

Biomarkers and Attention-Deficit/Hyperactivity Disorder: A Systematic Review and Meta-analyses

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Objective: To determine if peripheral biochemical markers (biomarkers) might differentiate patients with attention-deficit/hyperactivity disorder (ADHD) from non-ADHD individuals.

Method: We conducted a systematic search and a series of meta-analyses of case-control studies comprising studies from 1969 to 2011.

Results: We identified 210 studies in the following categories: 71 studies of the main metabolites and metabolism enzymes of monoaminergic neurotransmission pathway; 87 studies of environmental risk factors divided into heavy metals (18 studies), substance/chemical exposures (16 studies), and nutritional factors (trace elements: 29 studies; essential fatty acids: 24 studies); 22 studies of the hypothalamic–pituitary–adrenal axis (HPA) pathway; 31 studies indicated with “other”. After screening for the availability for meta-analyses of drug naïve/free case-control studies and Bonferroni correction, five comparisons were statistically significant (Norepinephrine [NE], 3-Methoxy-4-hydroxyphenylethylene glycol [MHPG], monoamine oxidase [MAO], Zinc [Zn], cortisol), five of the significant findings found support in studies of response to ADHD medications (NE, MHPG, MAO, b-Phenylethylamine [PEA], cortisol), six in studies of symptoms severity (NE, MHPG, MAO, ferritin, Zn, cortisol) and three in studies of neurophysiological or cognitive functioning (lead-ferritin-Zn). No evidence of publication bias was found, whereas significant heterogeneity of effect sizes across studies was found for three of the five biomarkers that differentiated ADHD from control subjects. Suggestive associations were evidenced for neuropeptide Y (NPY), Manganese, Dehydroepiandrosterone, (DHEA).

Conclusions: This study provides evidence for several peripheral biomarkers as being associated with ADHD both in diagnosis and treatment efficacy. Further studies are warranted to replicate these findings, assess their specificity for ADHD and quantify the degree to which they are sufficiently precise to be useful in clinical settings.