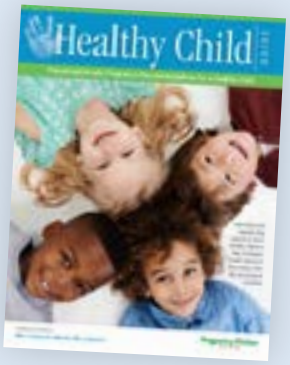
Neurological Health Foundation

Pregnancy Kitchen

The Science Behind *The Healthy Child Guide*



Introduction In a stunning report in 2016, the CDC stated that their National Survey of Children's Health "found that 1 out of 7 U.S. children aged 2 to 8 years were reported to have a diagnosed mental, behavioral or developmental disorder." This rate of over 15% does not even count serious physical health disorders such as asthma, cancer, muscular dystrophy, life-threatening food allergies, obesity, and other serious conditions. To learn more on this, click here: http://www.cdc.gov/ncbddd/childdevelopment/features/key-finding-factors-mental-behavioral-developmental-early-childhood.html

The Healthy Child Guide was written by the Scientific Advisory Board of the Neurological Health Foundation to provide an easy-to-read guide for parents who wish to reduce pregnancy/birth complications and improve the chances of having a healthy child. The recommendations in *The Healthy Child Guide* are based on a large body of scientific research as well as the knowledge and experience of the physicians, researchers, scientists and clinicians on the NHF Scientific Advisory Board. The purpose of this document, "*The Science Behind The Healthy Child Guide*," is to provide interested parents and medical professionals with a summary of some of the most relevant and current medical and scientific research behind the recommendations of the Guide.

This document is divided into 17 major recommendations. At the beginning of each recommendation is a brief summary of the research studies, followed by a sampling of some of the most relevant studies (for some recommendations there have been dozens or even hundreds of studies, so we only present a few here). Each study starts with a brief conclusion, followed by a short summary of the study, and then the citation and a link to the full research study. We hope you find this format easy to navigate as you dive deeper into the science supporting *The Healthy Child Guide*.

The 17 Key Research Areas Include:

1. Prenatal Vitamin at Conception or Earlier
2. Vitamin D
3. Iron
4. Healthy Diet – Rich in Vegetables, Fruit, Protein
5. Organic Foods
6. Avoid GMO Foods
7. Consume Clean Seafood
8. Probiotics
9. Pure Water
10. Clean Air
11. Reduce Exposure to Toxic Chemicals and Toxic Metals
12. Avoid Endocrine Disruptors
13. Prenatal Care and Medical Testing
14. Exercise
15. Waiting Between Pregnancies
16. Reducing Stress During Pregnancy
17. Maintaining Optimal Weight Throughout Pregnancy

Research is an ongoing process. We will continue to update this document as well as *The Healthy Child Guide* as we learn more.

Sincerely,

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Richard Frye, M.D., Ph.D.
Member, NHF Scientific Advisory Board

on behalf of the Neurological Health Foundation and its Scientific Advisory Board

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Referencing/ Copyright Note:

The following sections contain summaries of abstracts either in their original wording or slightly re-written to make them more easily understood. In some cases the original wording from the original abstracts has been used directly.

Neurological Health Foundation
BEYOND ORGANIC

Pregnancy Kitchen

The Science Behind *The Healthy Child Guide*

❶ Prenatal Nutritional Supplements at Conception or Earlier

Summary: *We recommend taking prenatal supplements starting several months before conception. Prenatal supplement use has been shown to greatly decrease the risk of autism spectrum disorder (if started first month of pregnancy), neural tube defects, preterm birth, low birthweight, preeclampsia (toxemia), and may reduce the risk of other birth defects and pregnancy/birth complications.*

Scientific Evidence

A. Folic acid intake during the first month of pregnancy is associated with reduced risk of having a child with autism. A study in California evaluated 429 mothers of children with autism and 278 mothers of children with typical development. A mean daily folic acid intake of ≥600 mcg (compared with <600 mcg) during first month of pregnancy was associated with reduced risk for autism spectrum disorders (ASD); risk was estimated to decrease with increased folic acid supplementation. The association between folic acid and reduced ASD risk was strongest for mothers and children with the gene variant that causes impaired conversion of folic acid to active folate forms (MTHFR 677C>T).

