler et al., 2005), (2) the Wender Utah rating scale (WURS) rating retrospectively reported ADHD related symptoms in childhood (Ward et al., 1993), (3) the cyclothymic subscale of the temperament evaluation of Memphis, Pisa, Paris and San-Diego (TEMPS-A) (Akiskal et al., 2005) and (4) and the Mood Disorder questionnaire (MDQ)(Hirschfeld et al., 2000), a screening questionnaire for bipolar disorder. The ASRS consists of 18 items corresponding to DSM-IV criteria for ADHD, the first 9 assessing symptoms of inattention (ASRS In), the last 9 symptoms of hyperactivity/impulsivity (ASRS Hyp/Imp). A more detailed description of the methodology used to recruit patients and controls, and also the questionnaires used in the study, can be found in a previous publication (Halmoy et al., 2009, 2010; Landaas et al., 2012).

The total sample in the current study ($n=73$) was comprised of 44 adult ADHD patients and 29 controls. The controls were selected based on blood sample availability whereas patient selection was additionally based on the availability of *CDH13* genotype information. The patient sample consisted of 27 randomly selected carriers of wild type *CDH13* and 17 heterozygous carriers of either one of seven rare coding mutations in the *CDH13* gene (V112I (rs200199969), G113R (rs183971768), R174W (novel), A376T (rs35549391), I585V (rs199759196), L643R (rs34106627), and N39S (rs72807847)) previously detected in a sample of 641 adult ADHD patients with a combined allele frequency of 3.24% (Mavroconstanti et al., 2013). The effects of *CDH13* mutations on adiponectin levels were investigated in the subgroups of patients carrying wild type or mutant CDH13.

2.2. Ethics statement

The study was approved by the Norwegian Regional Medical Research Ethics Committee West (IRB #3 FWA00009490, IRB00001872) and conducted according to the principles of the declaration of Helsinki (2008). All participants signed a written informed consent form.

2.3. Serum total and HMW adiponectin measurements

The measurements of total and HMW adiponectin levels in the serum obtained from 44 patients and 29 healthy controls were performed using a commercially available enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's instructions (Quantikine ELISA Human Total and HMW Adiponectin/Acrp30 Immunoassays, R&D systems). For the measurements, serum samples were centrifuged at 1000*g* for 10 min and diluted 100-fold. According to the manufacturer (R&D systems), the sensitivity (mean minimum detectable dose) is 0.246 ng/ml for total adiponectin and 0.195 ng/ml for HMW adiponectin. The intra-assay precision (coefficient of variation; CV) was specified to be 2.5–4.7% for total adiponectin and 2.6–3.7% for HMW adiponectin. The inter-assay precision was specified to be 5.8–6.9% for total adiponectin and 8.3–8.6% for HMW adiponectin. All assays were performed in duplicate. Ten random samples were subjected to four repeated measurements over a 6 month period. The observed intra-assay CV varied between 2.2% and 3.8% for total adiponectin, 0.8–3.7% for HMW adiponectin and the inter-assay CV varied between 7.5% and 17.0% for total adiponectin and 6.3–18.4% for HMW adiponectin.

2.4. Statistical analyses

IBM SPSS version 19 (SPSS Inc., Chicago, Illinois) was used for the statistical analyses. Differences in adiponectin levels, as well as other differences of continuous variables between groups, were analyzed using either a *t*-test for normally distributed variables or a nonparametric Mann Whitney test for variables with skewed distributions. The distribution of each variable in the total sample was examined by both the Kolmogorov–Smirnov and the Shapiro–Wilk normality tests. Pearson's chi-squared exact test was used to analyze differences of categorical variables between groups. To study correlations between adiponectin levels and psychiatric symptoms, based on self-report questionnaire scores (WURS, ASRS, TEMPS-A, MDQ), we performed partial correlations for controlling the effects of body mass index (BMI) and age in the total sample of patients and controls.

