Mostafa 2008 (8)	Case control	Egypt	**N=80** Case (n=40) Patients with Autism [mean age 7.35±2.6 yrs] Control (n=40) healthy children [mean age 7.68±2.5 yrs]	Autistic children had higher serum serotonin levels than healthy children controls [125 (250.75) vs. 41.5 (41.5) ng/mL, P<0.001]. Serum serotonin and total immunoglobulin E (IgE) levels in autistic patients (r=0.8, P< 0.001)	Childhood Autism Rating Scale "CAR". Standford Binet test to calculate the intelligence quotient (IQ) Measure the amount of serotonin to the correlation of IgE amount.	Hyperserotonemia may be a contributing factor to the increased frequency of allergic manifestations in some children. Serotonin has an important role in initiation of delayed-type hypersensitivity responses, which are important to in autoimmunity.
Mostafa 2008 (9)	Case-control	Egypt	**N=100** Case (n=50) Patients with Autism [mean age 8.4±3.3 yrs] Control (n=50) healthy children [mean age 8.6±3 yrs]	Serum total IgE (IU/mL) in autistic children vs Control (mean±SD 204±186.3 vs 70.3±57.2) (p<0.001) The frequency of allergic manifestations in Autism vs control (52% vs 10%) p<0.001	Measure the serum total immunoglobulin E.	Frequency of allergic manifestations was significantly higher in autistic children.
Mrozek 2013 (10)	Case-control	Poland	**N=288** Case (n=96) Autistic children Control (n=192) children match by birth, gender physician's practice. [mean age 7.5±2.6 yrs]	Case affected by asthma (5.2%) and allergy (25%), controls affected by asthma (4.7%) and allergy (21.9%) respectively. Not significant. Allergy in father was the risk factor of allergic disease in children with autism [OR: 9.3, 95% CI (1.6-52.9)] P=0.012	Measure the frequency of asthma and allergy in children with autism by physician's diagnoses and skin prick test in comparison to controls and the risk factors of allergic diseases and asthma in both groups.	Similar frequency between case and control. Not significant.
Renzoni 1995 (11)	Case-control	Italy	**N=86** Case (n=43) autistic patients Control (n=43) mental retardation of various kind	Patients with IgEtot >200 kU/L Case, 9/43 (20.9%) vs control, 11/43 (25.5%). No significance Eosinophils (M ± SE): absolute count (cells/cram) Case, (259.1 ±27), vs control, (193.4 ± 18) p<0.05	Allergological assessment was by prick tests. Total serum IgE including specific IgE were measured, and blood eosinophils was determined.	Increased prevalence of eosinophilia could alternatively be attributed to other factors unrelated to immune system disorders. No statistical difference in the mean value of total serum IgE or in the presence of increased total and food-specific serum IgE between autistic and control children.

Shibata 2013 (12)	Population-based epidemiological study	Japan	Total population of children **N=1409** (kindergarten n = 1073, nursery school n = 333, response rate 59.7%)	Nasal allergy [OR: 1.61, 95% CI: (1.01–2.56)] were shown to be significantly positively related to higher ASD score	Questionnaires regarding (asthma, nasal allergy, Japanese cedar pollinosis, eczema) Japanese version of the Autism Screening Questionnaire (ASQ Japanese version: Dairoku et al.)	This study also showed that children with an ASD score of 8 points or more had a higher prevalence of allergic disease.
Tsai 2014 (13)	Prospective cohort study	Taiwan	Population (n=2134) asthmatic infants and children [mean age: 1.35 ±1.02 yrs] Control (n=8536) infants and children 2002 follow-up to December 2010	Asthmatic infants and children exhibited a higher accumulative incidence rate of ASD than did the controls (1.3% vs 0.7%, P = .007). Asthmatic infants and children exhibited an elevated risk of developing ASD [hazard ratio: 2.01, 95% CI: (1.19–3.40)] Comorbid allergic diseases, namely, allergic rhinitis (69.4% vs 27.8%, P < .001), atopic dermatitis (28.3% vs 11.5%, P < .001), and allergic conjunctivitis (36.7% vs 26.3%, P < .001), than did the control group.	Psychiatrists diagnosed ASD (ICD-9-CM code: 299)	This prospective study indicated a temporal relation between asthma and subsequent ASD diagnosis, supporting the immune hypothesis of ASD pathogenesis.