Schmidt, R., Tancredi, D.J., Ozonoff, S., et al. Maternal periconceptional folic acid intake and risk of autism spectrum disorders and developmental delay in the CHARGE (Childhood Autism Risks from Genetics and Environment) case-control study. *American Journal of Clinical Nutrition.* 2012; 96 (1) 80-89.

http://ajcn.nutrition.org/content/96/1/80.full.pdf+html

B. Use of prenatal folic acid supplements around the time of conception was associated with a 39% lower risk of autistic disorder. A longitudinal study of over 100,000 women in Norway recruited at 18 weeks gestation compared children's outcomes based on maternal use of folic acid from 4 weeks before to 8 weeks after the start of pregnancy. Follow-up data from 87,456 children found that 270 children had been diagnosed with ASDs. In children whose mothers took folic acid 4 weeks prior to conception, 0.10% had autistic disorder, compared with 0.21% in those unexposed to folic acid.

Surén P, Roth C, Bresnahan M, et al. Association Between Maternal Use of Folic Acid Supplements and Risk of Autism Spectrum Disorders in Children. *JAMA.* 2013; 309(6): 570-577.

http://www.ncbi.nlm.nih.gov/pubmed/23403681/

C. Prenatal use of folic acid significantly reduced the recurrence of neural tube defects (NTDs) in women with a history of pregnancy affected by NTDs. In this Cochrane review the authors searched studies evaluating the effect of periconceptional folate supplementation alone, or in combination with other vitamins and minerals. This review of five trials, involving 6105 women (1949 with a history of a pregnancy affected by a NTDs and 4156 with no history of NTDs), shows the protective effect of daily folic acid supplementation in doses ranging from 0.36 mg (360 µg) to 4 mg (4000 µg) a day before conception and up to 12 weeks of pregnancy, for preventing the recurrence of these diseases.

De-Regil LM, Fernández-Gaxiola AC, Dowswell T, Peña-Rosas JP. Effects and safety of periconceptional folate supplementation for preventing birth defects. *Cochrane Database of Systematic Reviews* 2010, Issue 10. Art. No.: CD007950.

http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD007950.pub2/epd

D. Pre-conception use of folic acid oral supplementation or dietary folate intake combined with a multivitamin/micronutrient supplement was associated with a decrease in neural tube defects and perhaps a decrease in other birth defects and obstetrical complications. This was the conclusion from an extensive review of published literature from 1985 to June 2014 (PubMed, Medlien, CINAHL, Cochrane Library 2011), on pre-conception folic acid and multivitamin supplementation for the primary and secondary prevention of neural tube defects and other folic acid-sensitive congenital anomalies.

Wilson RD, Audibert F, et al. Pre-conception Folic Acid and Multivitamin Supplementation for the Primary and Secondary Prevention of Neural Tube Defects and Other Folic Acid-Sensitive Congenital Anomalies. *J Obstet Gynaecol Can.* 2015 Jun; 37 (6):534-52.

http://sogc.org/wp-content/uploads/2015/06/gui324CPG1505E.pdf

E. Folic acid, alone or in combination with vitamins and minerals, prevents neural tube defects (NTD). This is a review of 5 research studies involving 7391 women (2033 with an NTD affected pregnancy and 5358 without an NTD history) who were compared based upon variations including folate supplementation vs no intervention, placebo or other nutrients, and supplementation with folate and other micronutrients vs other micronutrients without folate.

Luz Maria De-Regil, Juan Pable Pena-Rosas, Ana C Fernandez-Gaxiola, Pura Rayco-Solon. Editorial Group: Cochrane Pregnancy and Childbirth Group. Effects and safety of periconceptional oral folate supplementation for preventing birth defects. Published on line: 14, Dec 2015. Assessed as up-to-date 31 Aug 2015.

http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD007950.pub3/epdf/standard

F. Existing data show that the majority of pregnant (and presumably lactating) women are not achieving the target intake levels of choline, a vital micronutrient, and because choline is not found in most varieties of prenatal vitamins, increased consumption of choline-rich foods may be needed. Choline serves as the starting material for several important metabolites that play key roles in fetal development, particularly the brain. An adequate intake level of 450 and 550 mg/day was established for women with during pregnancy and lactation, respectively. The importance of choline in human development is supported by observations that a human fetus receives a large supply of choline during gestation; pregnancy causes depletion of choline pools in the livers of rats consuming a normal diet; human neonates are born with blood levels that are three times higher than maternal blood concentrations; and large amounts of choline are present in human milk. The development of the central nervous system is particularly sensitive to choline availability with evidence of effects on neural tube closure and cognition.

