2014/06/09

自閉症や発達障害の子どもとアレルギー等の関連について

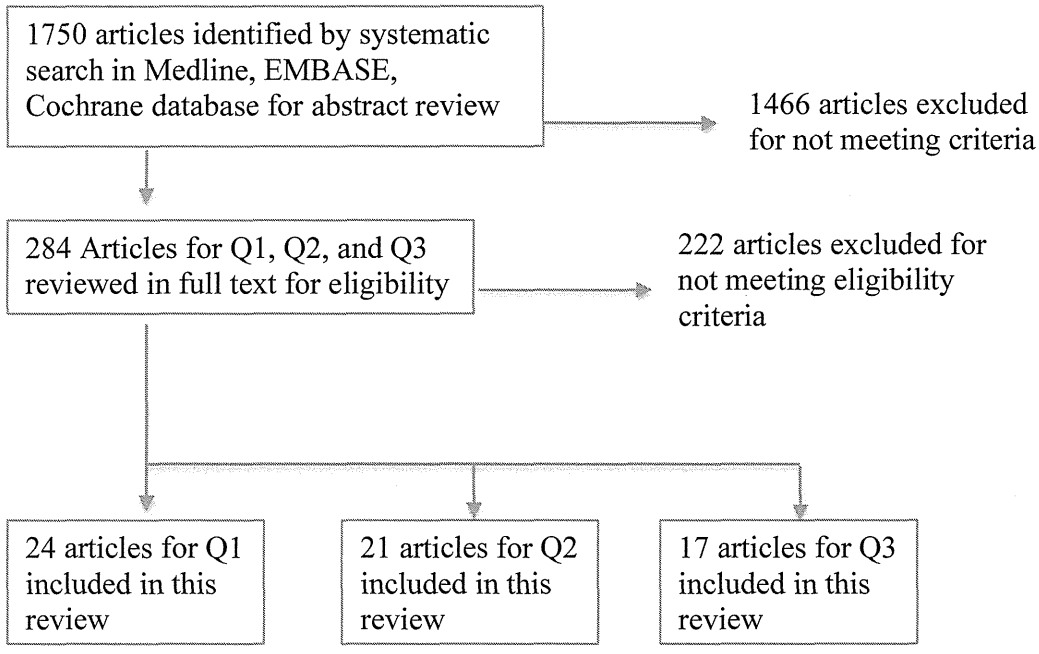
成育医療研究センター政策科学部
宮崎セリーヌ・大田えりか・森臨太郎

以下の３つのリサーチクエスチョンについて系統的レビュー実施:

1. 自閉症や発達障害の子どもは、アレルギー疾患のリスクが高いか？
2. 自閉症や発達障害の子どもに対して、マルチビタミンやミネラルのサプリメントは症状改善効果があるか？
3. 重金属は、子どもの自閉症や発達障害のリスクと関連があるか？

網羅的文献検索と文献抽出:

関連用語を３つのデータベースで検索して、1750 件の論文が該当した。6 名のレビューワーでリサーチクエスチョン Q1、Q2、Q3 に関する論文をタイトルとアブストラクトから探し、該当する可能性のあるものを、フルテキストを取り寄せて、検証し、Q1 は 24 論文、Q2 は 21 論文、Q3 は 17 論文該当した。
それぞれの研究を表にまとめ、日本語で概要を記載した。
（詳細な検索式は Appendix 参照）



科学的根拠のまとめ１：

1. 自閉症や他の発達障害の子どもは、アレルギー疾患のリスクが高いか？

該当する文献は 24 件であった。11 件が自閉症について、12 件が ADHD、1 件が学習障害であった。

自閉症
自閉症に関しては、11 件中 9 件がアレルギー免疫反応と自閉症とポジティブな有意差を示した。しかし、ほとんどの研究が横断研究またはケースコントロール研究であり、関連性を証明できるようなエビデンスはない。喘息と、胃腸障害、アレルギー性鼻炎、食物アレルギー、アトピー性皮膚炎など全身性のアレルギーが自閉症を発展させるというエビデンスはなかった。仮説として関連を示していたバイオマーカーである制御性サイトカインと、自閉症の抗ミエリン塩基性タンパク質の抗体は、神経免疫疾患または脳の炎症を引き起こす可能性がある。