Attention deficit-Hyperactivity Disorder (ADHD)

Authors	Study design	Country	Participants and Sample size	Results	Outcome measures	Comment
Biederman 1994 (14)	Case-control	US	**N=260** Case (n=140) ADHD Normal Controls (n=120) [mean age 11.0±3.3]	Asthma in ADHD proband (N=17) did not differ from normal controls (N=12) (13.1% vs 10.4%, X^2=0.4). Not significant.	The characteristics of the clinical presentation of asthma covered by the questionnaire included source of diagnosis, severity of asthma. ADHD diagnosis by interviews based upon DSM-III-R	
Boris 2004 (15)	Cross sectional	US	**N=45** ADHD (n=18) ASD (n=27)	Regression behavior after direct nasal pollen challenge ADHD vs. ASD 12 out of 18 (67%) vs. 16 out of 29 (55%) p<0.01	Blood drawn to measure IgE level and RAST tests The Aberrant Behavior Checklist consists of 58 items and scoring ranges from 0 to 3	Nasal pollen challenge produced significant neurobehavioral regression, occurred in both allergic and non-allergic children.

Chen 2013 (16)	Case-Control	Taiwan	**(N=6,160)** Total ADHD children ADHD alone (n=5,811); ADHD + Tic (n=349) Control (n=31,904)	ADHD / ADHD+Tic vs. Control Asthma 1.649 (28,4%) / 96 (27,5%) vs. 2.939 (11,9%) p<0.001 Allergic Rhinitis 1.649 (28.4%) / 150 (43,0%) vs. 4.866 (19.7%) p<0.001	Diagnosis determined by ICD-9-CM	Patients with dial diagnoses of ADHD and tic disorder had a significantly higher prevalence of allergic diseases and psychiatric bidities than the other groups. A significant association among ADHD, tic disorder and allergic diseases was noted in the study.
Chou 2013 (17)	Cross-sectional	Taiwan	**N=221,068** Patients (n=469) ADHD group Control (n=220,599) general population 2005 [Age range 0-17]	Prevalence of AR in the ADHD and control group Case vs. Control Age <6: 23 (29.5%) vs. 12.126 (16.6%) [OR 2.1, 95% CI: 1.29~3.41] p=0.005 Age 6-11: 94 (29,0%) vs. 13.443 (16,9%) [OR 2.0, 95% CI: (1.57~2.50)] p<0.001 Age 12-17: 16 (23.9%) vs. 7.894 (11,6%) [OR 2.4, 95% CI: (1.37~4.42)] p=0.004	Diagnosis were determined by the presence of ICD-9-CM	Patients with ADHD had an increased rate of AR. Psychiatrists should be more aware of the comorbidity of AR when treating ADHD
Kwon 2014 (18)	Case-Control	South Korea	**N=4,113** Case (n=549) ADHD children group [mean age 7.83±1.20] Control (n=3,564) [mean age 7.78±1.17]	Case vs. Control: Asthma 200 (36.6%) vs. 859 (24.3%) p=0.000 Asthma with treatment 37 (6,8%) vs. 153 (4.3%) p=0.031 Relative risk of asthma was 1.60 times higher (confidence interval 1.301-1.964), the relative risk of allergic rhinitis was 1.38 times higher (confidence interval 1.124-1.681), which showed statistical significance.	The evaluation for asthma and the allergic disorders was based on the items defined by the International Study of Asthma and Allergies in Children (ISAAC) DSM-IV from clinical interviews	Significant association between ADHD and childhood asthma and allergic rhinitis is found. Treatment is required for asthmatic children with ADHD syndromes.
McGee 1993 (19)	Cross-sectional analysis	New Zealand	Population (**N=815**) [Age from 9-13 years]	Allergic disorders (by history at age 9 and age 13) associate to ADDH were no significant ($p > .05$).	Inattentive and hyperactive behaviors based upon DSM-III criteria were gathered at age 9 via questionnaires Atopic responses were assessed by a skin prick test	The results of this study provide little support for the hypothesized relationship between allergic disorders in childhood and ADDH.