To study the associations between adiponectin levels and (1) an ADHD diagnosis, or (2) the subcategories of patients carrying wild type or mutant CDH13 we used logistic regression models (method enter). Statistically significant results were adjusted for the effects of BMI, age and gender. To examine the association between adiponectin levels and an ADHD diagnosis, we defined the binary categorical variable ADHD (yes/no) as the outcome variable and the levels of total, HMW, or the percentage of HMW to total adiponectin as the predictor variables. Total, HMW or the percentage of HMW/total adiponectin was entered individually in step one of the model to observe the unadjusted associations of each variable with an ADHD diagnosis. Statistically significant results were subsequently adjusted for the effects of age, gender and BMI which were added in step 2, both individually and as a group. In an analogous logistic regression model we examined the association of adiponectin levels with the binary outcome variable of the subcategories of patients carrying wild type or mutant *CDH13*. Moreover, to investigate possible effects of ADHD co-morbid disorders or medication use on adiponectin levels, we performed logistic regression analyses stratified for each comorbid disorder or medication use, in patients only.

3. Results

3.1. Sociodemographic and clinical characteristics of the study participants

The sociodemographic and clinical characteristics of (1) the ADHD patient and control groups and (2) the subgroups of ADHD patients who were carriers of wild type or mutant *CDH13* are presented in Tables 1 and 2, respectively. No statistically significant differences were observed for the distribution of gender, age and BMI between ADHD patients and controls. Compared to controls, ADHD patients had significantly lower levels of total ($P=0.001$) and HMW ($P<0.001$) adiponectin as well as a lower

Table 1
Sociodemographic and clinical characteristics of the patient and control groups.

	ADHD	*N*	Controls	*N*	*P* value
Female (%)	26 (59%)	44	17 (59%)	29	1.000[a]
Age	25 (23,29.8)[b]	44	24 (22,27.5)[b]	29	0.504[c]
BMI	24.9 (22.1,30.0)[b]	35	24.2 (21.3,25)[b]	27	0.091[c]
Total adiponectin (μg/ml)	10.35 (5.5,14.8)[b]	43	14.95 (9.0,22.96)[b]	29	0.001[c]
HMW adiponectin (μg/ml)	3.0 (1.5,5.5)[b]	44	5.86 (3.74,11.73)[b]	29	< 0.001[c]
HMW/total	30.34 (8.8)[d]	43	48.9 (11.6)[d]	29	< 0.001[e]
Depression/anxiety (%)	25 (60%)	41	2 (7%)	29	< 0.001[a]
Dyslexia (%)	20 (48%)	42	1(3%)	29	< 0.001[a]
Migraine (%)	12 (28%)	43	4 (14%)	29	0.248[a]
Asthma (%)	13 (30%)	43	3 (10%)	29	0.081[a]
Substance abuse (%)	10 (23%)	43	0	29	0.004[a]
Epilepsy (%)	5 (12%)	43	0	29	0.077[a]
Bipolar (%)	4 (9%)	43	0	29	0.143[a]
Current central stimulant use (%)	27 (79%)	34	n/a		n/a
Autism/Tourette/Asperger	6 (14%)	43	0	29	0.075[a]
ASRS In (range 0–36)	22.3 (6.8)[d]	44	13.51 (5.0)[d]	29	< 0.001[e]
ASRS Hyp/Imp (range 0–36)	20 (12,24)[b]	44	12 (9,15)[b]	29	< 0.001[c]
ASRS total (range 0–72)	44.5 (28.5,53)[b]	44	26 (20,30.5)[b]	29	< 0.001[c]
WURS (range 0–100)	55 (47.3,75.5)[b]	44	15(8.5,27)[b]	29	< 0.001[c]
TEMPS-A (range 0–21)	14 (9.5,17)[b]	41	4 (2,6)[b]	29	< 0.001[c]
MDQ (range 0–13)	8 (5,11)[b]	41	3 (0.5,6)[b]	29	< 0.001[c]

Abbreviations: attention deficit hyperactivity disorder (ADHD), the adult ADHD self-report scale (ASRS), ASRS In=inattentive component of ASRS, ASRS Hyp/imp=hyperactive/impulsive component of ASRS, the Wender Utah rating scale (WURS), temperament evaluation of Memphis, Pisa, Paris and San-Diego (TEMPS-A), the mood disorder questionnaire (MDQ), body mass index (BMI), high molecular weight (HMW).

