

## REVIEW

# Attention-deficit hyperactivity disorder in adults: A systematic review and meta-analysis of genetic, pharmacogenetic and biochemical studies

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The adult form of attention-deficit/hyperactivity disorder has a prevalence of up to 5% and is the most severe long-term outcome of this common disorder. Family studies in clinical samples as well as twin studies suggest a familial liability and consequently different genes were investigated in association studies. Pharmacotherapy with methylphenidate (MPH) seems to be the first-line treatment of choice in adults with attention-deficit hyperactive disorder (ADHD) and some studies were conducted on the genes influencing the response to this drug. Finally some peripheral biomarkers were identified in ADHD adult patients. We believe this work is the first systematic review and meta-analysis of candidate gene association studies, pharmacogenetic and biochemical (metabolomics) studies performed in adults with ADHD to identify potential genetic, predictive and peripheral markers linked specifically to ADHD in adults. After screening 5129 records, we selected 87 studies of which 61 were available for candidate gene association studies, 5 for pharmacogenetics and 21 for biochemical studies. Of these, 15 genetic, 2 pharmacogenetic and 6 biochemical studies were included in the meta-analyses. We obtained an association between adult ADHD and the gene *BAIAP2* (brain-specific angiogenesis inhibitor 1-associated protein 2), even after Bonferroni correction, with any heterogeneity in effect size and no publication bias. If we did not apply the Bonferroni correction, a trend was found for the carriers allele 9R of dopamine transporter *SLC6A3* 40 bp variable tandem repeat polymorphism (VNTR) and for 6/6 homozygotes of *SLC6A3* 30 bp VNTR. Negative results were obtained for the 9-6 haplotype, the dopamine receptor *DRD4* 48 bp VNTR, and the enzyme *COMT* SNP rs4680. Concerning pharmacogenetic studies, no association was found for the *SLC6A3* 40 bp and response to MPH with only two studies selected. For the metabolomics studies, no differences between ADHD adults and controls were found for salivary cortisol, whereas lower serum docosahexaenoic acid (DHA) levels were found in ADHD adults. This last association was significant even after Bonferroni correction and in absence of heterogeneity. Other polyunsaturated fatty acids (PUFAs) such as AA (arachidonic acid), EPA (eicosapentaenoic acid) and D<sub>5</sub>LA (dihomogammalinolenic acid) levels were not different between patients and controls. No publication biases were observed for these markers. Genes linked to dopaminergic, serotonergic and noradrenergic signaling, metabolism (*DBH*, *TPH1*, *TPH2*, *DDC*, *MAOA*, *MAOB*, *BCHE* and *TH*), neurodevelopment (*BDNF* and others), the SNARE system and other forty genes/proteins related to different pathways were not meta-analyzed due to insufficient data. In conclusion, we found that there were not enough genetic, pharmacogenetic and biochemical studies of ADHD in adults and that more investigations are needed. Moreover we confirmed a significant role of *BAIAP2* and DHA in the etiology of ADHD exclusively in adults. Future research should be focused on the replication of these findings and to assess their specificity for ADHD.

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## INTRODUCTION

Attention-deficit hyperactivity disorder (ADHD), which is commonly known to occur during childhood, is characterized by excessive inattention and/or hyperactivity and impulsivity as well as executive dysfunction, lack of emotional self-control and motivation. However a significant number of affected children (65%) continue manifesting symptoms into adulthood.<sup>1,2</sup>

The prevalence of ADHD was reported as 5.3% in childhood,<sup>3–5</sup> whereas it is estimated as 2.5–4.9% in adulthood.<sup>6,7</sup> Clinical research showed that the predominant features of ADHD in adults differ from ADHD in children, with adults showing less obvious symptoms of hyperactivity or impulsivity and more inattentive

symptoms.<sup>8</sup> A recent study reported follow-back analyses of ADHD cases diagnosed in adulthood, alongside follow-forward analyses of ADHD cases diagnosed in childhood in a representative birth cohort from Dunedin.<sup>9</sup> The findings suggested that adults with ADHD may not have a childhood-onset disorder. There was little overlap between participants who had been diagnosed with ADHD in childhood and those diagnosed in adulthood. This finding is intriguing but difficult to interpret because it is not consistent with a very large literature documenting the persistence of ADHD into adulthood. Pharmacological treatment is considered effective and safe both for children and adults, but there is considerable inter-individual variability among patients

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regarding response to medication, required doses, and adverse events. Pharmacotherapy with methylphenidate (MPH) seems to be the first-line treatment of choice both in children<sup>10,11</sup> and in adults<sup>12–15</sup> with ADHD.

ADHD is a complex and heterogeneous disorder and its etiology is not yet completely understood. Despite evidences that environmental factors have an important role in its etiology, classical genetics studies support a strong genetic contribution for ADHD with the heritability estimates averaging 75% in children.<sup>16</sup> Genetic liability comprises a polygenic liability with both common and rare variants involved. Individuals with large, rare copy-number variations (CNVs) require less loading of multiple common genetic risk variants for developing ADHD.<sup>17</sup>

In adults, initial heritability estimates of ADHD were substantially lower (~30–50%),<sup>18–20</sup> even though other evidence had suggested a stronger genetic component to the etiology of adult ADHD.<sup>21–24</sup> A more recent review suggests that the low heritability of ADHD in adults is unlikely to reflect a true developmental change. Instead, the drop in heritability is better explained by rater effects related to a switch from using one rater for both twins in a pair (parent/teacher) in childhood, to relying on self-ratings (where each twin rates themselves) of ADHD symptoms in adulthood. When rater effects are addressed using cross-informant approaches, the heritability of ADHD in adults appears to be comparable to the heritability of ADHD in childhood.<sup>25</sup> Many candidate gene association studies (<http://adhd.psych.ac.cn/index.do>), several meta-analyses including the most recent,<sup>26</sup> genome-wide association (single nucleotide polymorphism, SNP-GWA) and CNV studies, summarized in some recent reviews,<sup>27–29</sup> have been reported for children with ADHD. These studies have implicated dopaminergic, serotonergic and glutamatergic signaling along with synaptic vesicle, neurite outgrowth and cell adhesion pathways. A recent review of the literature on ADHD pharmacogenetics in childhood supported a significant effect of neurodevelopmental and noradrenergic systems in the MPH response, whereas no or contrasting results were obtained for dopaminergic and serotonergic signaling, synaptosomal-associated protein 25 (SNAP25), metabolic enzymes.<sup>30</sup> Finally, the results of a series of meta-analyses reviewed in Scassellati *et al.*<sup>31</sup> on biochemical studies performed in childhood, showed a significant association with peripheral biomarkers linked to monoaminergic pathways and to the hypothalamic–pituitary–adrenal (HPA) axis.

In contrast to a large genetics literature about childhood ADHD, fewer studies have addressed the adult form of the disorder. A summary of genetic studies of adult ADHD was reported in Franke *et al.*<sup>32</sup> in a comprehensive review. The literature about adult ADHD now comprises six meta-analyses of candidate genes in International multi-center persistent ADHD collaboration (IMPACT) samples,<sup>33–38</sup> two SNP-GWAS,<sup>39,40</sup> two CNV-GWAS<sup>41,42</sup> studies and three reviews of pharmacogenetics studies.<sup>30,43,44</sup> No meta-analyses of biochemical studies of adult ADHD have been reported.