Roth 1991 (20)	Case-Control	Germany	**N=142** Case (n=81) Atopic children Control (n=71) non-AT children	AT group, 50% of the children obtained scores greater than 10 as compared to only 19.7% of the controls. A score greater than 15 points was found for 14.8% of the AT and 4.2% of the controls, respectively (X^2 [1, 1] = 15.64; p < .001). Hyperactivity ratings were higher in younger children of both groups (r = -.73; p < .01); sex differences (boys/girls = 3/2) were non significant.	Abbreviated Parent Rating Scale (APRS; Conners, 1973)	
Schmitt 2010 (21)	Systematic review	Germany	Total 122 citations yielded 20 articles Cross-sectional (n = 14; 70%) or case–control studies without incident expo- sure measurement (n = 5; 25%)	Six studies consistently reported a positive association between eczema and ADHD. Twelve studies consistently found a positive association between asthma and ADHD; however, appeared to be by concurrent or previous eczema. Rhinitis and serum-IgE level were not related to ADHD symptomatology	Electronic literature search in PubMed and PsycINFO (until 02/2010) supplemented by hand search yielded 20 relevant studies	We conclude that not atopic disease in general, but rather that eczema appears to be independently related to ADHD.
Shyu 2012 (22)	Cohort Study	Taiwan	**N=226,550** Allergic disorders (n=48,457) General population (n=178,093) (Age range 0-17 yrs)	Allergic patients had a higher prevalence of ADHD than the general population (0.9% vs. 0.5%, p < 0.001). Allergic disorders vs. general population Age <6: 123 (0.6%) vs. 219 (0.4%); OR 1.38 [95%CI 1.11-1.72] p=0.005 Age 6-11: 257 (1.5%) vs. 519 (0,8%); OR 1,86 [95%CI 1.60~2.17] p<0.001 Age 12-17: 48 (0.5%) vs. 141 (0.2%); OR 2.16 [95%CI 1.56~3.00] p<0.001	International Classification of Diseases [ICD- 9], 9th revision	Patients with allergic disorders had a substantially increased rate of developing ADHD in terms of period prevalence and odds ratio In comparison with the general population, allergic patients showed an overall higher risk for developing ADHD [OR1.56, 95% CI: (1.38-1.75)]

Suwan 2011 (23)	Case-control	Thailand	**N=80** Case (n=40) ADHD children Control (n=40) non-ADHD children from outpatients.	The prevalence of any positive skin prick test in ADHD patients was higher then the control, 67% and 45% respectively, (p=0.043) The frequency of allergic rhinitis was higher in the ADHD groups (p=0.008)	Diagnostic and Statistical Manual of Mental Disorders, fourth edition. Skin prick testing to common allergens	There were increased rates of allergic sensitization and allergic rhinitis in ADHD children.
Tsai 2013 (24)	Case-Control	Taiwan	**N=23,460** Case (n=4,692) ADHD mean age 8.91±3.02 Control (n=18,768) Non-ADHD mean age 8.93±3.03	Case vs. Control atopic diseases: Allergic rhinitis 2.172 (46,3%) vs. 6.062 (32,3%) [OR 1.81, 95%CI 1.69-1.93] p<0,001 Asthma 165 (3.5%) vs. 450 (2.4%) [OR 1.48, 95%CI (1.24-1.78)] p<0,001	Longitudinal Health Insurance Database (LHID), established by the National Health Research Institutes Assessment of ADHD or AD were made by clinical physicians in charge at medical institutions base on ICD-9-CM.	Children with ADHD had a strong association with atopic diseases.
Yang 2013 (25)	Case-control	Taiwan	**N=144** Case: Total AR (allergic rhinitis) (n=105) [Mean age 10.78±2.57 years] ADHD (n=10) [Mean age 9.35±2.20 years] Control (n=29) [Mean age 10.91±2.77 years]	Case (AR, ADHD) vs Control TNSS score (5.57±2.69, 1.00±1.41) vs (0.33±0.62) p<0.001 T5SS (6.79±3.39, 1.50±2.12) vs (0.67±1.110) p<0.001 AR children had higher ADHD symptom scores (SNAP-IV and DSM-IV-TR) and commission errors (CPT) than the control children. (p<0.001)	AR symptom scores by TNSS and T5SS SNAP-IV scale is a 26-item questionnaire in a 4-point Likert scale that is used to evaluate ADHD symptoms The continuous performance test (CPT)	

Learning Disabilities (LDs)

Authors	Study design	Country	Participants and Sample size	Results	Outcome measures	Comment

Biederman 1995 (26)	Cross-sectional	US	**N=260** Subject (n = 140) ADHD subjects were 6- to 17-year-old boys with DSM-III-R Controls (n = 120) normal children.	No significant in asthma (13% vs. 10%, $X^2 = 0.4$, df = 1, p = .53) were found between ADHD and normal controls. Similarly, the rates of asthma (14% vs. 12%, $X^2 = 0.1$, df = 1, p = .7) did not differ between probands with and without reading disability.	The characteristics of the clinical presentation of asthma covered by the questionnaire included source of diagnosis, severity of asthma Intellectual functioning was assessed with Wechsler Intelligence Scales for Children Academic achievement was assessed with the Arithmetic sub-test of the Wide Range Achievement Test-Revised and the Gilmore Oral Reading Test.	Neither ADHD nor reading disability was associated with either asthma.
Conduct Disorders (CDs) (Not found)						