[a] Chi exact test.
[b] Median (first, third quartile).
[c] Mann Whitney test.
[d] Mean (standard deviation).
[e] *T*-test.

Table 2
Sociodemographic and clinical characteristics of the groups of patients carrying wild type or mutant CDH13.

	Carriers of mutant CDH13	*N*	Carriers of WT CDH13	*N*	*P* value
Female (%)	11 (65%)	17	15 (55%)	27	0.754[a]
Age	28 (23,42)[b]	17	25 (22,28)[b]	27	0.066[c]
BMI	24.3 (22.2,28.6)[b]	16	26 (20.1,31.3)[b]	27	0.619[c]
Total adiponectin (μg/ml)	13.3 (6,15.4)[b]	17	6.8(4,11.3)[b]	27	0.051[c]
HMW adiponectin (μg/ml)	3.8 (1.6,5.8)[b]	17	2.4 (1.3,4.9)[b]	27	0.273[c]
HMW/total (%)	29.5 (7.6)[d]	17	30.9 (9.9)[d]	26	0.619[e]
Depression /anxiety (%)	9 (60%)	15	16 (62%)	26	1.000[a]
Dyslexia (%)	7 (44%)	16	13 (50%)	26	0.758[a]
Migraine (%)	4 (25%)	16	8 (30%)	27	1.000[a]
Asthma (%)	6 (38%)	16	7 (26%)	27	0.502[a]
Substance abuse (%)	4 (25%)	16	6 (22%)	27	1.000[a]
Autism/Tourette/Asperger	3 (19%)	16	3 (13%)	27	0.655
Bipolar (%)	1 (6%)	16	3 (11%)	27	1.000[a]
Epilepsy (%)	1 (6%)	16	4 (14%)	27	0.635[a]
ASRS In (range 0–36)	24.7 (6.4)[d]	17	20.8 (6.7)[d]	27	0.062[e]
ASRS Hyp/Imp (range 0–36)	21.47 (7.1)[d]	17	18.18 (7.55)[d]	27	0.158[e]
ASRS total (range 0–72)	46.17 (13)[d]	17	38.96 (12.29)[d]	27	0.085[e]
WURS (range 0–100)	60.44 (17)[d]	17	59.35 (16.2)[d]	27	0.814[e]
TEMPS-A (range 0–21)	12.87 (5.8)[d]	17	13.28 (4.8)[d]	27	0.811[e]
MDQ (range 0–13)	7.7 (4.4)[d]	16	8.1 (4.6)[d]	27	0.766[c]
Current central stimulant use	9 (69%)	13	18 (86%)	21	0.387[a]

Abbreviations: attention deficit hyperactivity disorder (ADHD), the adult ADHD self-report scale (ASRS), ASRS In=inattentive component of ASRS, ASRS Hyp/imp=hyperactive/impulsive component of ASRS, the Wender Utah rating scale (WURS), temperament evaluation of Memphis, Pisa, Paris and San-Diego (TEMPS-A), the mood disorder questionnaire (MDQ), body mass index (BMI), high molecular weight (HMW)

[a] Chi exact test.
[b] Median (first, third quartile).
[c] Mann Whitney test.
[d] Mean (standard deviation).
[e] *T*-test.

fraction of HMW relative to total adiponectin ($P < 0.001$) (Fig. 1). Concerning other characteristics, ADHD patients scored higher than controls on the self-report questionnaires related to ADHD diagnosis (WURS, ASRS) and also on affective and temperament dimensional scales (MDQ,TEMPS-A), $P < 0.001$. Likewise, there was a higher incidence of self-reported co-morbidity among patients