Caudill, M. A. (2010). Pre-and postnatal health: evidence of increased choline needs. *Journal of the American Dietetic Association*, 110(8), 1198-1206.

http://www.andjrnl.org/article/S0002-8223(10)00529-8/abstract

G. In low income, urban women, use of prenatal multivitamin/mineral supplements may have the potential to diminish infant morbidity and mortality. In a study of prenatal supplement use and preterm delivery in over 1000 women, supplement use starting in the first or second trimester was associated with approximately a twofold reduction in risk of preterm delivery. Risk of very preterm delivery (< 33 weeks' gestation) was reduced more than fourfold for first trimester users and approximately twofold when use dated from the second trimester. Risk of low birth weight was reduced approximately twofold with supplement use during the first and second trimester.

Scholl TO, Hediger ML, et al. Use of multivitamin/mineral prenatal supplements: influence on the outcome of pregnancy. *American Journal of Epidemiology*. 1997; 146 (2): 134-141.

http://aje.oxfordjournals.org/content/146/2/134.long

H. Pregnant women of healthy weight who took a multivitamin had a 71% reduction in preeclampsia risk compared with overweight women who did not take vitamins. 1,835 pregnant women were enrolled in the Pregnancy Exposures and Preeclampsia Prevention Study at less than 16 weeks' gestation and asked whether they regularly used multivitamins or prenatal vitamins in the past 6 months. Regular use of multivitamins was associated with a 45% reduction in preeclampsia risk compared with non-use. Prepregnancy overweight modified this effect.

Bodnar LM, Tang G, et al. Periconceptional multivitamin use reduces the risk of preeclampsia. *American Journal of Epidemiology*. 2006; 164 (5):470-477.

http://aje.oxfordjournals.org/content/164/5/470.long

I. Review of benefits and risks of various nutrient supplements during pregnancy, included folic acid, omega-3 fatty acids, vitamin D, iron, vitamin A, vitamin E, iodine, multivitamin / micronutrient supplements. Folic acid decreases the incidence of neural tube defects and may be beneficial for preventing other congenital anomalies such as cleft lip/palate and heart defects. Omega-3 fatty acids (EPA and DHA) affect fetal brain development. In a study of 2,000 women receiving fish oil capsules with 800 mg of DHA vs placebo vegetable oil, there was a lower rate of preterm birth and a smaller incidence of low birth weight in the experimental group. Other studies found significantly longer gestation along with a lower risk of preterm delivery. For omega-3 fatty acids, the risk of supplementation is low. Vitamin D supplementation in pregnancy has demonstrated significantly increased vitamin D level in the mother, however improved clinical outcomes have not been observed. The current recommendations for vitamin D intake are directed toward the maintenance of bone health in the mother, fetus, and newborn. Adequate elemental iron intake is important in pregnancy to maintain the increase in red blood cell mass and meet oxygen requirements of the uteroplacental circulation. Vitamin C is noted to improve iron absorption. Maternal anemia has been associated with low birth weight, preterm delivery, perinatal mortality and maternal depression. Iron can increase constipation and excess iron has been associated with gestational diabetes. Vitamin A excess (over 10,000 IU/day) is associated with

fetal malformations, yet it is necessary to support healthy vision and immune function, so prenatal vitamins tend to include 4000 to 5000 IU of vitamin A. Vitamin E supplementation at 400 IU and vitamin C at 1000 mg have been linked to premature rupture of membranes. Multivitamin use has been associated with a decreased risk of Small Gestational Age infants in non-overweight women, black women, and low-income urban women. The effect on preterm birth is mixed with some studies showing a decreased risk. The observational studies are inherently limited. Vitamin and mineral supplements do not replace a healthy diet.

Sfakianaki AK, Prenatal vitamins: A review of the literature on benefits and risks of various nutrient supplements. Jan 31, 2013

http://formularyjournal.modernmedicine.com/formulary-journal/RC/clinical/clinical-pharmacology/prenatal-vitamins-review-literature-benefits-a

J. Medline and Cochrane review of maternal supplementation of DHA, vitamin D, folic acid or iodine supplementation during pregnancy and/or lactation. Maternal DHA intake during pregnancy and/or lactation can prolong high risk pregnancies, increase birth weight, head circumference and birth length, and can enhance visual acuity, hand and eye coordination, attention, problem solving and information processing in the infant. Vitamin D helps maintain pregnancy and promotes normal skeletal and brain development. Folic acid is necessary for normal fetal spine, brain and skull development. Iodine is essential for thyroid hormone production and necessary for normal brain and nervous system development during gestation, which impacts childhood function.