This work has the aim to review candidate gene association studies, pharmacogenetic and biochemical (metabolomics) studies performed in adults with ADHD and to conduct meta-analyses where possible in order to identify potential genetic, predictive and peripheral markers linked specifically to ADHD in adults.

## MATERIALS AND METHODS

### Search strategy and selection

To identify eligible studies for the review and meta-analyses, we searched these electronic databases: PubMed, EMBASE (Ovid), PsycINFO (Ovid), Biosis (Web of Science) from inception 1971 until August 2015. We searched for all available original studies regarding candidate gene associations, pharmacogenetics and

biochemical markers in adults with ADHD. The search was limited to articles published in English (399 studies were reported in other languages, most in German). The following keywords were employed: adults, attention-deficit/hyperactivity disorder or ADHD combined with the following terms: gene\*, genetics, polymorphism, association, pharmacogen\*, response to medication, stimulant response, MPH, amphetamine, atomoxetine, peripheral levels, biomarkers, plasma, serum, saliva, urine, cerebrospinal fluid and red blood cells. The initial search produced 7746 on Pubmed, 4708 on EMBASE (Ovid), 3425 on PsycINFO (Ovid) and 9796 on Biosis (Web of Science).

We selected articles that met the following inclusion criteria: (1) ADHD diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders—version IV (DSM-IV) or the International Classification of Diseases—10th Revision (ICD-10); (2) having a case–control or family-based study design for candidate gene association studies; (3) having a drug-with/without placebo design for pharmacogenetic studies; (4) having a drug-free/naive case–control study design for biochemical studies. We excluded Dresler *et al.*<sup>45</sup> and Hirvikoski *et al.*<sup>46</sup> in the analyses of SLC6A3 40 bp variable tandem repeat polymorphism (VNTR) genotyping and salivary cortisol levels respectively, because they did not use a structured interview tool with high reliability and less reliable methods for the assessment of childhood ADHD were applied.

Supplementary Figure 1 presents a PRISMA flow diagram depicting our selection procedure for review and meta-analysis.

Meta-analyses were performed for all markers for which usable data were reported in at least three published studies.

### Data extraction for meta-analyses and statistical analyses

The literature search was performed by two individuals independently (CS and CB). When data were not available, authors were contacted. For candidate gene association studies, we extracted the following data from the original publications: biological systems, genes analyzed, location and polymorphisms, first author, populations studied, sample size, results and eligibility for meta-analysis (Table 1). For pharmacogenetic studies on MPH drug, we extracted: genes analyzed, location and polymorphisms, first author, populations, sample size, dosages, duration times, results and eligibility for meta-analysis (Table 2). For biochemical studies, we extracted: biological systems, biomarkers analyzed, biological fluids, first author, populations, sample size, results and eligibility for meta-analysis (Table 3). In Supplementary Tables 1, 2, 3, we showed the candidate gene association, pharmacogenetic and biochemical studies for which the meta-analyses were not possible to conduct due to insufficient data.

Review Manager was used to analyze the data (RevMan Version 5.1.6; Copenhagen, The Nordic Cochrane Centre, The Cochrane Collaboration, 2008). We used the fixed-effects model to generate a pooled effect size and 95% confidence interval (CI) from individual study effect sizes (the odd ratios for genetic/pharmacogenetic studies or the standardized mean difference for biochemical studies) using the Mantel–Haenszel and inverse variance methods, respectively. The significance of the pooled effect sizes was determined by the z-test. Between-study heterogeneity was assessed using a  $\chi^2$  test of goodness of fit test and the  $I^2$  statistic. We used a *P*-value of 0.05 to assert statistical significance. Where the results showed a significant effect in the presence of significant between-study heterogeneity, a random effects model was used, with effect sizes pooled using the DerSimonian and Laird method.

Publication bias was estimated by the method of Egger *et al.*<sup>47</sup> which uses a linear regression approach to measure funnel plot asymmetry on the natural logarithm scale of the effect size. The significance of the intercept (*a*) was determined by the *t*-test.<sup>47</sup> The rank correlation method and regression method



**Table 2.** Pharmacogenetic studies on MPH drug available for meta-analysis

Genes	Location	Polymorphisms	Authors	Populations	Sample size		Dosages	Duration times	Results	Eligibility	Reasons
					R	NR /PL					
SLC6A3	3'UTR	40 bp VNTR	Kooij <i>et al.</i> <sup>66</sup>	Netherlands	16	26	0.5 mg kg <sup>-1</sup> per day; 1 mg kg <sup>-1</sup> per day	3 Weeks	No	Included	
			Contini <i>et al.</i> <sup>67</sup>	Brazil	136	35	0.3 mg kg <sup>-1</sup> per day	4 Weeks	No	Included	
			Mick <i>et al.</i> <sup>68</sup>	Boston	66	40	0.5 mg kg <sup>-1</sup> per day; 1 mg kg <sup>-1</sup> per day	6 Weeks	No	Excluded	Placebo arm
	5'UTR	rs2652511	Contini <i>et al.</i> <sup>67</sup>	Brazil	136	35	0.3 mg kg <sup>-1</sup> per day	4 Weeks	No	Excluded	Another polymorphism
Intron 8	30 bp VNTR	Contini <i>et al.</i> <sup>67</sup>	Brazil	136	35	0.3 mg kg <sup>-1</sup> per day	4 Weeks	No	Excluded	No enough studies	

Abbreviations: NR, no responders; PL, placebo (Mick *et al.*<sup>68</sup>); R, responders; SLC6A3, dopamine transporter; UTR, untranslated region; VNTR, variable tandem repeat polymorphism. The results indicating no mean absence of association.

**Table 3.** Biochemical studies (metabolomics) available for meta-analysis

Systems	Biomarkers	Biological fluids	Authors	Populations	Sample size		Results	Eligibility	Reasons
					ADHD (N)	CTRL (N)			
Circadian rhythms	Cortisol	Saliva	Hirvikoski <i>et al.</i> <sup>46</sup>	Swedish	28	28	No	Excluded	No diagnosis available
			Lackschewitz <i>et al.</i> <sup>59</sup>	German	18	18	No	Included	
			Baird <i>et al.</i> <sup>70</sup>	UK	13	19	Alterations	Included	
			Raz <i>et al.</i> <sup>71</sup>	Israel	24	25	No	Included	
PUFAs	AA	RBC Serum	Young <i>et al.</i> <sup>72</sup>	Canada	36	35	No	Excluded	No enough studies
			Young <i>et al.</i> <sup>72</sup>	Canada	36	35	No	Included	
			Laasonen <i>et al.</i> <sup>73</sup>	Finland	26	36	No	Included	
			Irmish <i>et al.</i> <sup>74</sup>	Germany	15	15	Alterations	Included	
	DHA	RBC Serum	Young <i>et al.</i> <sup>72</sup>	Canada	36	35	Alterations	Excluded	No enough studies
			Young <i>et al.</i> <sup>72</sup>	Canada	36	35	Alterations	Included	
			Laasonen <i>et al.</i> <sup>73</sup>	Finland	26	36	No	Included	
			Irmish <i>et al.</i> <sup>74</sup>	Germany	15	15	Alterations	Included	
	EPA	RBC Serum	Young <i>et al.</i> <sup>72</sup>	Canada	36	35	No	Excluded	No enough studies
			Young <i>et al.</i> <sup>72</sup>	Canada	36	35	No	Included	
			Laasonen <i>et al.</i> <sup>73</sup>	Finland	26	36	No	Included	
			Irmish <i>et al.</i> <sup>74</sup>	Germany	15	15	Alterations	Included	
DyLA	RBC Serum	Young <i>et al.</i> <sup>72</sup>	Canada	36	35	No	Excluded	No enough studies	
		Young <i>et al.</i> <sup>72</sup>	Canada	36	35	No	Included		
		Laasonen <i>et al.</i> <sup>73</sup>	Finland	26	36	No	Included		
		Irmish <i>et al.</i> <sup>74</sup>	Germany	15	15	Alterations	Included		