胃腸の慢性炎症性疾患と自閉症との関連
関連なし（１ケースコントロール研究）

バイオマーカー (IgE, serotonin, proinflammatory, cytokines) と自閉症との関連
7 件中 4 件の研究では、IgE に有意な差はなく、関連する二次的なバイオマーカーのみ関連がみられた。7 件中 3 件は、ケースコントロール研究で血清 IgE に関連があったと報告している。

アトピー、喘息、アレルギー性鼻炎、食物アレルギーと自閉症との関連
アトピーと自閉症の関連をみた 1 研究では関連はなかった。鼻炎アレルギーと ASD のスコアが有意に関連していたという研究があった[OR: 1.61, 95% CI: (1.01-2.569]。また、ケースコントロール研究では、自閉症の子どもの間で喘息の発症率が高かったという [hazard ratio: 2.01, 95% CI: (1.19-3.40)].

ADHD
12 件中 10 件の研究でポジティブな関連を示した。しかし、ほとんどの研究が横断研究またはケースコントロール研究であり、関連性を証明できるようなエビデンスはない。喘息と ADHD の研究をまとめた系統的レビューでは、12 の研究がポジティブな相関がみられたが、同時または以前に皮膚炎に罹患しているという交絡として説明がつくため、そのレビューでは ADHD とアレルギー性皮膚炎は独立したものと考えるべきと結論づけている。ある年齢に到達すると、ADHD との関連するというアレルギー症状がもとからのものか、一時的にでてきたものか判別が難しい。

喘息、アレルギー性鼻炎と ADHD
喘息と ADHD の関連をみた 1 研究は関連なし（n=260）。もうひとつの研究は、喘息と ADHD と有意な関連があった（n=4113, 549 children with ADHD and 3,564 normal control children, 200 (36.6%) case vs 859 (24.3%) control p=0.000).

2 研究では、喘息とアレルギー性鼻炎と ADHD では有意な関連がみられ ($p<0.001$)、3 研究ではアレルギー性鼻炎と ADHD で有意な関連があった (significance range $p<0.005$-$p<0.001$)

学習障害

1 横断研究のみ、喘息と ADHD の失読症男児の関連なし (13% vs 10%, $x^2=0.4$, df=1,p=0.53)

科学的根拠のまとめ２：

2. 自閉症や発達障害の子どもに対して、マルチビタミンやミネラルのサプリメントは症状改善効果があるか？

自閉症や発達障害の子どもに対して、サプリメントの有効性を検証したRCTに関して、系統的レビューを行ったところ、21の研究が該当した。4件が自閉症（ADSs）、16件がADHD、1件が学習障害であった。行為障害conduct disorders: CDs)に関してのRCTはなかった。

自閉症（ASDs）
4件中1件だけ自閉症の子どもに有効性があるとした（アスコルビン酸介入）そのほかの3件は有意差なかった。研究のアウトカムはスケールによるアセスメントのみで、バイオロジカルな指標は用いられていなかった。自閉症の症状改善のためのサプリメント介入に関する、科学的根拠はほとんどない。

ビタミンミネラルサプリメントと自閉症
１つの研究では、マルチビタミン介入は、自閉症症状には関連なく、消化器症状がよくなったという結果であった。ほかの２つの研究では、ビタミンB12とB6とマグネシウムは、自閉症の子どもで行動に違いがでなかった。
１つの研究のみ、アスコルビン酸の介入で、感覚運動スコアの症状の重症度が有意に減少した($p<0.05$)。

