B vitamins

- In autistic children, lower levels of vitamins B6, B12 or folate were found with elevated homocysteine, suggesting impaired methylation (Belardo A, J Nutr Biochem, 2019; Kałużna-Czaplińska J, Acta Biochim Pol, 2013; Yektaş Ç, Neuropsychiatr Dis Treat, 2019). Despite this, some studies found elevated vitamin B12 (Hope S, FASEB J, 2020).
- Although folic acid supplementation is recommended prior to and during pregnancy to prevent neural tube defects, there is now concern that rising serum levels of unmetabolised folic acid has become a risk factor for autism. Overall, studies are inconclusive. (Wiens D, Brain Sci, 2017; Castro K, Nutr Neurosci, 2016)
- Nevertheless, 800 µg/day folic acid for 3 months improved sociability, cognitive verbal/preverbal receptive language and affective expression and communication (Sun C, Nutrients, 2016).
- A study giving 75 µg/kg vitamin B12 to autistic children by injection every 3 days for 8 weeks induced significant improvement in autism scores (Hendren RL, J Child Adolesc Psychopharmacol, 2016). An earlier study found no improvement, except in a sub-group of children for whom the B12 had increased plasma glutathione levels (Bertoglio K, J Altern Complement Med, 2010).
- Autistic children given 6 mg/kg/day magnesium and 0.6 mg/kg/day vitamin B6 for 6 months significantly improved social interactions, communication, stereotyped restricted behaviour and abnormal/delayed functioning in a majority of the children (Mousain-Bosc M, Magnes Res, 2006). A 2005 Cochrane Review found inconclusive results (Nye C, Cochrane Database Syst Rev, 2005).

L-carnitine

- A 2019 review found that results from 3 human trials suggested that carnitine administration could be helpful in treating symptoms in non-syndromic ASD and was particularly useful for improving intellectual disability and muscular strength. Side effects observed with a dose of 200 mg/kg/day consisted of gastrointestinal symptoms and a strong, heavy skin odour but doses of 50-100 mg/kg/day were generally well tolerated. (Malaguarnera M, Molecules, 2019)
- A carnitine, CoQ10 and α-lipoic acid combination for 3 months reduced the abnormal Complex I to Complex IV ratio and improved several behaviour scales (Delhey LM, J Clin Med, 2017).
- ASDs have shown a close association with impaired lipid metabolism. Reduced carnitine availability can result in decreased long-chain fatty acid β-oxidation in neural stem cells of the developing mammalian brain. In Chinese pre-school children with ASD blood levels of free carnitine and other bound carnitines were significantly lower than those in the control group. The changes in the acyl-carnitine spectrum indicate potential mitochondrial dysfunction and abnormal fatty acid metabolism. (Bankaitis VA, J Biol Chem, 2019; Lv QQ, Psychiatry Res, 2018)
- Between 10% and 20% of people with autism seem to have L-carnitine metabolism disorders, some of which may be genetic (Demarquoy C, World J Biol Chem, 2019; Beaudet AL, Bioessays, 2017; Longo N, Ann Nutr Metab, 2016).

L-carnosine

- In autistic children, 800 mg/day L-carnosine for 2 months induced significant improvements on 2 autism rating scales (Chez MG, J Child Neurol, 2002).
- In children with ASDs, 800 mg/day L-carnosine in addition to risperidone, there was no effect on irritability, lethargy/social withdrawal, stereotypic behaviour or inappropriate speech but there was a significant improvement in hyperactivity/noncompliance over and above the effect of risperidone alone (Hajizadeh-Zaker R, J Child Adolesc Psychopharmacol, 2018).
- In a study of autistic children with sleep disorders, 500 mg/day carnosine for 2 months had no effect on autism severity but significantly reduced sleep duration, parasomnias and total sleep disorders score (Mehrazad-Saber Z, Basic Clin Pharmacol Toxicol, 2018).