Abbreviations: AA, arachidonic acid; ADHD, attention-deficit hyperactivity disorder; DHA, docosahexaenoic acid; DyLA, dihomogammalinolenic acid; EPA, eicosapentaenoic acid; N, sample size; PUFAs, polyunsaturated fatty acids; RBC, red blood cells. No indicates absence of alterations on levels of a biomarker.

tests were conducted by MIX version 1.7. (<http://www.mix-for-meta-analysis.info>).

Because we conducted 6, 1 and 2 meta-analyses to assess the significance of genetic, pharmacogenetic and biochemical markers, respectively, our Bonferroni corrected significance levels were 0.008, 0.05 and 0.025, respectively. This provides a stringent approach for preventing false-positive findings, with the cost of reducing statistical power. In contrast, for our analyses of publication biases and heterogeneity, we use an uncorrected alpha level to ensure that any of these potential problems with the findings could be detected.

## RESULTS

During the screening of 5129 records, we selected 87 studies meeting our eligibility criteria: 61 were available for candidate gene association studies, 5 for pharmacogenetics and 21 for

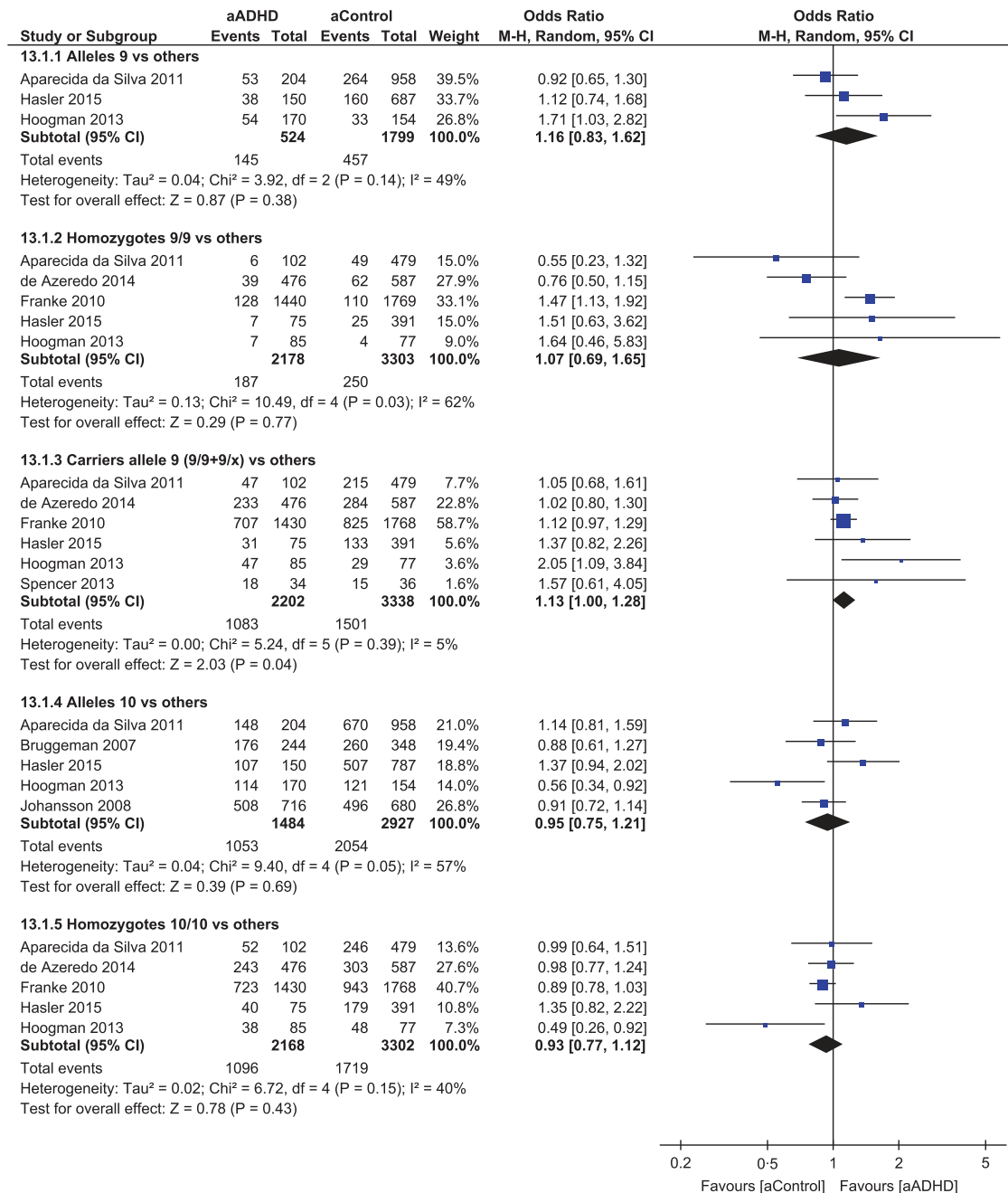
biochemical studies (Supplementary Figure 1). Of these, 15 candidate gene association, 2 pharmacogenetic and 6 biochemical studies were included in the meta-analyses.

Because most of the meta-analyses did not show significant heterogeneity in effect size across studies, meta-regressions were not run.

Here below we described candidate gene association studies (Table 1),<sup>33,34,45,48–65</sup> pharmacogenetic (Table 2)<sup>66–68</sup> and biochemical (metabolomic) (Table 3)<sup>46,69–74</sup> studies for which it was possible to conduct meta-analysis. Moreover we described the studies for which the meta-analyses were not possible.