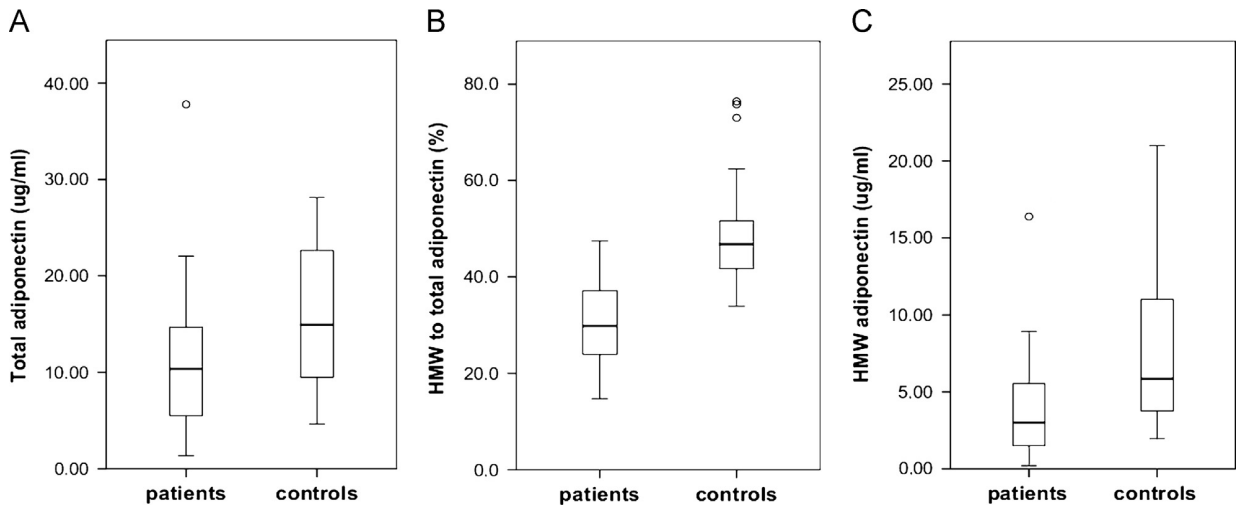

Fig. 1. Boxplots showing differences in the serum levels of total adiponectin ($P=0.001$) (A), the fraction of high molecular weight (HMW) to total adiponectin ($P<0.001$) (B), and the levels of HMW adiponectin ($P<0.001$) (C) between ADHD patients and controls. The boxes indicate the first, second (median) and third quartiles and the vertical bars indicate the range. The open circles indicate individual values that are outside the range.

Table 3
Partial correlations between serum adiponectin levels and psychiatric questionnaire scores in the total sample of patients and controls controlling for the effects of body mass index and age.

Adiponectin	Total		HMW		%HMW/Total	
Questionnaires	*r*	*P* value	*r*	*P* value	*r*	*P* value
ASRS In	−0.062	0.640	−0.205	0.117	−0.330	0.010**
ASRS Hyp/Imp	−0.160	0.223	−0.251	0.053	−0.321	0.012*
ASRS total	−0.116	0.375	−0.239	0.065	−0.341	0.008**
WURS	−0.187	0.153	−0.299	0.020*	−0.471	< 0.001**
TEMPS	−0.139	0.302	−0.245	0.066	−0.387	0.003**
MDQ	−0.203	0.129	−0.259	0.052	−0.349	0.008**

Abbreviations: attention deficit hyperactivity disorder (ADHD), the adult ADHD self-report scale (ASRS), ASRS In = inattentive component of ASRS, ASRS Hyp/imp = hyperactive/impulsive component of ASRS, the Wender Utah rating scale (WURS), temperament evaluation of Memphis, Pisa, Paris and San-Diego (TEMPS-A), the mood disorder questionnaire (MDQ).

* Correlation is significant at 0.05 level.
** Correlation is significant at 0.01 level.

Table 4
Association between serum adiponectin levels and diagnosis of attention deficit hyperactivity disorder: logistic regression results adjusted for the effects of body mass index, age, and gender.