Morse, N. L. (2012). Benefits of docosahexaenoic acid, folic acid, vitamin D and iodine on foetal and infant brain development and function following maternal supplementation during pregnancy and lactation. *Nutrients*, 4(7), 799-840.

http://www.mdpi.com/2072-6643/4/7/799/htm

K. Deficiencies of copper and zinc increase the risk of preeclampsia. This study assessed maternal serum copper and zinc levels in preeclampsia to determine the role of trace element disorder in the etiology of preeclampsia. Preeclampsia increases the risk for premature delivery and presents as hypertension, protein in the urine and edema. Sixty participants aged 18 to 39 years were diagnosed with preeclampsia after the twentieth week of pregnancy. Thirty women with normal blood pressure and no pregnancy complications served as the control group. Serum copper and zinc levels were measured and the data was compared between the women with preeclampsia and the normotensive pregnant women. In those with preeclampsia, low serum zinc (hypozincemia) was found in 13% and low serum copper (hypocupremia) was found in 38%. The study researchers concluded that trace element disorders may be involve in the etiology of preeclampsia.

Ferdousi S, Akhtar S, Begum S. Copper and zinc status in patients with preeclampsia in Bangladesh. *Mymensingh Medical Journal*. 2015 Oct (4):780-6.

http://europepmc.org/abstract/med/26620020

L. Serum zinc levels in preeclampsia are significantly lower than in healthy pregnancy controls. A systematic literature search was performed for relevant articles which were limited to those in English from January 1990 to April 2015. Seventeen observational studies were included. In 14 studies, preeclampsia patients had lower serum zinc levels. Results from this meta-analysis indicate that, compared with healthy pregnancy controls, preeclampsia patients had lower serum zinc levels. The authors concluded that a moderate amount of zinc supplementation during pregnancy is advocated to reduce the incidence of preeclampsia.

Ma Y, Shen X, Zhang D. The relationship between serum zinc levels and preeclampsia: a meta-analysis. *Nutrients*. 2015 Sep 15;7 (9):7806-20.

http://www.mdpi.com/2072-6643/7/9/5366/htm

M. Total antioxidant status is significantly lower in women who have had a miscarriage. During pregnancy, there is an important oxidant/anti-oxidant balance. This study evaluated the total antioxidant status, glutathione peroxidase activity, and levels of selenium, zinc, copper and manganese in women who have had a miscarriage. The study group consisted of 83 women who had miscarriages. The control group included 35 women in the first trimester of pregnancy and 35 pregnant women after childbirth. Compared with women in the first trimester, women who experienced a miscarriage had significantly lower total antioxidant status and copper levels, and higher manganese levels. The content of selenium, copper and manganese in placental tissue in patients who have had a miscarriage was significantly higher, while zinc content was lower than in pregnant women at full-term delivery. The authors concluded that total antioxidant status is significantly lower in miscarriage and that low zinc and high manganese in the biological material may be indicative of miscarriage.

Omeljaniuk, W. J., Socha, K., Borawska, M. H., Charkiewicz, A. E., Laudanski, T., Kulikowski, M., & Kobylec, E. (2015). Antioxidant status in women who have had a miscarriage. *Advances in Medical Sciences,* 60(2), 329-334.

http://www.sciencedirect.com/science/article/pii/S1896112615000358

❷ Vitamin D

Summary: *We recommend testing levels of vitamin D and supplementing if marginal or low (below 50 nmol/l). Low levels of vitamin D in mothers are associated with significantly greater risk of preeclampsia, C-section birth, and pre-term births, and with a greater incidence of eczema, schizophrenia and autism spectrum disorder in their children. Also, supplementation of infants with vitamin D was shown to decrease the risk of type-1 diabetes.*

Scientific Evidence

A. Low prenatal vitamin D may act as a risk factor for ASD. This study of 58 sibling pairs, one with ASD and one typically developing examined Vitamin D levels at birth using dried blood samples given during routine metabolic screening. The siblings with ASD had significantly lower vitamin D levels as compared with their siblings. The difference was most likely accounted for by a difference in season of birth between ASD and non-ASD siblings since the mean 25(OH)D levels differed with similar effect size between the sibling pairs born during winter and summer, respectively. All children with African/Middle East background, both the children with ASD and their non-ASD siblings, had vitamin D deficiency.