Candidate gene association studies available for meta-analysis

From the selection of 61 studies, 15 association studies were included in the meta-analyses (Table 1). Ten studies were excluded in which no enough data were reported on a



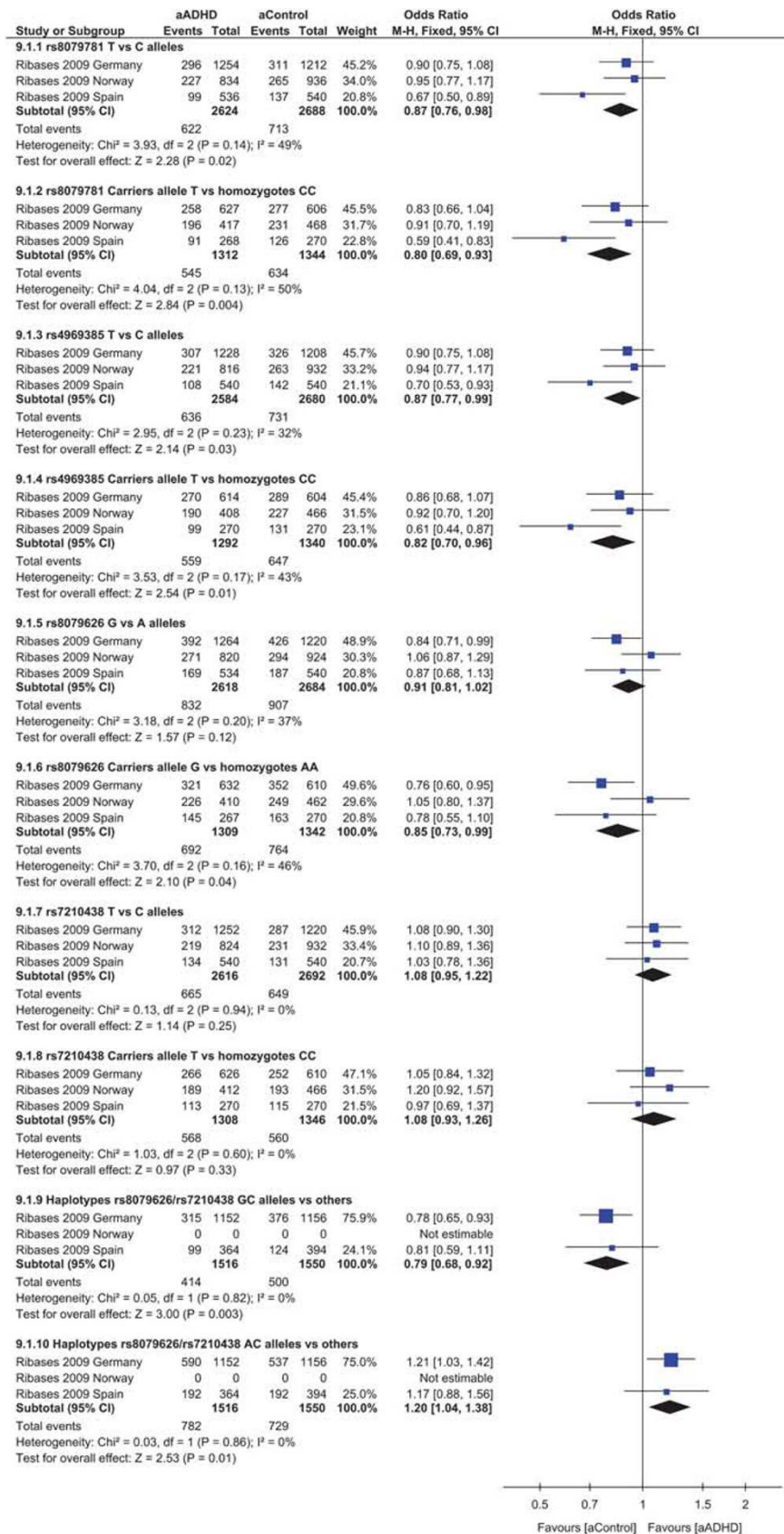
**Figure 1.** Forest plot for odds ratio from meta-analysis of the 40 bp variable tandem repeat polymorphism (VNTR) in the dopamine transporter *SLC6A3* gene. ADHD, attention-deficit hyperactive disorder; CI, confidence interval; Chi<sup>2</sup>,  $\chi^2$  test of goodness of fit; Tau<sup>2</sup>, estimate of the between-study variance in a random-effects meta-analysis.

polymorphism; 43 on a gene; and 5 lacking statistical data for patients and controls (Supplementary Table 1).

#### Neurotransmitter systems

**Dopamine transporter gene (*SLC6A3*).** The main function had by the dopamine transporter (DAT1) is to regulate dopamine (DA) availability in the synapse. It removes DA from the synaptic cleft into the pre-synaptic neuron or releases DA into the extracellular space. Its involvement in the etiology of ADHD is supported by the fact that DAT1 is the main target for the stimulant drugs that treat ADHD.

The most studied *SLC6A3* variant is a VNTR of 40 base pairs located at the 3'-untranslated region (3'-UTR) of the gene. The ten repeat (10R) and nine repeat (9R) alleles are the most common. A recent meta-analysis,<sup>75</sup> assessing the association of this variant with DAT1 activity, showed that the 9R allele regulates dopamine activity in the striatal brain regions independent of the presence of neuropsychiatric illness. In childhood, the 10R allele has been associated to ADHD susceptibility.<sup>26</sup> In adults, nine studies<sup>34,49,50,52-55,57</sup> were available for this polymorphism. Brown *et al.*<sup>56</sup> was excluded because they performed the analyses in a selected sample of patients and controls carrying only 9/9, 9/10 and 10/10 genotype. Because the authors showed different calculations for this VNTR, we reported the results according to:



**Figure 2.** Forest plot for odds ratio from meta-analysis of the polymorphisms rs8079781, rs4969385, rs8079626 and 7210438 in the BAI1-associated protein 2 (*BAIAP2*) gene. ADHD, attention-deficit hyperactive disorder; Chi<sup>2</sup>,  $\chi^2$  test of goodness of fit. CI, confidence interval.

(a) allele 9 versus the others<sup>52,55,57</sup> (Figures 1,  $Z=0.87$ ,  $P=0.38$ , absence of heterogeneity in effect size across studies  $P=0.14$ ,  $I^2=49\%$ ); (b) 9/9 homozygotes versus the other genotypes<sup>34,49,52,55,57</sup> (Figure 1,  $Z=0.29$ ,  $P=0.77$ , slight heterogeneity in effect size across studies  $P=0.03$ ,  $I^2=62\%$ ); (c) carriers allele 9 (9/9+9/x) versus others<sup>34,49,52,53,55,57</sup> (Figure 1,  $Z=2.03$ ,  $P=0.04$ , no heterogeneity in effect size  $P=0.39$ ,  $I^2=5\%$ ). This trend of association was lost after Bonferroni correction; (d) allele 10 versus others<sup>50,52,54,55,57</sup> (Figure 1,  $Z=0.39$ ,  $P=0.69$ , slight heterogeneity in effect size  $P=0.05$ ,  $I^2=57\%$ ); (e) 10/10 homozygotes versus other genotypes<sup>34,49,52,55,57</sup> (Figure 1  $Z=0.78$ ,  $P=0.43$ , no heterogeneity in effect size  $P=0.15$ ,  $I^2=40\%$ ).