Adiponectin	Unadjusted			Adjusted		
	OR	95% C.I	*P* value	OR	95% C.I	*P* value
Total	0.903	0.841, 0.970	0.005	0.929	0.856, 1.009	0.082
HMW	0.748	0.635, 0.882	0.001	0.771	0.639, 0.931	0.007
% HMW/Total	0.792	0.709, 0.884	< 0.001	0.736	0.617, 0.878	0.001

Abbreviations: high molecular weight (HMW), odds ratio (OR), 95% confidence interval (95% C.I).

compared to controls. Statistically significant differences ($P<0.01$) were observed for the following conditions: dyslexia, depression/anxiety, and substance abuse.

In the subgroups of ADHD patients carrying wild type or mutant *CDH13* (Table 2) a non significant trend ($P=0.051$) for higher levels of total adiponectin was observed in carriers of *CDH13* mutations compared to carriers of wild type *CDH13*. The groups were otherwise similar.

3.2. Associations between adiponectin levels, dimensional scores, and ADHD diagnosis

Having established that a clinical diagnosis of ADHD was associated with lower levels of HMW and total adiponectin and a lower fraction of HMW to total adiponectin, it was also important to examine whether any specific symptoms or traits were particularly associated with these biochemical findings. In addition to categorical diagnoses, we obtained dimensional scores rating present and past ADHD symptoms (ASRS and WURS), symptoms of mood disorders (MDQ) and cyclothymic temperament traits (TEMPS-A) from all patients and controls (Tables 1 and 2).

The results of partial correlation analyses between psychiatric symptomatology scores and adiponectin levels in the total sample of ADHD patients and controls are shown in Table 3. The correlations were adjusted for the effects of BMI and age. The levels of total adiponectin did not show correlations with psychiatric symptoms. In contrast, the levels of HMW adiponectin were negatively correlated with WURS scores ($P=0.020$). In addition, a non significant trend for an inverse correlation of HMW adiponectin levels with scores on the hyperactivity/impulsivity component of ASRS and mood symptoms (MDQ scores) was observed. The strongest correlations were, however, observed for the fraction of HMW to total adiponectin, which was negatively correlated with scores on ASRS In ($p=0.010$), ASRS Hyp/Imp ($P=0.012$), and ASRS total, WURS, TEMPS-A and MDQ ($P<0.01$). Thus, significant negative correlations were found between serum levels of HMW adiponectin and symptoms of ADHD, mood disorder and affective temperament, the strongest correlations being observed for childhood symptoms of ADHD, the weakest for the inattentive symptom cluster of ADHD.

In logistic regression analyses, low levels of total and HMW adiponectin, as well as a decreased ratio of HMW to total adiponectin, were associated with ADHD before adjusting for the effects of BMI, gender and age ($P<0.01$). After these adjustments, absolute (OR = 0.78, $P=0.007$) and relative HMW adiponectin (OR = 0.74, $P=0.001$), but not total adiponectin, were predictive for an ADHD diagnosis (Table 4). In these analyses, we observed that BMI was the only factor that significantly affected specifically the association of total adiponectin levels and ADHD resulting in a

loss of significant association after adjusting for the effects of BMI. Age and gender on the other hand did not affect significantly the associations between total adiponectin levels and ADHD. In contrast, the associations between HMW adiponectin levels or the ratio of HMW/total and ADHD were mainly unaffected by all three factors (BMI, age, and gender).

Many ADHD patients had several co-morbid disorders, which are commonly observed in this patient group. Moreover, the majority of patients reported use of central stimulants (Table 1). In logistic regression stratified for comorbidities or medication use we did not observe significant associations between any of these possible confounders and adiponectin levels in the corresponding patient subgroups (data not shown).

3.3. Associations between adiponectin levels and CDH13 mutations

In logistic regression analysis no statistically significant associations were observed between adiponectin levels and the subgroups of patients carrying wild type or mutant *CDH13:* total adiponectin OR=1.064 (C.I: 0.968, 1.169), P=0.202, HMW adiponectin OR=1.048 (C.I: 0.859, 1.278), P=0.647 and fraction of HMW/total O.R= 0.982 (C.I: 0.982, 1.054), P=0.610.