Fernell, E., Bejerot, S., Westerlund, J., Miniscalco, C., Simila, H., Eyles, D., & Humble, M. B. (2015). Autism spectrum disorder and low vitamin D at birth: a sibling control study. *Molecular Autism,* 6(1), 3.

http://www.biomedcentral.com/content/pdf/2040-2392-6-3.pdf

B. Maternal vitamin D insufficiency during pregnancy demonstrated an almost twofold increase in offspring with language impairment. Serum 25(OH)-vitamin D concentrations of 743 Caucasian women in Perth, Western Australia were measured at 18 weeks pregnancy and grouped into quartiles. Offspring behavior was measured with the Child Behavior Checklist and receptive language was assessed with the Peabody Picture Vocabulary Test—Revised. Analyses revealed no significant associations between maternal vitamin D serum quartiles and offspring behavioral/emotional problems at any age. In contrast, there were significant trends between quartiles of maternal vitamin D levels and language impairment at 5 and 10 years of age. Analysis found that the risk of women with vitamin D insufficiency (≤46 nmol/L) during pregnancy having a child with clinically significant language difficulties was increased close to twofold compared with women with vitamin D levels >70 nmol/L. Maternal vitamin D supplementation during pregnancy may reduce the risk of developmental language difficulties among their children.

Whitehouse, A. J., Holt, B. J., Serralha, M., Holt, P. G., Kusel, M. M., & Hart, P. H. (2012). Maternal serum vitamin D levels during pregnancy and offspring neurocognitive development. *Pediatrics*, 129(3), 485-493.

http://pediatrics.aappublications.org/content/129/3/485.short

C. Low levels of vitamin D serum concentrations double the risk of preeclampsia. Subjects included pregnant women with singleton pregnancies who developed preeclampsia (n = 55) or did not develop preeclampsia (n = 219) and their vitamin D serum concentrations. Adjusted serum 25(OH) D concentrations in early pregnancy were lower in women who subsequently developed preeclampsia compared with controls. After confounder adjustment, decline in 25(OH)D concentration doubled the risk of preeclampsia. Newborns of preeclamptic mothers were twice as likely as control newborns to have 25(OH)D less than 37.5 nmol/liter.

Bodnar, L. M., Catov, J. M., Simhan, H. N., Holick, M. F., Powers, R. W., & Roberts, J. M. (2007). Maternal Vitamin D Deficiency Increases the Risk of Preeclampsia. *The Journal of Clinical Endocrinology and Metabolism*, 92(9), 3517–3522.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4288954

D. Vitamin D deficiency was associated with increased odds of primary cesarean section. This study of vitamin D deficiency in 253 women found that 28% of women with serum 25(OH)D less than 37.5 nmol/liter had a cesarean section, compared with only 14% of women with 25(OH)D 37.5nmol/liter or greater. After an analysis controlling for various confounders, women with 25(OH)D less than 37.5 nmol/liter were almost 4 times as likely to have a cesarean than women with 25(OH)D 37.5 nmol/liter or greater.

Merewood, A., Mehta, S. D., Chen, T. C., Bauchner, H., & Holick, M. F. (2009). Association between Vitamin D Deficiency and Primary Cesarean Section. *The Journal of Clinical Endocrinology and Metabolism*, 94(3), 940–945.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2681281/

E. Maternal vitamin D status closest to delivery date was more significantly associated with preterm birth, suggesting that later intervention as a rescue treatment may positively impact

the risk of preterm delivery. The datasets from NICHD (n = 333) and Thrasher Research Fund (n = 154) vitamin D supplementation pregnancy studies were combined. The results of this analysis were that 25(OH)D values closer to delivery were more strongly correlated with gestational age at delivery than values in the first two trimesters. A serum concentration of 100 nmol/L (40 ng/mL) in the 3rd trimester was associated with a 47% reduction in preterm births.

Wagner, C. L., Baggerly, C., McDonnell, S. L., Baggerly, L., Hamilton, S. A., Winkler, J., & Hollis, B. W. (2015). Post-hoc comparison of vitamin D status at three time points during pregnancy demonstrates lower risk of preterm birth with higher vitamin D closer to delivery. *The Journal of Steroid Biochemistry and Molecular Biology*, 148, 256-260.

http://www.ncbi.nlm.nih.gov/pubmed/25448734

F. Vitamin D supplementation during the first year of life is associated with a reduced risk of schizophrenia in males. Subjects from the Northern Finland 1966 Birth Cohort (n=9,114) were evaluated for their Vitamin D supplementation in the first year, and presence of schizophrenia, psychotic disorders other than schizophrenia, and nonpsychotic disorders diagnosed by age 31 years. In males, the use of either irregular or regular vitamin D supplements of at least 2000 IU was associated with a reduced risk of schizophrenia compared with no supplementation. There were no significant associations between either the frequency or dose of vitamin D supplements and (a) schizophrenia in females, nor with (b) nonpsychotic disorder or psychotic disorders other than schizophrenia in either males or females.