Another VNTR in intron 8 of the DAT gene was investigated by several studies. This VNTR is a 30-bp repeat sequence with two common alleles of five (5R) and six (6R) repeats. The 6R allele has been associated with ADHD susceptibility in childhood.<sup>26</sup> In adults, six studies<sup>34,49–53</sup> were available for this polymorphism. As above, the authors reported different calculations, therefore we showed the results according to: (a) allele 5 versus others<sup>34,51,52</sup> (Supplementary Figure 2,  $Z=1.72$ ,  $P=0.09$ , no heterogeneity in effect size  $P=0.06$ ,  $I^2=64\%$ ); (b) 5/5 homozygotes versus others<sup>34,49,51,52</sup> (Supplementary Figure 2,  $Z=0.48$ ,  $P=0.63$ , no heterogeneity in effect size  $P=0.63$ ,  $I^2=0\%$ ); (c) allele 6 versus others<sup>51,52</sup> (Supplementary Figure 2,  $Z=2.46$ ,  $P=0.01$ , no heterogeneity in effect size  $P=0.64$ ,  $I^2=0\%$ ). This trend of association is due to only two studies; (d) 6/6 homozygotes versus others<sup>34,49,51,52</sup> (Supplementary Figure 2,  $Z=2.28$ ,  $P=0.02$ , no heterogeneity in effect size  $P=0.13$ ,  $I^2=47\%$ ). This association was lost after Bonferroni correction; (e) carriers allele 6 versus others<sup>34,49,51–53</sup> (Supplementary Figure 2,  $Z=0.58$ ,  $P=0.56$ , no heterogeneity in effect size  $P=0.92$ ,  $I^2=0\%$ ).

Concerning the haplotype formed by the two polymorphisms, the results indicated no association between carriers of 9–6 haplotype and ADHD susceptibility<sup>34,49,52</sup> (Supplementary Figure 3,  $d=1.45$ , 95% CI: 0.90–2.34,  $Z=1.55$ ,  $P=0.12$ ) with significant heterogeneity in effect size among the studies ( $P=0.002$ ,  $I^2=84\%$ ).

Finally according to Egger's test, the results indicated for the all meta-analyses related to the two polymorphisms 30 and 40 bp, no publication bias (see Supplementary Table 4 for all allele/genotype/haplotype combinations).

Further studies investigated other polymorphisms in this gene (Table 1), however no meta-analyses were possible due to the small number of studies.

**Dopamine D4 receptor gene.** The dopamine D4 receptor (DRD4) is a G-protein-coupled receptor belonging to the DA D2-like receptor family. It has been considered a candidate for the etiology of ADHD because of its high expression in brain regions implicated in attention and inhibition such as anterior cingulate cortex. Moreover, DRD4 was first associated with a personality trait common in ADHD (novelty seeking).

A highly polymorphic functional VNTR in the third exon of DRD4 has been frequently studied in association studies. It comprises 11 copies of a 48-bp repeat sequence, where the 4, 7 and 2 repeat alleles are the most prevalent. The 7R allele has been associated with ADHD in many studies of youth.<sup>26,28,29,76,77</sup> The current meta-analysis included six studies.<sup>33,53,54,57,58,60</sup> Tovo-rodrigues et al.<sup>59</sup> was excluded because insufficient data were reported. Also for this polymorphism different calculations were performed. Thus we represented the results according to: (a) allele 7 versus others<sup>33,54,57,58</sup> (Supplementary Figure 4,  $Z=0.79$ ,  $P=0.43$ , in absence of heterogeneity in effect size across the studies  $P=0.06$ ,  $I^2=60\%$ ); (b) 7/7 homozygotes versus others<sup>33,57</sup> (Supplementary Figure 4,  $Z=1.24$ ,  $P=0.21$ , in presence of heterogeneity in effect size across the studies  $P=0.006$ ,  $I^2=87\%$ ). These results considered only two studies; (c) carriers allele 7 versus others<sup>33,53,57,60</sup> (Supplementary Figure 4,  $Z=0.76$ ,  $P=0.44$ , no heterogeneity in effect size  $P=0.57$ ,  $I^2=0\%$ ). No publication bias

was observed (see Supplementary Table 4 for all allele/genotype combinations).

Concerning the rs4646984 polymorphism (120-bp tandem insertion/deletion up stream of exon 1), not enough studies were available for meta-analysis (Table 1).

#### Metabolic enzymes

**Catechol-O-methyltransferase.** Catechol-O-methyltransferase (COMT) is an enzyme responsible for the degradation of DA and NE. It is highly expressed in frontal lobe where it regulates synaptic DA levels. Most of the association studies between COMT and ADHD susceptibility examined a well-known Val158Met functional polymorphism in exon 4. Homozygotes for the valine allele show greater COMT activity than homozygotes for the methionine allele. Several meta-analyses<sup>26,78,79</sup> indicated no association between ADHD and the Val158Met in childhood. For the current meta-analysis in adults, three studies were available for COMT.<sup>60,62,63</sup> Here we showed the results in relation to: (a) allele Val versus Met (Supplementary Figure 5,  $Z=1.16$ ,  $P=0.25$ , no heterogeneity in effect sizes across the studies was found  $P=0.31$ ,  $I^2=15\%$ ); (b) homozygotes Val/Val versus carriers allele Met (Supplementary Figure 5,  $Z=0.22$ ,  $P=0.82$ , no heterogeneity in effect sizes across the studies was found  $P=0.66$ ,  $I^2=0\%$ ); (c) carriers allele Val versus homozygotes Met/Met (Supplementary Figure 5,  $Z=0.37$ ,  $P=0.71$ , no heterogeneity in effect sizes across the studies was found  $P=0.80$ ,  $I^2=0\%$ ). No publication bias was observed (see Supplementary Table 4 for all allele/genotype combinations). Further studies investigated other polymorphisms (Table 1).

#### Neurodevelopmental network

**BAI1-associated protein 2.** There is evidence suggesting that abnormal left-right brain asymmetries in ADHD patients are involved in a variety of ADHD-related cognitive processes, including sustained attention, working memory, response inhibition and planning. Although mechanisms underlying cerebral lateralization are unknown, left-right cortical asymmetry has been associated with transcriptional asymmetry at embryonic stages and several genes differentially expressed between hemispheres have been identified. One of these is brain-specific angiogenesis inhibitor 1-associated protein 2 (BAIAP2). rs8079781, rs4969385, rs8079626 and 7210438 were genotyped in samples from Spain, German and Norway.<sup>65</sup> The results of our meta-analyses indicated significant differences for rs8079781 (Figure 2 allele T versus C,  $Z=2.28$ ,  $P=0.02$ ; carriers allele T versus homozygotes CC  $Z=2.84$ ,  $P=0.004$ ) with no significant heterogeneity in effect sizes across studies ( $P=0.14$ ,  $I^2=49\%$ ;  $P=0.13$ ,  $I^2=50\%$ , respectively). This last difference survived to Bonferroni correction. Similarly a significant association was observed for rs4969385 with allele T versus C ( $Z=2.14$ ,  $P=0.03$ ) and carriers of allele T versus homozygotes CC ( $Z=2.54$ ,  $P=0.01$ ), with no significant heterogeneity in effect size across the studies ( $P=0.23$ ,  $I^2=32\%$ ;  $P=0.17$ ,  $I^2=43\%$ , respectively; Figure 2). After applying the Bonferroni correction, this difference was lost. For the other two polymorphisms no associations were observed, except for a slight trend for the rs8079626 carriers allele G versus homozygotes AA ( $Z=2.10$ ,  $P=0.04$ ). Interesting results came from the meta-analysis of rs8079626-rs7210438 haplotypes. The GC haplotype versus others showed a protective effect ( $d=0.79$ , 95% CI: 0.68–0.92,  $Z=3.00$ ,  $P=0.003$ ), which remained significant after Bonferroni correction. The AC haplotype was the risk haplotype ( $d=1.20$ , 95% CI: 1.04–1.38,  $Z=2.53$ ,  $P=0.01$ ). In all cases, there was no heterogeneity in effect sizes across studies ( $P=0.82$ ,  $I^2=0\%$ ;  $P=0.86$ ,  $I^2=0\%$ , respectively). No publication bias were observed (see Supplementary Table 4 for all allele/genotype combinations).