4. Discussion

This is, to our knowledge, the first study to investigate serum levels of total and HMW adiponectin in ADHD patients and also the effects of rare coding variants in *CDH13* on adiponectin levels. We show that adult ADHD patients have significantly decreased serum levels of HMW adiponectin and a decreased ratio of HMW to total adiponectin after adjusting for factors known to influence adiponectin levels like age, gender and BMI. Significantly decreased serum levels of total adiponectin were also observed but these did not remain significant after these adjustments. High intra-assay precision was observed in the adiponectin measurements. Although a slightly high inter-assay variability was also observed, the coefficient of variation was within the limits considered acceptable in such immunoassays (Findlay et al., 2000).

A specific role for HMW adiponectin has been suggested in other disorders. In anorexia nervosa patients the percentage of HMW to total adiponectin was decreased whereas the percentage of low molecular weight (LMW) to total adiponectin was increased compared to healthy controls. The ratio of HMW to total adiponectin was positively correlated with BMI and psychological symptoms whereas the latter was negatively correlated with BMI only (Amitani et al., 2013). A decreased ratio of HMW to total or LMW adiponectin was found to be negatively correlated with depression severity in elderly subjects but not total adiponectin (Narita et al., 2008). Lower levels of the HMW form and the HMW to total adiponectin ratio were also reported in insulin resistance and metabolic syndrome (Hara et al., 2006; Seino et al., 2007). Moreover, lifestyle changes that lead to a decrease in BMI in obese patients were found to increase selectively the HMW form and also administration of insulin sensitizing drugs to diabetics had the same effects on specifically the HMW form of adiponectin (Hirose et al., 2010).

Decreased serum levels of total adiponectin have been reported in psychiatric disorders including major depression (Lehto et al., 2010; Leo et al., 2006), in patients with mild cognitive impairment, and Alzheimer's disease (Teixeira et al., 2012), in adults with a history of childhood maltreatment (Lehto et al., 2012), in obsessive compulsive disorder (Ari et al., 2012; Atmaca et al., 2009), autism (Fujita-Shimizu et al., 2010), panic disorder (Unsal et al., 2012), and drug-naïve schizophrenia patients (Cohn et al., 2006). In these studies however, only the levels of total adiponectin were measured. Our findings and those of previous studies suggest that HMW adiponectin may indeed be more biologically relevant and specifically involved in human disease (Oh et al., 2007). We suggest that measuring HMW adiponectin in the context of psychiatric disease may be a more sensitive and informative measure than total adiponectin levels. This is important to investigate as it may reflect yet unknown, specific biological effects of HMW adiponectin playing a role in the pathogenesis of psychiatric disorders and their complications.

As previously reported, there was a significantly higher frequency of other common ADHD co-morbid conditions such as dyslexia (Germano et al., 2010), anxiety and depression (Michielsen et al., 2013), and substance abuse (Klassen et al., 2012), in patients compared to controls in our sample. In logistic regression analyses stratified for each comorbid disorder we investigated the potential effects of these disorders on adiponectin levels, in patients only. We did not find any associations between adiponectin levels and each additional disorder. Although adiponectin levels were not associated with any comorbid disorder in ADHD patients in our sample, further studies on larger samples are needed to determine potential effects of comorbidities in ADHD patients.

Furthermore, we found that the fraction of HMW to total adiponectin exhibited a significant negative correlation with scores on self-report questionnaires related to ADHD diagnosis and affective and temperament traits (WURS, ASRS, MDQ and TEMPS-A) in partial correlation analyses. The strongest correlation was observed between the fraction of HMW to total adiponectin and ADHD related symptoms in childhood as reported on the WURS questionnaire. The absolute levels of HMW adiponectin were also significantly negatively correlated only with WURS questionnaire scores, and borderline significant negative correlations were also observed between HMW adiponectin levels and scores on the hyperactivity/impulsivity component of ASRS and MDQ scores. The levels of total adiponectin were not correlated with the measured symptoms. Thus, the fraction of HMW to total adiponectin showed the strongest correlations with ADHD symptomatology and also with symptoms of bipolar disorder. The finding in our study that adiponectin is related also to symptoms of mood and affective temperament, underlines the basic and cross-disorder nature of putative neurobiological risk factors for psychiatric disorders (Rivero et al., 2012; Smoller et al., 2013).