Magnesium

- Autistic children given 6 mg/kg/day magnesium and 0.6 mg/kg/day vitamin B6 for 6 months significantly improved social interactions, communication, stereotyped restricted behaviour and abnormal/delayed functioning in a majority of the children (Mousain-Bosc M, Magnes Res, 2006). An earlier Cochrane Review found inconclusive results (Nye C, Cochrane Database Syst Rev, 2005).
- In a study of autistic children, blood magnesium levels were significantly decreased (Lakshmi Priya MD, Biol Trace Elem Res, 2011; Strambi M, Biol Trace Elem Res, 2006).

Melatonin

- A 2020 RCT found that autistic children given 2 mg, 5 mg or 10 mg nightly for up to 104 weeks showed that improvements in child sleep disturbance and caregiver satisfaction with child sleep patterns, quality of sleep and quality of life were maintained throughout the trial but then declined once supplementation was stopped (Malow BA, J Am Acad Child Adolesc Psychiatry, 2020). A 2019 RCT showed that the improvement in the children's externalising (but not internalising behaviour) meant that caregivers' quality of life had also improved (Schroder CM, J Autism Dev Disord, 2019).
- A 2020 systematic review has confirmed the improvement in sleep duration and sleep latency onset (Parvataneni T, Cureus, 2020).
- A 2011 meta-analysis found that all 9 studies surveyed reported at least 1 melatonin abnormality, with below average physiological levels of melatonin and/metabolites and a positive correlation between these levels and autistic behaviour, while other studies reported gene abnormalities for melatonin production or receptor function. (Rossignol DA, Dev Med Child Neurol, 2011)
- Early morning melatonin level and pineal gland volume were found to be lower in autistic subjects (Maruani AMaruani A, Front Psychiatry, 2019). A further study found lower melatonin levels in mothers of autistic children (Braam W, Res Dev Disabil, 2018).

Omega 3 (ω3) fatty acids

- A 2020 systematic review of RCTs of PUFAs in autism, dosage ranging from 200 mg/day to 1540 mg/day, found that they could reduce anxiety but might worsen quality of sleep. There was no effect on aggression, hyperactivity, adaptive functioning, irritability, restricted and repetitive interests and behaviours and communication. (De Crescenzo F, Health Qual Life Outcomes, 2020)
- Similarly, a 2019 meta-analysis found that omega-3s were efficacious for some autism symptoms but evidence was insufficient to support a recommendation for supplementation (Fraguas D, Pediatrics, 2019).
- Yet a study of ω3 fats (962mg/day and 1155mg/day for children and adolescents, respectively) showed significantly improved erythrocyte membrane ω6/ω3 ratio (Parellada M, Eur Neuropsychopharmacol, 2017).
- Supplementing ω3 with ω6 fats in pre-term toddlers improved gesture use for communication (Sheppard KW, J Autism Dev Disord, 2017). A combination of ω3 fats and arachidonic acid (important for neuronal maturation) improved social interaction (Yui K, J Clin Psychopharmacol, 2012).
- A trial of vitamin D (2000 IU/day) and omega-3 (722 mg/day) for 12 months showed a reduction in irritability and hyperactivity, but this was not seen with omega-3 alone (Mazahery H, J Steroid Biochem Mol Biol, 2019).
- A 2017 meta-analysis found that autistic children had lower blood levels of DHA, EPA and arachidonic acid and higher total omega 6 fats (Mazahery H, Nutrients, 2017), while a 2019 meta-analysis found that autistic children consumed more polyunsaturated fat overall but less omega-3 fats (Esteban-Figuerola P, Autism, 2019).