ADHD
ADHDの子ども対象の16件中6件の研究でポジティブな改善があった。ビタミンとミネラルのサプリメントに関しては、有意な関連はみられなかった。しかしながら、オメガ3とオメガ6とビタミンEのコンビネーションに関してはいくつか有意な改善がみられた。ポリ不飽和脂肪酸（オメガ6とオメガ3）の役割は、脂質介在の前駆体であり炎症の制御を行い、抗炎症脂質として仲介し、サイトカインや炎症による酵素を抑制する(1)。バランスのよいポリ不飽和脂肪酸（オメガ6とオメガ3）は、健康な人に対しても脳内の炎症抑制に有効であり、鬱予防などに用いられているので、ADHDに特有に効いたというよりは、脳内の炎症作用抑制の効果があったと考えられる。

ビタミンとミネラルサプリメントとADHD
3研究は、亜鉛の介入でありADHDのスコアに有意な差はみられなかった。
1研究は、鉄の介入でADHDの両親と先生のConnersスケールが改善の傾向があったが有意差はなかった($p=0.076$)。

必須脂肪酸, eicosapentaenoic (EPA), DHA, linolenic acid (LA) サプリメントとADHD
3研究では、DHA, EPA, GLA, and vitamin Eの介入で運動機能、行為、注意と学習能力が改善した。1研究は、DHA, EPA, GLA and AAがADHDの子どもの認知問題を改善し、不注意の不安行為を減少させた。1研究では、n-3 fatty acidとEPAとDHAは、ADHDの子どものConners' Abbreviated Questionnaires

(ASQ-P) score と学習障害を改善した ($p<0.005$)。5 研究では、必須脂肪酸、EPA と DHA, EPA と DHA と LA, LA と alpha LA, または DHA のみの介入で有意な効果はみられなかった。

微量栄養素、他の栄養素と ADHD

2 研究で、微量栄養素と acetyl-L-carnitine の介入は、ADHD の症状の改善がみられなかった。

学習障害（LDs）

1 研究で、Dcomplex ビタミン介入で、4 年後のフォローアップ時の学校の成績の平均値の改善が有意にみられたが、サンプルサイズが合計で 20 名のみであった ($p<0.01$)。

科学的根拠のまとめ３：

3. 重金属は、子どもの自閉症や発達障害のリスクと関連があるか？

重金属と子どもの自閉症や発達障害の関連をみた論文が 17 あった。自閉症が 7 論文、ADHD が 5 論文、学習障害が 4 論文、行為障害が 1 論文であった。

自閉症（ASDs）
7 つ中 6 論文で、自閉症と重金属との間にポジティブな相関が示された。6 論文では、自閉症の子どもの間で鉛と水銀のレベルが高かった。 鉛や水銀は神経発達の障害を引き起こすことが明らかになっており、関連がある可能性はある。しかし、ほとんどの研究が横断研究またはケースコントロール研究であり、関連性を証明できるようなエビデンスはない。

水銀と自閉症（ASDs）
1 研究では、自閉症の子どもの髪の毛の水銀レベルとコントロールの子どもたちの水銀レベルを比較し、自閉症の子どもで高い数値がでた(p=0.01)。1 研究は、ワクチン中に含まれたチメロサールの暴露を受けた子ども（1994 年 1 月から 2002 年 12 月）と、含まれていないワクチンだった子ども（2002 年 1 月から 2005 年 6 月）の自閉症発症率とスピーチ障害の発症をみた研究で発症率が有意に減少した(p<0.0005 for autism and p<0.005)。

重金属: lead (Pb), cadmium (Cd), aluminum (Al), copper (Cu), chromium (Cr)などと自閉症（ASDs）
1 研究で、歯の重金属の暴露と自閉症の子どもとコントロールの子どもで比較したところ有意な差はみられず自閉症の子どもの方が若干低かった (r=-.28, p=0.08)。
3 研究では、子どもの髪の毛の重金属を比較し、コントロールと比較して自閉症の子どもに有意に高い割合がみられた (p=0.01- p< 0.05)。1 研究では、鉛で高い値がみられ (p=0.002)、自閉症グループの血液と尿中の重金属の値と自閉症の診断スケールスコアが関連していた [R^2 of 0.38-0.47, p<0.0003]。