McGrath J, Saari K, Hakko H, et al. Vitamin D supplementation during the first year of life and risk of schizophrenia: a Finnish birth-cohort study. *Schizophr Res.* 2004; 67:237 245.

http://dx.doi.org/10.1016/j.schres.2003.08.005

G. Infants supplemented with Vitamin D in the first year of life had a significantly lower risk of developing type 1 diabetes. Meta-analysis of data from 5 case-control studies showed that the risk of type 1 diabetes was significantly reduced by 29% in infants who were supplemented with vitamin D compared to those who were not supplemented. There was also some evidence of a dose-response effect, with those using higher amounts of vitamin D being at lower risk of developing type 1 diabetes. Finally, there was a suggestion that the timing of supplementation, from 7-12 months as opposed to 0-6 months might also be important for the subsequent development of type 1 diabetes.

C S Zipitis, A K Akobeng. Vitamin D supplementation in early childhood and risk of type 1 diabetes: a systematic review and meta-analysis. *Arch Dis Child* 2008; 93:512-517.

http://adc.bmj.com/content/93/6/512.long

H. Infants born to parents living farther from the equator, therefore getting less natural Vitamin D, were 9 times more likely to have multiple food allergies than infants born to parents living overseas. There is some evidence that infants born farthest from the equator have higher rates of allergies, suggesting a possible link to Vitamin D insufficiency. Blood samples and skin prick tests were available for 577 infants born to Australian-born parents, and those parents born overseas. Serum 25-hydroxyvitamin D (25(OH)D) levels were measured and associations between serum 25(OH)D and food allergy were examined. Infants of Australian-born parents, but not of parents born overseas, with vitamin D insufficiency were 10 times more likely to be peanut and almost 3 times more likely to be egg allergic than were those with adequate vitamin D levels. Among those with Australian-born parents, infants with vitamin D insufficiency were 9 times more likely to have multiple food allergies (≥2) rather than a single food allergy. These results provide the first direct evidence that vitamin D sufficiency may be an important protective factor for food allergy in the first year of life.

Allen, K. J., Koplin, J. J., Ponsonby, A. L., Gurrin, L. C., Wake, M., Vuillermin, P., ... & Tey, D. (2013). Vitamin D insufficiency is associated with challenge-proven food allergy in infants. *Journal of Allergy and Clinical Immunology*, 131(4), 1109-1116.

http://www.jacionline.org/article/S0091-6749(13)00154-1/abstract

I. Infants who developed eczema had lower cord blood vitamin D status. In 231 children whose cord blood was tested for 25(OH) vitamin D3, those with a level below 50 nmol/L had a greater risk of developing eczema than those with concentrations ≥75 nmol/L. Maternal intake of supplemental Vitamin D influenced cord blood levels, but dietary consumption did not.

A P Jones, D, Z Guicheng, S L Prescott. Cord Blood 25-Hydroxyvitamin D3 and Allergic Disease During Infancy. *Pediatrics* 2012; 130(5):e1128-35.

http://pediatrics.aappublications.org/content/130/5/e1128.long

J. Neonatal complications from vitamin D deficiency include low birth weight, growth restriction, and respiratory tract infection. Vitamin D deficiency in the mother has been associated with altered glucose homeostasis

and increased risk of gestational diabetes mellitus, pre-eclampsia, and bacterial vaginosis. This is a review of all papers published since 1980 on the maternal-fetal impact of gestational vitamin D deficiency and the benefits of vitamin D supplementation during pregnancy.

Weinert LS, Silveiro SP. Maternal-fetal impact of vitamin D deficiency: a critical review. *Maternal Child Health* J. 2015 Jan; 19(1):94-101.

http://link.springer.com/article/10.1007/s10995-014-1499-7

K. Supplementing breastfeeding mothers with 4000 IU of Vitamin D sustained an adequate amount of circulating 25(OH)D concentrations, whereas amounts less than 4000 IU did not. A study of 2000 breastfeeding mothers with groups receiving either 400, 2000 or 4000 IU of Vitamin D to determine how much circulating 25(OH)D2 was available for infants from their mothers. Nursing infant circulating 25(OH)D2 concentrations reflected maternal intake and the amount contained in the milk. With limited sun exposure, an intake of 400 IU/d vitamin D would not sustain circulating 25(OH) D concentrations and thus would supply only limited amounts of vitamin D to nursing infants in breast milk. A maternal intake of 2000 IU/d vitamin D would elevate circulating 25(OH)D concentrations for both mothers and nursing infants, albeit with limited capacity, especially with respect to nursing infants. A maternal intake of 4000 IU/d could achieve substantial progress toward improving both maternal and neonatal nutritional vitamin D status.