Table summary 2

Are vitamin and mineral supplements intake effective for improving autism spectrum disorders and other related developmental disorders in children?					
Clinical Trails					
Autism Spectrum Disorders (ASDs)					
Study ID	**Participants**	**Daily Dose**	**Length of trial**	**Measure(s)**	**Outcomes**
Adams 2004 (27)	N=20 Autistic-Spectrum disorder children 3-8 years old	Commercial supplement Spectrum Support II (SSII) and (SSIII): full dosage 1mL/5pounds body weight, daily 3 ml/5 pounds body weight Placebo (Kosher vegetable glycerine base)	3 months	Global impressions Parental questionnaire survey. Vitamin diagnostics by ciliate protozoan Tetrahymena pyriformis	Supplement group reported improvement of sleep and gastrointestinal problems compare to placebo group.
Bertoglio 2010 (28)	N=30 autism children. 3-8 years old. 28 male and 2 female. 9 subjects demonstrated clinically significant improvement	Methyl B12 (injection)= 64.5ug/kg every three days for 6 weeks. Placebo (saline)= 64.5ug/kg every three days for 6 weeks	12 weeks	PIA-CV CGI-I CARS PPVT-III ABC CBCL MCDI	Plasma concentrations of glutathione (GSH) show no significant between active and placebo group. No mean difference in behavior tests.
Dolske 1993 (29)	N=18 autistic subjects, 13 male and 5 female. (age range from 6 to 9)	Ascorbic Acid 8g/70kg/day Placebo tablets	30 weeks	Ritvo-Freeman Real Life rating scale for Autism	Sensory motor scores indicating a reduction in symptom severity associated with ascorbic acid treatment ($p< 0.05$)
Findling 1997 (30)	N=12. 3- 17 years old. Diagnosis: Autism.	638.9 mg of pyridoxine and 216.3 mg of magnesium vs. placebo.	10 weeks	CPRS CGI NIMH GOCS	No improvement.
Attention deficit-Hyperactivity Disorder (ADHD)					
Study ID	**Participants**	**Daily Dose**	**Length of trial**	**Measure(s)**	**Outcomes**
Abbasi 2011 (31)	N=40 ADHD outpatients 28 boys and 12 girls Ages (7-13)	Acetyl-L-carnitine dose range from 500 to 1500mg/day depending on weight with methylphenidate at a dose of 20-30 mg/day Placebo plus methylphenidate	6 weeks	Teacher and Parent attention deficit/hyperactivity disorder Rating scale-IV.	No difference was observed between the two groups.
Arnold 2011 (32)	N=52 ADHD (age ranged 6-14 years)	Zinc=dose 15 mg/ day Zinc= 15mg/ 2 times a day [b.i.d]. Zinc + amphetamine (5-15mg) base on weight Placebo Placebo + amphetamine	13 weeks	Parents Teacher ratings of attention, impulsivity and hyperactivity. ASHD check list of 18 DSM-IV ADHD SNAP-IV Conner's parent Rating Scale-Revised	No effect with zinc treatment.
Brue 2001 (33)	N=60. 4-12 years old. (85% boys) ADHD diagnosis.	1st scheme: Dietary supplement + essential fatty acid (flaxseed 1000 mg) vs. dietary supplement. 2nd scheme: Methylphenidate+ dietary supplement + essential fatty acid (flaxseed 1000 mg) vs. Methylphenidate+ dietary supplement.	12 weeks	CRS RL	Mixed results. Overall, the treatment was not reliable / effective in reducing ADHD symptoms.