Sulphoraphane

- A 2020 systematic review of 5 clinical trials found that sulphoraphane use showed a significant positive correlation with improved ASD behaviour and cognitive function (McGuinness G, EXCLI J. 2020).
- Autistic children taking risperidone and were also given 50 µmol (≤45 kg) or 100 µmol (>45 kg) sulphoraphane showed greater improvements in irritability score and hyperactivity/noncompliance score but no difference was seen in other scores (Momtazmanesh S, Psychiatry Clin Neurosci, 2020).
- In an RCT of males aged 13-27 given 50-150 µmol sulphoraphane for 18 weeks there was substantial improvement in behaviour scores, social interaction, and verbal communication (Singh K, Proc Natl Acad Sci USA, 2014). Follow-up after some years showed that many caregivers used sulphoraphane supplements in order to maintain improvements (Lynch R, Glob Adv Health Med, 2017).
- An open label study of sulphoraphane found that after 12 weeks there was significant improvement in social responsiveness but not in other measures (Bent S, Mol Autism, 2018).
- Mouse studies show that sulphoraphane can reduce autistic behaviour and increase social interaction and correct Th17 immune dysfunction and brain oxidant-antioxidant imbalance (Nadeem A, Behav Brain Res, 2019).
- *In vitro* studies show that autistic children have decreased induction of Nrf2 after stimulation; sulphoraphane can activate Nrf2, and hence upregulate the antioxidant response element (ARE), and decrease inflammation and nitrative stress through reduction in NF-κB signalling (Nadeem A, Psychoneuroendocrinology, 2020; Klomparens EA, Brain Circ, 2019). In peripheral blood mononuclear cells from autistic patients, sulphoraphane can reduce oxidative stress, upregulate heat shock proteins and reduce immune dysregulation and inflammation (Liu G, Sci Rep, 2020).
- It may be the upregulation of heat shock proteins (HSPs) in fever to allow the correct folding of misfolded proteins that is responsible for the phenomenon of temporary ‘recovery’ from autism in fever. Sulforaphane can induce cellular stress responses with a similar effect as the upregulation of heat shock proteins when ASD children develop a fever, which is associated with improved cognition and behaviour (Calabrese V, J Neurosci Res, 2016; Singh K, CNS Neurol Disord Drug Targets, 2016).

Vitamin A

- After vitamin A supplementation, there was a significant improvement in autism symptoms and elevated serum 5-HT (serotonin) levels were decreased (Guo M, Brain Res Bull, 2018).
- In autistic Chinese children, there was no difference in autism severity scores after 6 months of intervention, but the proportion of bacteroidetes in gut bacteria increased (Liu J, BMC Microbiol, 2017).
- Serum retinol levels and dietary intake of vitamin A in children with ASD were significantly lower than in control children (Guo M, Brain Res Bull, 2018; Guo M, Nutr Neurosci, 2018; Liu X, Nutrients, 2016; Sun C, J Nutr Sci, 2013); however, another study found that serum vitamin A did not differ between autistic and normal children (Sweetman DU, Child Care Health Dev, 2019).
- Autistic children with gastrointestinal symptoms also had significantly lower serum retinol compared to autistic children without gastrointestinal symptoms; serum retinol correlated with many autism severity scores (Cheng B, Pediatr Res, 2020;).

Vitamin D3

- An RCT of 2000 IU/day vitamin D for 12 months found a significant reduction in irritability and hyperactivity; a similar study by the same team had found no improvement in ASD core symptoms (Mazahery H, J Steroid Biochem Mol Biol, 2019; Mazahery H, J Autism Dev Disord, 2019).
- Autistic children given 2000 IU/day for 20 weeks showed no difference in stereotypic behaviour but there was an improvement in self care (Kerley CP, Arch Dis Child, 2017).
- Autistic children with 25(OH)D <75nmol/l participated in an open label study of 300 IU/kg/day vitamin D3 (not to exceed 5000 IU/day) for 3 months; the children showed significantly improved autism severity scores, particularly relating to behaviour, stereotypy, eye contact and attention span (Saad K, Nutr Neurosci, 2016).
- A meta-analysis of 11 studies found that levels of serum 25(OH)D in ASD children were significantly lower than in controls; serum 25(OH)D levels correlated with ASD severity (Wang T, Eur Child Adolesc Psychiatry, 2016; Saad K, Nutr Neurosci, 2016). A later prospective study found that neonatal 25(OH)D was associated with significantly reduced ASD only in females and non-Hispanic white children (Schmidt RJ, Autism Res, 2019), although another found no correlation between newborn vitamin D levels and ASD development (Windham GC, Autism Res, 2019).
- A meta-analysis of studies of prenatal 25(OH)D levels showed that higher levels were associated with improved cognitive development and reduced risk of autism-related traits later in life but did not correlate with language development and behavioural difficulties (García-Serna AM, Mol Psychiatry, 2019).
- Vitamin D deficiency in early life can alter brain development, dysregulate neurotransmitter balance, decrease body and brain antioxidant status and alter the immune system in ways resembling pathological features commonly seen in ASD (Alzghoul L, Curr Pharm Des, 2019). Serum 25(OH)D levels also inversely correlated with serum levels of anti-myelin-associated glycoprotein auto-antibodies, which were found in 70% of autistic children, and indicate autoimmunity (Mostafa GA, J Neuroinflammation, 2012).