Candidate gene association studies not available for meta-analysis  
There are several genes for which there are not enough studies to perform meta-analysis. These are shown in Supplementary Table 1.<sup>35–38,48,53,54,57,60,64,80–113</sup> In particular, among the most known, *DRD5*, whose highly polymorphic dinucleotide repeat (CA)<sub>n</sub> has been the most studied in adults, three studies<sup>54,60,80</sup> were available, but Squassina *et al.*<sup>80</sup> was excluded because no frequencies were reported. Ribases *et al.*<sup>48</sup> investigated other polymorphisms. Similar conclusions are reached for other dopamine receptor genes (*DRD3*, *DRD2* and *DRD1*).

Serotonin transporter gene (*SLC6A4*, *5-HTT*) is a further well-known gene. The 5HTTLPR, a 44-bp insertion/deletion yielding long and short alleles, was investigated in adults by two studies,<sup>35,53</sup> whereas Ribases *et al.*<sup>83</sup> studied other polymorphisms. Similar conclusions were reported for other serotonin receptor genes among which serotonin 1B receptor gene (*HTR1B*) whose G861C polymorphism, rs6296, was investigated by only two studies,<sup>60,83</sup> and serotonin 2A receptor gene (*HTR2A*; *5HT2A*).

Studies on norepinephrine transporter gene (*NET1*, *SLC6A2*) along with alpha-2A-adrenergic receptor gene (*ADRA2A*), were not enough to conduct meta-analyses in adults.

Among the metabolic enzymes, there are dopamine beta hydroxylase (*DBH*), tryptophan hydroxylases (*TPH1*, *TPH2*), of which a meta-analysis on IMPACT samples was available for both genes,<sup>36</sup> Dopamine decarboxylase (*DDC*), Monoamine oxidases *MAOA* and *MAOB*, acetylcholine metabolizing butyrylcholinesterase (*BCHE*) and tyrosine hydroxylase (*TH*).

Concerning the neurodevelopmental network, brain-derived neurotrophic factor (*BDNF*), ciliary neurotrophic factor receptor (*CNTFR*), neurotrophin *NTF3*, nerve growth factor (*NGF*) were too infrequent to perform meta-analyses. Similarly also for *LPHN3*, *CDH13*, GTP-binding RAS-like 2 (*DIRAS2*) genes no enough studies were available.

As regard the genes for synaptic vesicle proteins, *SNAP25*, showed in adults, a significant association of the Mnl polymorphism with ADHD susceptibility,<sup>97</sup> even though this result was not confirmed by Olgiati *et al.*<sup>98</sup> Other SNARE genes such as for instance Synaptobrevin-2 (*VAMP-2*), Syntaxin 1A (*STX1A*), Synapsin III (*SYNIII*) were investigated in some studies,<sup>98–101</sup> however, because different polymorphisms were genotyped, no meta-analyses can be performed.

Finally the neuronal isoform (NOS-I, encoded by *NOS1*), the main source of nitric oxide in the central nervous system, was investigated by two studies that reported an association with *NOS1* gene.<sup>102,103</sup>

Other genes were studied in single studies: for instance circadian locomotor output cycles kaput (*CLOCK*),<sup>105</sup> protein kinase G (*PRKG1*),<sup>106</sup> mineralocorticoid receptor (*NR3C2*),<sup>107</sup> CKLF-like MARVEL transmembrane domain containing 8 (*CMTM8*)/diacylglycerol kinase eta (*DGKH*)/neuronal PAS domain protein 3 (*NPAS3*)/solute carrier family 39 (zinc transporter), member 3 (*SLC39A3*)/deafness, autosomal recessive 31 (*DFNB31*)/epidermal growth factor receptor (*EGFR*),<sup>108</sup> neural cell adhesion molecule 1 (*NCAM1*)/tetratricopeptide repeat domain 12 (*TTC12*)/ankyrin repeat and kinase domain containing 1 (*ANKK1*),<sup>82</sup> Ca(2+)-binding extracellular heparan/chondroitin sulfate proteoglycan (*SPOCK3*),<sup>109</sup> disrupted in schizophrenia 1 (*DISC1*),<sup>110</sup> Kv channel-interacting protein 4 (*KCNIP4*),<sup>111</sup> phosphatase 2, regulatory subunit B, gamma (*PPP2R2C*),<sup>112</sup> forkhead box P2 (*FOXP2*),<sup>113</sup> αN-catenin protein (*CTNNA2*),<sup>96</sup> u-opioid receptor (*OPRM1*), and others.<sup>60</sup> Thus we did not perform meta-analyses.

#### Pharmacogenetic studies available for meta-analysis

Five studies were conducted on the pharmacogenetics of MPH in adults, of these only two studies were available to perform meta-analysis (Supplementary Figure 1). The gene implicated is *SLC6A3* and its 40 bp VNTR and was investigated with MPH response in three studies<sup>66–68</sup> (Table 2). However Mick *et al.*<sup>68</sup> was not

estimable due to a placebo study design, whereas the other studies<sup>66,67</sup> showed the results in relation to responders versus non responders. Notwithstanding we performed the meta-analysis. We report different combinations as showed by the authors: (a) allele 10 versus the others (Supplementary Figure 6,  $Z=1.20$ ,  $P=0.23$ ); (b) homozygotes 10/10 versus others (Supplementary Figure 6,  $Z=1.59$ ,  $P=0.11$ ), in absence of heterogeneity in effect sizes across the studies (Supplementary Figure 6,  $Z=0.53$ ,  $I^2=0\%$ ;  $Z=0.23$ ,  $I^2=30\%$ , respectively). The Egger test was not applied due to the presence of only two studies.

#### Pharmacogenetic studies not available for meta-analysis

The studies are reported in Supplementary Table 2.<sup>66,114,115</sup> Kooij *et al.*<sup>66</sup> investigated polymorphisms in *DRD4* (120-bp insertion/deletion, 48-bp VNTR) and *SLC6A2* (4-bp insertion/deletion in the promoter region) in 42 adults treated with IR-MPH. The primary study outcome was clinical response, defined *a priori* as a decrease of at least two points on the Investigator-based Clinical Global Impression-Severity scale for ADHD (CGI-S), as well as a 30% or greater symptom reduction as measured with the self-reported DSM-IV ADHD-rating scale (ADHD-RS). The two secondary measures of response were the same scales, taken separately. No associations were found with outcomes of treatment response.

Negative associations were also found for *ADRA2A* (rs1800544, rs1800545 and rs553668)<sup>115</sup> and other 11 polymorphisms in 7 genes (*HTR1B*, *SLC6A4*, *TPH2*, *DBH*, *DRD4*, *COMT* and *SNAP25*).<sup>114</sup> These studies were naturalistic and investigated almost 200 patients, treated with IR-MPH. The outcome measures of MPH response were the Swanson, Nolan and Pelham Rating Scale version IV (SNAP-IV) and the CGI-S scale. The final measurements were taken after the 30th day of treatment and the *a priori* definition of clinical response was a 30% or greater symptom reduction in SNAP-IV and a CGI-S score of two points or less.