Hollis BW, Wagner CL. Vitamin D requirements during lactation: high-dose maternal supplementation as therapy to prevent hypovitaminosis D for both the mother and the nursing infant. *Am J Clin Nutr*. 2004 Dec: 80 (6 Suppl):1752S-1758S.

http://ajcn.nutrition.org/content/80/6/1752S.short

L. The Department of Nutrition for Health and Development of the World Health Organization (WHO) in collaboration with the Executive Committee of the 18th Vitamin D Workshop (VDW), organized a joint symposium on the prevention and consequences of vitamin D deficiency in pregnant women and children, convening experts on vitamin D, clinicians and policy-makers. The overall aim was to identify priority areas for research and to discuss the need for global options for policy, with a focus on the prevention of rickets in infants and children and vitamin D deficiency in pregnant women.

Schoenmakers, I., Pettifor, J. M., Peña-Rosas, J. P., Lamberg-Allardt, C., Shaw, N., Jones, K. S., ... & Bouillon, R. (2015). Prevention and consequences of vitamin D deficiency in pregnant and lactating women and children: A symposium to prioritise vitamin D on the global agenda. *The Journal of Steroid Biochemistry and Molecular Biology,* in press.

http://www.sciencedirect.com/science/article/pii/S0960076015301308

M. Vitamin D insufficiency is associated with increased risk of first-trimester miscarriage. Vitamin D deficiency is implicated in immune cell regulation at the feto-maternal interface and several diseases of pregnancy. The Odense Child Cohort investigators evaluated the serum 25-hydroxyvitamin D test in 1683 pregnant women before gestational week 22. Concentrations of 25-hydroxy vitamin D below 50 nmol/L were associated with a two-fold increased risk for miscarriage. The vitamin D concentrations were not associated with risk of second-trimester miscarriage. The investigators suggested that vitamin D deficiency is a modifiable risk factor for miscarriage and offered that in order to decrease the risk of miscarriage, further randomized controlled trials should investigate the effect of vitamin D supplementation before conception and in early pregnancy.

Andersen LB, Jorgensen JS, Jensen TK, Dalgard C et al. Vitamin D insufficiency is associated with increased risk of first-trimester miscarriage in the Odense Child Cohort. *American Journal of Clinical Nutrition.* 2015 Sep; 102(3):633-8.

http://ajcn.nutrition.org/content/102/3/633.full

Neurological Health Foundation
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Pregnancy Kitchen

❸ Iron

Summary: *We recommend that pregnant women maintain healthy iron levels, especially in the 3rd trimester, and that they are tested throughout pregnancy to monitor these levels. A meta-analysis of 49 studies found that iron supplementation during pregnancy significantly reduced iron deficiency and anemia. It may also help improve Apgar scores and reduce risk of problems with infant growth, cognition, behavior, and motor planning.*

Scientific Evidence

A. Prenatal supplementation with iron or iron + folic acid was effective in preventing anemia in pregnant women. This Cochrane review of iron and iron + folic acid supplementation contained a meta-analysis of 49 trials, involving 23,200 pregnant women. Universal prenatal supplementation with iron or iron+folic acid provided either daily or weekly is effective to prevent anemia and iron deficiency at term. There were no effects of this supplementation for low birth weight in infants, however neonates of mothers receiving iron + folic acid supplements were heavier on average than those who did not.

Peña-Rosas JP & Viteri FE. Effects and safety of preventive oral iron or iron+folic acid supplementation for women during pregnancy. *Cochrane Database Syst Rev.* 2009 Oct 7;(4).

http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004736.pub3/epdf

B. Iron supplementation during pregnancy reduced the risk of anemia and iron deficiency in mothers during and after delivery, and in infants at 3 and 6 months post birth. The subjects were 197 pregnant women in Niamey, Niger who received either 100 mg elemental iron throughout the remainder of their pregnancies or placebo. The prevalence of anemia and iron deficiency decreased markedly during the last trimester of pregnancy in the iron-supplemented group but remained constant in the placebo group. Three months after delivery, the prevalence of anemia was significantly higher in the placebo group (59%) than the iron supplemented group (43%). Serum ferritin concentrations were significantly higher in infants of women in the iron-supplemented group. Mean length and Apgar scores were significantly higher in infants with mothers in the iron group than in those with mothers in the placebo group.