ADHD
ADHD と重金属は、5 研究中すべてポジティブな相関がみられた。すべての研究で、鉛、水銀、カドミウムが有意に ADHD の症状と相関していた。しかし、ほとんどの研究が横断研究またはケースコントロール研究であり、関連性を証明できるようなエビデンスはない。 低暴露でも神経発達障害を起こすことがあるという研究もある (2).

鉛と ADHD
3 研究中 1 研究で血液中の鉛値と ADHD の症状（スケールのスコア）と有意な相関がみられた。ほかの 2 研究では ADHD の子どもの血液中の鉛濃度が有意にコントロールと比較して高かった [OR 4.1, 95% CI: (1.2-14.0)], [OR 2.52, 95% CI: (1.07-5.92)]。

水銀 (Hg), カドミウム (Cd)と ADHD
1 研究で ADHD グループにおける血中水銀レベルが 29 nmol/L であり、コントロールと比較して 9.69 倍 (95% CI 2.57 – 36.5)交絡因子を調整したあとでも高かった。

学習障害 LDs
4研究すべてが、重金属と学習障害についてポジティブな相関を示した。知的パフォーマンスと重金属のレベルが有意に相関していた。鉛や水銀は神経発達障害を引き起こすことがわかっているため、学習障害にもなんらかの影響がある可能性はあるが、複雑の要因がいくつかあるので一つの原因だけと特定することは難しい。

鉛 (Pd),カドミウム (Cd)と学習障害 LDs
2 研究で、鉛と学習障害との相関を示していた。1 研究では累積した水銀値が医学的リスク要因がある子どもを除外したあとにオッズ比が 2.2 倍から 4.3 倍まで上昇した (p=0.05)。
1 研究では、尿中のカドミウム値が高いグループと低いグループで比較したところ、交絡因子を調整したあと学習障害が 3.21 倍 (95% CI: 1.43, 7.17) 、特別な教育が必要が 3.00 倍 (95% CI: 1.12, 8.01) であった。とくに男児に関連が強かった。

複数の重金属: lead (Pb), cadmium (Cd), aluminum (Al), copper (Cu), chromium (Cr)そのほかと学習障害 LDs
1 研究で、失読症の子どもとコントロールの子どもの髪の毛中のマグネシウムとカドミウムの濃度を比較したところ有意に失読症の子どもが高かった (p<.05)。また、髪の毛中のアルミニウムとカドミウムの 濃度も有意に高かった(p<.05). 鉛、カルシウム、セレニウム、水銀の濃度は差はなかった。

行為障害 CDs
1 横断研究では、血中鉛値のレベルが 高値と低値で比較したところ、DSM-IV CD のクライテリアのオッズ比が 8.64 倍　(95% CI, 1.87-40.04)と高かった。