#### Biochemical studies (metabolomics) available for meta-analysis

Twenty-one studies were identified for peripheral biochemical/metabolomic measures. Of these, 6 studies provided data for meta-analyses (Supplementary Figure 1) and were reported in Table 3.<sup>46,69–74</sup>

#### HPA axis (salivary cortisol)

Individuals with ADHD suffer from increased vulnerability to environmental and mental stressors and may be at increased risk for chronic stress. The HPA axis is a critical physiological system that mediates responses to stress. In the face of environmental stressors, the HPA axis is activated, resulting in the secretion of cortisol from the adrenal cortex to the blood stream. The secretion of cortisol, which represents a biological indicator of arousal, is an adaptive response that alerts the individual to environmental changes and promotes the recovery of homeostasis. Studies have found the measurement of cortisol as an indicator of adrenocortical activity to be of high predictive value for psychological stress.

Some studies were conducted on adults with ADHD measuring salivary cortisol at baseline as compared with control subjects.<sup>69–71</sup> Corominas *et al.*<sup>116</sup> was excluded because it did not include a comparison group of healthy individuals. Also Hirvikoski *et al.*<sup>46</sup> was excluded. The results of our meta-analysis indicated no significant differences between patients and controls (Supplementary Figure 7,  $Z=1.52$ ,  $P=0.13$ ). Significant heterogeneity in effect sizes across studies was found ( $P<0.0003$ ,  $I^2=88\%$ ). No publication bias was observed ( $P=0.09$ ; Supplementary Table 5).

#### Mono- and polyunsaturated fatty acid

The connection between ADHD and lipids has not been sufficiently investigated so far in adults. It has been hypothesized that ADHD symptomatology in adults could be associated with a



deficiency or imbalance of polyunsaturated fatty acids (PUFAs), due to insufficient dietary intake of essential FAs, and/or impaired absorption of FAs, and/or an increased metabolism of FAs.<sup>74</sup>

Three studies investigated PUFA levels in adults with ADHD.<sup>72–74</sup> Young *et al.*<sup>117</sup> was excluded because it reported the effect of the FA treatment on the biochemical assays of the biomarker (Supplementary Table 3). The results of our meta-analyses indicated no significant differences between patients and controls for: serum arachidonic acid (AA) concentrations (Supplementary Figure 8,  $Z=0.99$ ,  $P=0.32$  with heterogeneity in effect size across the studies  $P=0.03$ ,  $I^2=72\%$ ), serum eicosapentaenoic acid (Supplementary Figure 8,  $Z=0.83$ ,  $P=0.41$ ; no heterogeneity in effect size across the studies  $P=0.11$ ,  $I^2=54\%$ ) and serum dihomo-gammalinolenic acid (Supplementary Figure 8,  $Z=0.70$ ,  $P=0.49$ ; heterogeneity in effect size across the studies  $P=0.005$ ,  $I^2=81\%$ ). A significant difference between patients and controls was observed for serum docosahexaenoic acid (DHA; Supplementary Figure 8,  $Z=4.14$ ,  $P<0.0001$ ), significant after Bonferroni correction. For DHA, no heterogeneity in effect size across the studies was observed ( $P=0.54$ ,  $I^2=0\%$ ) as well as no publication bias ( $P=0.19$ , Supplementary Table 5).

#### Biochemical studies (metabolomics) not available for meta-analysis

There are studies on biochemical levels of some proteins that are not enough to conduct meta-analysis (Supplementary Table 3).<sup>70,73,74,104,117–129</sup> Some studies regarded the circadian rhythms analyzing the melatonin levels,<sup>70,118</sup> others the oxidative stress pathway. In particular in a pioneering study,<sup>120</sup> plasma homocysteine levels were lower and serum folic acid levels higher in adult ADHD patients when compared with controls, whereas no difference was found in serum vitamin B12, total antioxidant status, total oxidant status and the oxidative stress index. Contrarily another study reported that patients' total antioxidant status, total oxidant status and oxidative stress index were significantly higher than controls.<sup>123</sup> Bulut *et al.*<sup>121</sup> demonstrated alterations in malondialdehyde level in patients as compared with controls. In a successive study the same authors reported higher malondialdehyde and lower paraoxonase and arylesterase levels in ADHD adult patients when compared with healthy subjects.<sup>119</sup> Finally a study demonstrated that the mean nitric oxide metabolite levels in patients were significantly higher than those of controls and superoxide dismutase activity of patients was significantly lower.<sup>122</sup> In contrast, in another study the ADHD adult group did not show significant differences regarding NOx—levels compared with controls.<sup>104</sup>

Other relevant peripheral biomarkers are represented by the serum BDNF,<sup>126</sup> adiponectin,<sup>124</sup> albumin<sup>125</sup> as well as the cerebrospinal fluid metabolites homovanillic acid and 5-hydroxy-indoleacetic acid.<sup>128</sup>

## DISCUSSION

This work meta-analyzed available candidate gene association, pharmacogenetic and biochemical (metabolomics) studies of ADHD in adults. The main result obtained from the systematic review is that there are not enough studies to perform meta-analyses. Indeed among a total of 87 studies, 23 were effectively suitable for meta-analyses. The genes and biochemical measures showed by the remaining were too infrequently reported for meta-analysis. We obtained a positive association between adult ADHD and rs8079781 in *BAIAP2* and with the rs8079626-rs7210438 GC haplotype, even after Bonferroni correction. A trend towards association was observed for rs4969385 in this gene. We found no heterogeneity in effect size and no publication bias for the *BAIAP2* analyses. If we did not apply the Bonferroni correction, a trend was found for the carriers allele 9R of *SLC6A3* 40 bp VNTR and for 6/6

homozygotes of *SLC6A3* 30 bp, whereas negative results were obtained for the 9-6 haplotype, the *DRD4* 48 bp VNTR, and the *COMT* SNP, rs4680. Concerning pharmacogenetic studies, a negative association was found for the *SLC6A3* 40 bp VNTR for response to MPH, with only two studies available. For the metabolomics studies, no differences between ADHD adults and controls were found for salivary cortisol, whereas lower serum DHA levels were observed in ADHD adults. This latter association was significant even after Bonferroni correction and heterogeneity was not significant. Other PUFAs such as AA, eicosapentaenoic acid and dihomo-gammalinolenic acid serum levels were not different between patients and controls. No publication biases were observed for these markers. Genes linked to dopaminergic, serotonergic and noradrenergic signaling, metabolism (*DBH*, *TPH1*, *TPH2*, *DDC*, *MAOA*, *MAOB*, *BCHE* and *TH*), neurodevelopment (*BDNF* and others), the SNARE system and other 40 genes/proteins related to different pathways were not meta-analyzed due to insufficient data.