Many studies have identified associations between single nucleotide polymorphisms in the region of the CDH13 gene, which codes for the adiponectin receptor T-cadherin, and variations in the serum levels of adiponectin (Morisaki et al., 2012; Wu et al., 2010). Moreover, higher levels of serum adiponectin (3.5-fold) have been reported in *CDH13* knockout mice (Denzel et al., 2010). In the second part of this study we examined the effects of seven rare missense mutations in *CDH13* on the serum levels of adiponectin in a subgroup of ADHD patients carrying the wild type or any of the seven heterozygous mutations in *CDH13*. The *CDH13* mutations studied here were recently identified in adult ADHD patients by our group (Mavroconstanti et al., 2013). In the present study, a trend for higher total adiponectin levels was observed in patients carrying CDH13 mutations compared to patients carrying wild type CDH13 in Mann Whitney test. In a logistic regression model we did not observe statistically significant associations between adiponectin levels in carriers of *CDH13* mutations compared to carriers of wild type *CDH13.* Since the patients were either homozygous for the wild type or heterozygous for either of the missense mutations and the mutations are rare, our findings on the effects of CDH13 mutations on adiponectin levels in this relatively small sample are not conclusive.

A limitation of this study is the small sample size used to study the effects of CDH13 variants on adiponectin levels. However,

these variants are rare and our observations suggest that the effects of heterozygous missense mutations in CDH13 on adiponectin levels may be weak. This implies that larger sample sizes, which were unavailable in this study, would be required to identify associations of rare CDH13 variants with adiponectin levels. The overall sample size in our study, however, was comparable to that used in previous investigations of adiponectin levels in other psychiatric disorders (Narita et al., 2008; Unsal et al., 2012). An advantage of this study was the use of information about comorbid disorders and dimensional scores. However, since this information was based on self-reported symptoms and treatment history and not on psychiatric evaluation it may have been inaccurate in some cases, and not necessarily generalizable to clinically diagnosed comorbidity. Moreover, information about other possible confounding factors such as socioeconomic status, inflammatory and metabolic markers, was unavailable in this study.

The majority of patients reported use of medication. Although central stimulant use to our knowledge has not been previously associated with adiponectin levels, possible medication effects were also tested in a logistic regression model stratified for medication use in patients only. However, the subgroups of patients taking or not taking medication were 27 and 7, respectively, while 10 patients had not responded to this question. Although adiponectin levels were not associated with medication use in these subsamples, further studies on larger samples are necessary to determine whether central stimulants affect adiponectin levels.

In conclusion, our findings show that the levels of adiponectin, and in particular its HMW form, may be a sensitive, albeit nonspecific, marker for ADHD. Similar findings of abnormal adiponectin levels in other psychiatric disorders suggest that these may reflect common pathophysiological mechanisms underlying cognitive and neuropsychiatric dysfunctions. In a mouse model of depression, plasma levels of total, HMW and hexameric adiponectin were decreased in mice subjected to social defeat (Liu et al., 2012). Moreover, adiponectin haploinsufficient mice having significantly reduced adiponectin levels were more susceptible to anxiety and depression and exhibited dysregulation of the hypothalamic pituitary adrenal axis negative feedback loop. Administration of adiponectin improved the observed depression-like symptoms (Liu et al., 2012).The mechanisms underlying the association between adiponectin levels and psychiatric symptoms are largely unknown. However, the distinct expression patterns of adiponectin receptors in different brain areas (Thundyil et al., 2012) and the behavioral effects of adiponectin administration in animal models suggest that this may not only be a promising biomarker but also a potential target for intervention.

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