Ghanizadeh 2013 (34)	Systematic review of randomized clinical trials of Zinc supplement to placebo 80 titles. Only 3 trials met the inclusion criteria	Zinc sulfate (55mg) per day, administered fixed dose zinc sulfate (150mg), zinc supplement very morning (15mg), Zinc plus fix dose 5-15mg based on body weight, Zinc+ amphetamine, Zinc supplement 10 mg per day for five days, and iron 30mg and zinc 30 mg tablets.	2 weeks to 6 months	Ankar Conner Teacher Questionnaire ADHD rating scale DSM-IV ADHD symptoms checklist BASC	On was effective on ADHD score, Another one was positive on hyperactivity measure but no effectiveness on inattentiveness measure. The last one have negative entirely.
Hariri 2012 (35)	N=103. 6-12 years) ADHD diagnosis. Medicated.	n-3 fatty acids (635 mg EPA, 195 mg DHA). Placebo: Olive oil	8 weeks	ASQ-P	Significant improvement in the ASQ-P scores (p=<0.005)
Hirayama 2004 (36)	N=40. 6-12 years old. 80% boys. ADHD diagnosis. 15% medicated. 82% co-morbid condition present.	100 mg EPA514 mg DHA 20 placebo (indistinguishable control foods) 20 PUFA.	8 weeks	DSM-IV ADHD DTVP CPT STM	No improvement. Controls higher on visual short term memory and CPT.
Johnson 2008 (37)	N = 75. 8-18 years old.	174 mg DHA 558 mg. EPA60 mg LA Placebo = olive oil.	12+12 (one way crossover).	DSM-IV CGI	No difference in the PUFA group compared to placebo. 25% decline in ADHD behavioral symptoms. 26% after 12 weeks; and 47% after 24 weeks. Following cross-over same effects as in the group previously treated with placebo.
Konofal 2008 (38)	N=23. 5-8 years old. ADHD diagnosis.	Iron (80 mg/day) vs. placebo	12 weeks	CGI ADHD RS Conners	Improvement in ADHD-RS and CGI. Improvement in parents and teachers' Conners RS (p=0.076).
Raz 2009 (39)	N=73. 7-13 year old. ADHD diagnosed. Un-medicated.	480 mg LA 120 mg alpha – LA- Placebo – Vit C.	7 weeks.	TOVA- teachers and parents questionnaires.	No improvements.
Richardson 2002 (40)	N= 29. 8-12 years old. 62% boys. Normal IQ. SLD-low reading ability. Above average ADHD scores on Conner's index. Treatment – none.	EPA= 186 mg/day; DHA = 480 mg/day; GLA= 96 mg; AA= 42 mg. 14 placebo (olive oil) 15 PUFA.	12 weeks+ 12 weeks CPRS crossover.	CPRS	Treatment > placebo on CPRS: cognitive problems/ in-attention anxious /child. Following cross-over same effects as in the group previously treated with placebo.
Richardson 2005 (41)	N=117. 5-12 years old. 77% boys. 1/3 with ADHD symptoms in clinical range. Dyspraxia (Developmental coordination disorder). Non medicated.	174 mg DHA558 mg EPAGLA= 10 mg 9.6 mg Vit E Placebo = olive oil.	12 weeks active vs. placebo. One way cross-over for active treatment for 12 weeks.	MABC WORD CTRS	Treatment > placebo. Treatment = placebo: MABC (motor function). Improvement in reading and spelling.
Rucklidge 2014 (42)	N=80. Adults. ADHD.	Micronutrients vs. placebo.	8 weeks	CGI-I-ADHD CGI-I	Improvement when asses by observer (p=0.026) and the person him/herself (P=0.009), though no change perceived by clinician (p=0.331).
Sin 2007 (43)	N= 132. 7-12 years old. 74% boys. ADHD symptoms in clinical range. Un-medicated.	174 mg DHA558 mg EPAGLA= 10 mg 9.6 mg Vit E Multivitamins (MVM) supplements Placebo= palm oil.	15 weeks active vs. placebo. One way cross-over for active treatment for 15 weeks.	CPRS CTRS	Treatment > placebo – treatment = placebo n CTRS No difference in the PUFA group with or without MVM. Significant improvement in vocabulary.

Stevens 2003 (44)	N=50. 6-13 years old. 78% boys. High FADS. Some on medications. They had no formal diagnosis of ADHD.	80 mg EPA 480 mg DHAGLA= 96 mg 24 mg Vit E 25 placebo (olive oil) 25 PUFA.	16 weeks	DBD ASQ CPT FADS WJPEB-R	Treatment > placebo: DBD-conduct (parents); DBD- attention (teachers).
Voigt 2001 (45)	N=54. 6-12 years old. 78% boys. Treated with medications successfully.	DHA=334 mg daily. 31 placebo (no name reported) 32 DHA.	16 weeks	CPRS CBC TOVA CCT	Treatment=placebo on all measures.
Zamora 2011 (46)	N=40. 7-14 years (70% boys). ADHD diagnosis.	Methylphenidate 0.3 mg/Kg/d + Zinc 10 mg/d vs. Methylphenidate 0.3 mg/Kg/d + placebo.	6 weeks	CGI	No significant change found in scales when assessed by parents or teachers.
Learning Disabilities (LDs)					
Study ID	**Participants**	**Daily Dose**	**Length of trial**	**Measure(s)**	**Outcomes**
Carlton 2000 (47)	N=20. 7-14 years old. Learning disability disorder.	Tailored diet adding micronutrients (mostly B complex vitamins and others).	12 months	Mean grade scores at school.	Improvement after 4 years of follow-up (p=<0.01).