Tables

Table summary 1

Is allergy a symptom for autism spectrum disorders and related developmental disorders in preschool children?						
Autism Spectrum Disorders (ASDs)						
Study ID	**Study design**	**Country**	**Participants and Sample size**	**Results**	**Outcome measures**	**Comment**
Black 2002 (3)	Nested Case-control	UK	**N=545** Case (n=96) children with autism [mean age (months) 50.2] Control (449) children without autism [mean age (months) 49.6]	Prevalence (9% case, 9% control) OR 1.0 [95% (CI 0.5 to 2.2)]	Chronic inflammation of the gastrointestinal tract	No evidence found that children with autism were more likely than children without autism to have had defined gastrointestinal disorders at any time before their diagnosis of autism
Jyonouchi 2008 (4)	Case-control	US	**N=238** Case (n=26) children with autism with frequent infection and immune insult (ASD test). [7.6yr (2.3-13.4)] Control (n=107) children with autism without frequent infection and immune insult (ASD control). [4.8yr (1.5–17.3)] Control (n=38) children with CRS/ROM [6.8 yrs(1.0–17.8)] Control (n=24) children with food allergies [2.5yr (1.0–13.7)] Control (n=43) normal children [7.0yrs(1.0–13.8)]	These results indicate that atopy is not closely associated with clinical features of the ASD test group. Compared to ASD and normal case controls, more IL-23 with a TLR4 agonist without LPS pre-treatment ($p<0.01$) and less IL-1ß with TLR4 agonists with LPS pre-treatment ($p<0.005$). Lower IL-1ß production with a TLR7/8 agonist in the ASD test group following LPS pre-treatment ($p<0.02$)	Atopy, asthma, food allergy, primary immunodeficiency and innate immune responses were assessed by measuring production of proinflammatory and counter-regulatory cytokines.	Clinical features of the ASD test group were not associated with atopy, asthma, FA, or PID in our study but may be associated with altered TLR responses mediating neuro-immune interactions.

Magalhaes 2009 (5)	Case-control	Brazil	**N=45** Case (n=15) children with Asperger syndrome [13.3 ± 2.9 years old] Control (n=15) atopic children [10.6 ± 3.1 yrs old] Control (n=15) non-atopic children [12.6 ± 3.1 yrs old]	Asperger group, allergic rhinitis was predominant in 53.3% (8/15) of patients, whereas 2/15 had rhinitis plus dermatitis, one showed coexistence of allergic rhinitis and asthma and one patient suffered just from asthma. An increase in eosinophils was observed when Asperger patients were compared to normal controls, ($p<0.003$). The Asperger group had high levels of serum total IgE (802.0± 905.5IU/mL/ $p<0.0017$) when compared to normal group (156.1± 233.4 IU/mL).	Incidence of atopy in Asperger group compared to healthy controls by measuring IgE levels and eosinophil counts.	The present findings may reflect a pattern of response in Asperger patients and implicate that analysis of the allergic response might be important to the approach of these patients
Mostafa 2013 (6)	Cross-sectional study	Egypt	**N=84** Case (n=42) children with autism. [age mean ± SD = 8.12 ± 2.03 yrs] Control (n=42) healthy children [age mean ± SD = 8.69 ± 2.19 yrs]	Autistic children with and without allergic manifestations had significantly higher serum levels of anti-MBP ($P< 0.001$ and $P = 0.001$, respectively) and anti-MAG auto-antibodies ($P< 0.001$ and $P< 0.01$, respectively) than healthy children.	Measurement of serum anti-myelin basic protein (anti-MBP) antibodies and Assessment of serum anti-myelin associated glycoprotein (anti-MAG) antibodies	Autism may be considered as one of the pediatric autoimmune neuropsychiatric disorders. Autistic children had significantly higher serum levels of anti-MBP and anti-MAG auto-antibodies than healthy children, $P < 0.001$ and $P < 0.001$, respectively.
Mostafa 2010 (7)	Case -control	Egypt	**N=60** Case (n=30) Patients with Autism [mean age 8.27±2.66 yrs] Control (n=30) healthy children [mean age 8.3±2.5 yrs]	73.3% deficient of $CD4^{+}CD25^{high}$ T cell count in autistic patients ($p<.001$) compare to healthy control	Measure $CD4^{+}CD25^{high}$ regulatory T cells that have an important role in limiting immune reactions and are essential regulators of self-tolerance.	Deficiency of $CD4^{+}CD25^{high}$ regulatory T cells may contribute to autoimmunity in a subgroup of children with autism. Autistic patients with allergic manifestations (40%) and those with a family hsiotry of autoimmunity (53.3%) had a significant lower frequency of $CD4^{+}CD25^{high}$ regulatory T cells than those without ($P<.01$ and $P<.001$)

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=l8 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)					