Zinc

- In autistic children, supplementation of zinc for 3 months (daily dosage = body weight in kg plus 15-20 mg) increased cognitive-motor performance and expression of metallothionine 1 and lowered serum levels of copper (Meguid NA, Acta Neurol Belg, 2019).
- There was no difference in serum zinc levels between autistic children and healthy controls (Sweetman DU, Child Care Health Dev, 2019; Saldanha Tschinkel PF, Biomed Pharmacother, 2018). However, hair zinc levels were significantly lower in autistic children (Yasuda H, Sci Rep, 2011).
- However, altered zinc-copper rhythmicity was found to precede the emergence of ASD, while measures of metal rhythmicity can distinguish ASD cases from controls (Curtin P, Sci Adv, 2018). Furthermore, the copper/zinc ratio was significantly higher in ASD children compared to controls and correlated positively with ASD symptoms severity (Crăciun EC, Metab Brain Dis, 2016; Li SO, Neuroreport, 2014).

Luteolin

- ASDs are associated with neuroinflammation (microglial activation) and elevated pro-inflammatory cytokines. After 26 weeks of treatment with luteolin, the cytokines were significantly reduced and this was associated with behavioural improvements. (Tsilioni I, Transl Psychiatry, 2015)
- 2 Greek studies showed that a mixture of luteolin with quercetin and rutin in a liposomal formulation of olive kernel oil in children with ASDs for at least 4 months improved adaptive functioning and overall behaviour. There was also improvement in gastrointestinal and allergy symptoms in about 75% of children, eye contact and attention improved in 50%, social interaction in 25% and resumption of speech in 10%. (Taliou A, Clin Ther, 2013; Theoharides TC, Int J Immunopathol Pharmacol, 2012) Theoharides speculated that autism could be due to immune involvement, specifically mast cell activation syndrome (MCAS); the combination of luteolin, quercetin and rutin have been shown to help MCAS patients.
- A combination of luteolin and the fatty acid amide palmitoylethanolamide (PEA) improved social and non-social behaviours in a mouse model of autism (Bertolino B, CNS Neurosci Ther, 2017).

Resveratrol

- In autistic children treated with risperidone, 500mg/day resveratrol for 10 weeks improved hyperactivity and non-compliance but there was no difference in other outcome measures (Hendouei F, J Clin Pharm Ther, 2020).
- In animal models of autism, resveratrol improved the core symptoms of social impairment and stereotypic behaviour, as well as hyperactivity, anxiety and cognitive function (Malaguarnera M, Antioxidants, 2020; Bhandari R, Neurochem Int, 2017; Bambini-Junior V, Neurosci Lett, 2014).
- The mechanism underlying these improvements appears to include normalisation of immune function, reduction in neuroinflammation and oxidative stress and increased expression of cortical GABA neurons. Resveratrol can also improve the impaired mitochondrial fatty acid oxidation seen in ASD and ameliorates prenatal progestin exposure-induced ASD through ERβ activation. (Malaguarnera M, Antioxidants, 2020; Barone R, Int J Mol Sci, 2019; Xie W, Mol Autism, 2018; Ahmad SF, Eur J Pharmacol, 2018; Ahmad SF, Neuromolecular Med, 2018; Bakheet SA, Mol Cell Neurosci, 2016; Bakheet SA, Mol Neurobiol, 2017)