Table summary 3

Is heavy metal a cause for autism spectrum disorders and other related developmental disorders in children?					
Autism Spectrum Disorders (ASDs) and associated conditions					
Study ID	**Study design**	**Country**	**Participants, sample size**	**Measure /exposure**	**Results**
Abdullah 2012 (48)	Case-control	US	**N = 84** 42 children (aged 9-14 yrs) with ASDs (n=22) or high levels of disruptive behavior (HDB) (n=20), matched against 42 typically developing (TD) children on child's gender and race, parents' education and marital status	Concentrations of lead, mercury, and manganese in prenatal and postnatal enamel regions of deciduous teeth	*No significant differences* between groups in levels of neurotoxicants. Marginal significance indicating that children with ASDs have lower manganese levels than TD children (r= -.28, p=.08).
Adams 2006 (49)	Case-control	US	**N = 145** Children with ASDs (n=51), a subset of their mothers (n=29), neurotypical children (n=40), and a subset of their mothers (n=25), matched by ages and genders Inclusion criteria for ASD children: 3-15 yrs, with a diagnosis by a psychiatrist or developmental pediatrician of ASD, including autism, PDD/NOS, and Asperger's syndrome	Levels of 39 toxic metals in hair samples	Autistic children with pica had a 38% lower level of chromium (p=.002). Autistic children with low muscle tone had high zinc levels (31%, p=.01).
Adams 2013 (50)	Case-control	US	**N = 99** 55 children with autism (aged 5-16 yrs) compared to 44 controls with similar age and gender Enrollment criteria: 1. Age 5-16 yrs 2. No usage of a vitamin/mineral supplement in last 2 months 3. No current use of any chelation treatment 4. Autism group: prior diagnosis of autism, PDD/NOS, or Asperger's by a psychiatrist or similar professional, with written verification (no additional assessment done) 5. Control group: in good mental and physical health and no siblings with autism spectrum disorders, and no evidence of attention deficit disorder by parent report (no additional assessment done)	Measurement of toxic metals in whole blood, red blood cells, and urine	Autism group had higher levels of lead in RBC (+41%, p=.002) and higher urinary levels of lead (+74%, p=.02), thallium (+77%, p=.0001), tin (+115%, p=.01), and tungsten (+44%, p=.00005). However, the autism group had slightly lower levels of cadmium in whole blood (-19%, p=.003). A stepwise, multiple linear regression analysis found a strong association of levels of toxic metals with variation in the degree of severity of autism for all severity scales (adjusted R^2 of 0.38-0.47, p<.0003. Cadmium (whole blood) and mercury (whole blood and RBC) were the most consistently significant variables.

Al-Farsi 2013 (51)	Case-control	Oman	**N = 54** 27 children with ASD and 27 matched non-ASD controls, matched by age, gender, and ethnicity Inclusion criteria for ASD group: 3-14 yrs, fulfilling the criteria for diagnosis of ASD according to threshold defined by *Childhood Autism Rating Scale* and *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* Inclusion criteria for control group: seeking consultation for trauma, routine physical examination, dental problems, and dermatological problems at the participating hospital's Department of Child Health ; absence of overt neurodevelopmental or behavioral disturbances or history of pervasive and persistent malnutrition	Analysis of 11 heavy metals (lead, aluminum, silicon, molybdenum, vanadium, chromium, cadmium, cobalt, nickel, boron, barium) in hair samples carried out by inductively coupled plasma mass spectrometry	Children with ASD had significantly higher levels of all 11 analyzed heavy metals in their hair samples ($p<.05$), ranging from 150 to 365% of control levels.
De Palma 2012 (52)	Case-control	Italy	**N = 105** (44 children with diagnosis of autism, 61 age-balanced controls)	Concentrations of aluminum, arsenic, cadmium, cobalt, chromium, copper, iron, mercury, lithium, manganese, molybdenum, nickel, lead, selenium, thallium, uranium, and zinc, measured using hair samples	Unadjusted comparisons showed higher concentrations of molybdenum, lithium, and selenium in autistic children. Logistic regression analysis showed a slight association with molybdenum concentrations as well.
Geier 2006 (53)	Retrospective cohort	US	Children aged less than or equal to 5 years	Thimerosal containing vaccines VAERS is Vaccine Adverse Event Reporting System CDDS is California Department of Developmental Services The total number in these databases is not reported	Results are reported for the trends of new cases of autism and speech disorder (from VAERS database) in two periods, Jan 1994 through Dec 2002 when thimerosal containing vaccines were used and during Jan 2002 through June 2005 when the thimerosal containing vaccines were removed. There was a significant difference in the trends from an increasing to a decreasing slope ($p<0.0005$ for autism and $p<0.005$ for speech disorder). In another set of results (from the CDDS database), from January 1994 through Jan 2003 (thimerosal vaccines present) and from Jan 2002 through October 2005(no thimerosal) for new cases of autism, the trends were significantly different ($p<0.0001$)
Majewska 2010 (54)	Case-Control study	Poland	n=91(autistic) n = 75(control) Group I :3-4 years old Group II:7-9 years old	Mercury levels in hair	Group I: Hair mercury levels were lower in autistic than in control children Group II: autistics had higher hair mercury levels than in controls ($p=0.01$)
Attention Deficit Hyperactivity Disorder (ADHD)					