*SLC6A3* is a well-known gene having an important role in the pathophysiology of different psychiatric illnesses including ADHD. Dopamine is an important neuromodulator that is released prominently in frontal and striatal areas known to have an important role in cognitive function. Moreover the DAT has a key role in regulating striatal dopamine levels and the amount of DAT expression in striatum has in previous meta-analyses been shown to be associated with the 40 bp VNTR polymorphism in the *SLC6A3* gene.<sup>75</sup> Finally, the DAT is a key pharmacological target of two ADHD medications, amphetamine and MPH.<sup>130</sup> Despite this robust rationale for being involved in ADHD, the meta-analyses on ADHD susceptibility as well as on MPH response showed no significant associations and lacking of consistent conclusions. If we do not apply the Bonferroni correction, the carriers of 9R allele seems to be associated to ADHD in adults, as well as the 6/6 homozygotes of 30 bp VNTR. Further studies are thus mandatory for confirming the hypothesized differential effect of the allele 9R associated to adults and of the allele 10R to children<sup>32,34,131</sup> as well as the susceptibility of allele 6R observed both in adults (present data) and in children.<sup>26</sup>

Negative results were obtained also for one of the most studied potential susceptibility genes for the disorder, *DRD4* and its well-known 48 bp VNTR, a potential functional polymorphism located in the third exon encoding the putative third cytoplasmic loop of the receptor that modulates the receptor's signal transduction properties by altering intracellular cyclic AMP levels.

Even the results for the *COMT* Val66Met variant showed no association to ADHD in adults, as has been observed for ADHD in children.<sup>78,79</sup> *COMT* is the major catecholamine-degrading enzyme involved in the degradation of catecholamines in synapses in the cerebral cortex, preferentially affecting prefrontal cortical dopamine metabolism. The Val66Met variant affects *COMT* enzyme activity, leading to significant alterations in dopamine levels in the post-synaptic neuron.

Thus all together these results suggest that it is needed to conduct further studies on *SLC6A3*, *DRD4* and *COMT* genes given their relevant importance in ADHD. For instance it could be needed to consider other polymorphisms and/or haplotypes inside of these gene and a deep sequencing of implicated genomic regions may allow identification of the functional variants directly involved in the genetic background of ADHD. In that regard it is interesting to note that an increased burden of rare variants has been observed in the 7R allele of *DRD4* in children with ADHD<sup>132</sup> and in adults.<sup>59</sup>

Interesting data were obtained for *BAIAP2*. There are consistent data that support the existence of functional asymmetry in the brain.<sup>133,134</sup> In addition to environmental effects, growing evidence supports that genes have an essential role in the development of the human brain.<sup>135,136</sup> Although little is known about genetic factors underlying brain lateralization, several genes

are differentially expressed in the two hemispheres, some of which could be involved in the development of right-left asymmetries. A relationship between genes differentially expressed in brain hemispheres and the vulnerability to ADHD was suggested, because patients with ADHD show deviations from the typical pattern of cerebral asymmetry that may account for a large number of ADHD-related symptoms.<sup>136,137</sup> Our meta-analyses conducted on three different population samples confirmed the role of *BAIAP2* in the ADHD susceptibility in adults. *BAIAP2* is expressed at higher levels in the left human cerebral cortex and participates in neuronal proliferation, survival and maturation. It encodes the insulin receptor tyrosine kinase substrate protein of 53 kDa (IRSp53), a member of a group of downstream signaling molecules that participate in the signal transduction pathways of insulin and insulin-like growth factor 1. Moreover *BAIAP2* expression in rat cerebral cortices is enhanced by treatment with MPH. As demonstrated by Ribases *et al.*<sup>65</sup> this association was found for ADHD in adults but not in children, suggesting a distinct genetic load between persistent and remitting ADHD<sup>22,24,83</sup> and a potential genetic marker for persistent ADHD.

With regards to the biochemical studies (metabolomics), our meta-analysis on basal salivary cortisol levels showed no difference between patients and controls. The presence of heterogeneity due to the paper from Baird *et al.*<sup>70</sup> suggests the need to replicate this finding. Contrarily our meta-analysis on PUFAs supported a significant role of DHA in adult ADHD. Irmisch *et al.*<sup>74</sup> showed that the DHA was associated with hyperactivity in adults with ADHD, and it seems to be essential for pre- and postnatal brain development.<sup>138</sup> The role of *n*-3PUFAs had in ADHD may be explained by their impact on the immune system through the formation of immunosuppressive prostaglandins, a system involved in ADHD.<sup>139</sup> Another hypothesis<sup>140</sup> is based on the evidence that PUFA deficiency in rodents results in behavioral changes such as increased motor activity and decreased learning abilities on the grounds of dysregulated monoamine neurotransmission. A differential impact of cortisol and DHA on ADHD in childhood and in adulthood can be suggested. In fact a recent meta-analysis<sup>31</sup> on peripheral biomarkers in ADHD childhood showed a significant role of salivary cortisol but not of serum DHA. Here in adults we demonstrated the opposite effect, supporting the idea that the concentrations of cortisol and FAs can vary in relation to age. However the course of salivary cortisol and serum FA composition during the lifespan needs to be further investigated.

It is intriguing that we found much more heterogeneity of results for the child studies<sup>26</sup> compared with the adult studies. This may be due to the fact that child samples comprise those who will persist with ADHD in adulthood and those who will not. Also, because biological and psychological development change markedly in childhood, differences in developmental stage could account for the greater heterogeneity in childhood. Another possibility is that there is greater phenotypic heterogeneity in the child samples. We could not, however, address these issues with the data available to us. Nevertheless, future studies should use these heterogeneity findings to better design studies and to more thoroughly report dimensions of phenotypic heterogeneity in their sample.

All data suffer from one important limitation, which is their specificity for ADHD. In fact *SLC6A3*, *DRD4*, *COMT* have each been associated to other psychiatric pathologies such as major depressive disorder, schizophrenia, anxiety disorders, bipolar disorder and obsessive-compulsive disorder.<sup>141</sup> The issue of comorbidity is vital because it is pervasive among adults with ADHD.<sup>142</sup> Despite this fact, many studies of Axis-I disorders in adults do not address comorbidity, possibly because, for many years, ADHD had been perceived as a childhood disorder. For example, most of the adult studies used the SCID as diagnostic interview. As ADHD is not included in the SCID, it would have

been overlooked. Thus, the lack of specificity for genetic associations could be due to the fact that studies of these other disorders did not assess ADHD. Non-specificity also suggests the possibility that common biological mechanisms linked to dopaminergic and noradrenergic systems are shared among different psychiatric disorders, as was recently supported.<sup>141</sup> Future studies should include ADHD in the assessment of comorbidities and also address the concomitant treatment of ADHD and comorbid Axis-I disorders, which is new and an important issue.

This work presents some limitations. (1) For some meta-analyses, the sample sizes were small and with only two studies. (2) Differential proportion of remitting and persisting ADHD within the children samples may also explain discordant results among studies. (3) With regard to the pharmacogenetic studies, one study included a placebo arm.<sup>68</sup>

In conclusion, we found that there were not enough genetic, pharmacogenetic and biochemical studies of ADHD in adults and that more investigations are needed. Moreover we confirmed significant role of *BAIAP2* and DHA in the etiology of ADHD exclusively in adults. Future research should be focused on the replication of these findings and to assess their specificity for ADHD.

## CONFLICT OF INTEREST

In the past year, Dr Faraone received income, potential income, travel expenses and/or research support from Arbor, Pfizer, Ironshore, Shire, Akili Interactive Labs, CogCubed, Alcobra, VAYA Pharma, Neurovance, Impax, NeuroLifeSciences. With his institution, he has US patent US20130217707 A1 for the use of sodium-hydrogen exchange inhibitors in the treatment of ADHD. The remaining authors declare no conflict of interest.

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