Study ID	Study design	Country	Participants, sample size	Exposure	Results
Braun 2006 (55)	Cross-sectional	US	**N = 4,704** 4,704 children at 4-15 yrs of age	Lead exposure measured using blood lead concentration	Higher blood lead concentration (first vs. fifth quintile, OR = 4.1; 95% CI, 1.2-14.0) was significantly associated with ADHD.
Cheuk 2006 (56)	Case-control	China	**N = 111** (52 children with ADHD, 59 normal controls, unmatched) Inclusion criteria for ADHD group: children <18 yrs with ADHD identified from the Child Assessment Center of the participating hospital, with diagnosis of ADHD according to the DSM IV criteria after a structured interview which incorporated parental and teachers' reports of behavioral symptoms, clinical observation of behavior, Aberrant Behavior Checklist, and tests of attention such as the Conners Continuous Performance Test / Exclusion criteria: children with identifiable perinatal insults, neurological deficits or mental retardation Inclusion criteria for control group: consecutive normal children <18 yrs admitted for acute upper respiratory infection to nearby University-based hospital during the same study period, assessed for absence of symptoms of ADHD listed in the DSM-IV criteria / Exclusion criteria: children with identifiable perinatal insults, neurological deficits or mental retardation	Blood mercury levels were measured by cold vapor atomic absorption spectrometry	There was a significant difference in blood mercury levels between cases and controls (geometric mean 18.2 nmol/L [95% CI 15.4 – 21.5 nmol/L] vs. 11.6 nmol/L [95% CI 9.9 – 13.7 nmol/L], p<.001), which persists after adjustment for age, gender, and parental occupational status (p<.001). The geometric mean blood mercury level was also significantly higher in children with inattentive (19.4 nmol/L, 95% CI 14.9 – 21.8 nmol/L) subtypes of ADHD. Children with blood mercury levels above 29 nmol/L had 9.69 times (95% CI 2.57 – 36.5) higher risk of having ADHD after adjustment for confounding variables.
Cho 2010 (57)	Cross-sectional	Korea	**N = 667** 667 children aged 8-11 yrs recruited from 9 schools in 5 Korean cities	Blood lead levels	A significant relationship was found between parent and teacher-rated ADHD symptoms (inattentiveness, hyperactivity, or total scores) and blood lead levels. This positive association between teacher-rated ADHD symptoms and blood lead levels was significant after controlling for age, gender, paternal education, maternal IQ, child IQ, residential area, and birth weight. Moreover, this relationship was still significant after further adjusting for urinary cotinine levels. In contrast, the parent-rated ADHD symptoms were not significantly associated with blood lead levels after controlling for the covariates.

Ciesielski 2012 (58)	Cross-sectional	US	**N = 2,195** Subset of participants in NHANES (1999-2004) who were 6-15 yrs of age and had spot urine samples analyzed for cadmium	Cadmium exposure assessed using urinary cadmium concentration, determined by inductively coupled plasma mass spectrometry	When children in the highest quartile of urinary cadmium were compared with those in the lowest quartile, the odds ratio adjusted for potential confounders was 0.67 (95% CI: 0.28, 1.61) for ADHD. The trend was only evident, however, in those with blood lead levels above the median.
Kim 2012 (59)	Case-control	US	71-ADHD cases and 58 controls, aged 5-12 years	Blood lead levels	Unit blood Pb had an odds ratio of 2.52 (95% CI 1.07-5.92)(Pb exposure may be associated with higher risk of clinical ADHD, but not Hg or Cd)
Learning Disabilities (LDs)					
Study ID	**Study design**	**Country**	**Participants, sample size**	**Exposure**	**Results**
Capel 1981 (60)	Case-control	UK	**N = 117** (73 dyslexic, 44 controls) Inclusion criteria for dyslexic group: aged 11-15 yrs, of IQ 90-138 (Wechsler Intelligence Scale for Children), attending special educational centers Inclusion criteria for control group: same age and IQ range, attending Comprehensive Schools	Concentrations of 8 toxic metals (magnesium, copper, aluminum, cadmium, lead, calcium, selenium, mercury) in hair sampled from central region of the nape of the neck, analyzed by flameless atomic absorption spectrometry	Hair from dyslexic children showed significantly higher concentrations of magnesium and copper than did hair from control subjects ($p<.05$). Hair from dyslexic children also contained significantly higher concentrations of aluminum and cadmium than that from control children ($p<.05$). There were no significant differences in the cases of lead, calcium, selenium, or mercury.
Ciesielski 2012 (58)	Cross-sectional	US	**N = 2,189** (for LD) / **2,196** (for special education) Subset of participants in NHANES (1999-2004) who were 6-15 yrs of age and had spot urine samples analyzed for cadmium	Cadmium exposure assessed using urinary cadmium concentration, determined by inductively coupled plasma mass spectrometry	When children in the highest quartile of urinary cadmium were compared with those in the lowest quartile, odds ratios adjusted for potential confounders were 3.21 (95% CI: 1.43, 7.17) for LD and 3.00 (95% CI: 1.12, 8.01) for special education. There were no significant interactions with sex, but associations were somewhat stronger in males.
Lyngbye 1990 (61)	Case cohort	Denmark	N = 198 198 cases (high-lead) and controls (low-lead); children in the 1st grade	Cumulated lead absorption as indicated by the lead concentration in the circumpulpal dentin	The influence of lead absorption became statistically significant only after exclusion of the children with proven medical risk factors, thereby the adjusted odds ratio in the weighted analysis was changed from 2.2 to 4.3 ($p=.05$).

Krall 1980 (62)	Case-control	US	47 lead-poisoned patients aged 6-1 to 14-1 yrs, 45 sibling controls aged 6-3 to 15-4 yrs		Verbal IQ exceeding performance IQ by 25 points or more on the Wechsler Intelligence Scale for Children was not statistically significant between the two groups (p>0.05) Performance less than Verbal IQ, Object Assembly less than Similaries, and Block Designs equal to or less than Vocabulary was statistically different between the two groups (p>0.05)
Conduct Disorders (CDs)					
Study ID	**Study design**	**Country**	**Participants, sample size**	**Exposure**	**Results**
Braun 2008 (63)	Cross-sectional	US	**N = 3,081** 3,081 children 8-15 yrs of age	Environmental lead exposure assessed using current blood lead concentration	Increased blood lead levels (fourth vs. first quartile) were associated with an 8.64-fold (95% CI, 1.87-40.04) increased odds of meeting DSM-IV CD criteria.

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Appendix

Cochrane TA
Search Name:
Date Run: 17/05/14 08:37:11.670
Description:
ID Search Hits
#1 MeSH descriptor: [Child Development Disorders, Pervasive] explode all trees 679
#2 MeSH descriptor: [Attention Deficit and Disruptive Behavior Disorders] explode all trees 1822
#3 MeSH descriptor: [Learning Disorders] explode all trees 454
#4 #1 or #2 or #3 2884
#5 MeSH descriptor: [Inorganic Chemicals] explode all trees 44967
#6 MeSH descriptor: [Inorganic Chemicals] explode all trees and with qualifier(s): [Diagnostic use - DU, Pharmacokinetics - PK, Pharmacology - PD, Radiation effects - RE, Therapeutic use - TU] 16114
#7 MeSH descriptor: [Inorganic Chemicals] explode all trees and with qualifier(s): [Adverse effects - AE, Poisoning - PO, Toxicity - TO] 4111
#8 #6 not #7 14539
#9 #5 not #8 30428
#10 MeSH descriptor: [Diet] explode all trees 12170
#11 MeSH descriptor: [Food and Beverages] explode all trees 23421
#12 MeSH descriptor: [Feeding Behavior] explode all trees 5831
#13 MeSH descriptor: [Vitamins] explode all trees 1654
#14 MeSH descriptor: [Maternal Exposure] this term only 36
#15 MeSH descriptor: [Prenatal Exposure Delayed Effects] this tem only 248
#16 MeSH descriptor: [Food Additives] explode all trees 534
#17 MeSH descriptor: [Agrochemicals] explode all trees 357
#18 MeSH descriptor: [Food Contamination] this term only 45
#19 MeSH descriptor: [Chemically-Induced Disorders] explode all trees and with qualifier(s): [Complications - CO] 1171
#20 MeSH descriptor: [Substance-Related Disorders] explode all trees and with qualifier(s): [Complications - CO] 1039
#21 #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 60250
#22 #4 and #21 134
#23 MeSH descriptor: [Child Development Disorders, Pervasive] explode all trees and with qualifier(s): [Chemically induced - CI, Diet therapy - DH]9
#24 MeSH descriptor: [Attention Deficit and Disruptive Behavior Disorders] explode all trees and with qualifier(s): [Chemically induced - CI, Diet therapy - DH] 29
#25 MeSH descriptor: [Learning Disorders] explode all trees and with qualifier(s): [Chemically induced - CI, Diet therapy - DH] 13
#26 #22 or #23 or #24 or #25 157
#27 MeSH descriptor: [Hypersensitivity] explode all trees 15553
#28 #26 not #27 149
Record #1 of 3