Preziosi, P., Prual, A., Galan, P., Daouda, H., Boureima, H., & Hercberg, S. (1997). Effect of iron supplementation on the iron status of pregnant women: consequences for newborns. *The American Journal of Clinical Nutrition,* 66(5), 1178-1182.

http://ajcn.nutrition.org/content/66/5/1178.full.pdf+html

C. Infants born to anemic mothers were at greater risk of having anemia in the first year of life. A sample of 107 anemic and 125 non-anemic mothers were selected at 37 weeks' gestation, and infant data at birth was obtained. The infants were reviewed for a year post birth. The incidence of iron-deficiency anemia was significantly higher in the infants born to anemic mothers at all stages of the year, with overall incidence of 81%, compared to 65% in controls. This was not explained by differences in environmental risk factors. Anemic mothers had not recovered adequate iron status at 6 months' postpartum, with implications for future pregnancy iron demands.

Kilbride, J., Baker, T. G., Parapia, L. A., Khoury, S. A., Shuqaidef, S. W., & Jerwood, D. (1999). Anaemia during pregnancy as a risk factor for iron-deficiency anaemia in infancy: a case-control study in Jordan. *International Journal of Epidemiology*, 28(3), 461-468.

http://ije.oxfordjournals.org/content/28/3/461.full.pdf+html

D. Iron supplementation in pregnant women did not affect prevalence of anemia or preterm births, but did lead to a higher mean birth weight. A study examining the effect of iron supplementation or placebo in 513 women and its impact on anemia, preterm birth and infant birth weight. Compared with placebo, iron supplementation from enrollment to 28th week of gestation did not significantly affect the overall prevalence of anemia or the incidence of preterm births. However, it did lead to a significantly higher mean birth weight, a significantly lower incidence of low-birth-weight infants (4% compared with 17%), and a significantly lower incidence of preterm low-birth-weight infants (3% compared with 10%).

Cogswell, M. E., Parvanta, I., Ickes, L., Yip, R., & Brittenham, G. M. (2003). Iron supplementation during pregnancy, anemia, and birth weight: a randomized controlled trial. *The American Journal of Clinical Nutrition*, 78(4), 773-781.

http://ajcn.nutrition.org/content/78/4/773.full.pdf+html

E. The effects of chronic iron deficiency in infancy impacts cognition, behavior and motor functioning even 10 years after the deficiency is corrected. Of the 162 children evaluated, those who had severe, chronic iron deficiency in infancy

scored lower on measures of mental and motor functioning. Differences remained statistically significant in arithmetic achievement and written expression, motor functioning, and some specific cognitive processes. More of the formerly iron-deficient children had repeated a grade and/or been referred for special services or tutoring. Their parents and teachers rated their behavior as more problematic in several areas, agreeing in increased concerns about anxiety/depression, social problems, and attention problems.

Lozoff, B., Jimenez, E., Hagen, J., Mollen, E., & Wolf, A. W. (2000). Poorer behavioral and developmental outcome more than 10 years after treatment for iron deficiency in infancy. *Pediatrics*, 105(4), e51-e51.

http://pediatrics.aappublications.org/content/105/4/e51.full.pdf+html

F. Low total body iron is more prevalent in pregnant women in the second or third trimesters, in Mexican American pregnant women, in non-Hispanic black pregnant women, and in women with parity ≥2. This study examined data from the National Health and Nutrition Examination Survey (NHANES) in 1999–2006 for 1171 pregnant women. Pregnant women in the first trimester had a higher mean total body iron than did pregnant women in the second or third trimesters. Iron deficiency (ID) prevalence in pregnant women increased significantly with each trimester. Pregnant women with parity ≥2 had the lowest mean total body iron and the highest prevalence of ID compared with values for pregnant women with parity of 0 or 1. The ID prevalence in non-Hispanic white pregnant women was significantly lower than in Mexican American or non-Hispanic black pregnant women.

Mei, Z., Cogswell, M.E., Looker, A.C., Pfeiffer, C. M., Cusick, S.E., Lacher, D.A., & Grummer-Strawn, L. M. (2011). Assessment of iron status in US pregnant women from the National Health and Nutrition Examination Survey (NHANES), 1999–2006. *The American Journal of Clinical Nutrition,* 93(6), 1312-1320.

http://ajcn.nutrition.org/content/93/6/1312 short

G. Maternal anemia in the second trimester of gestation influences postnatal infant growth. A cohort of pregnant Indian women included 211 which were followed from 13 to 22 weeks gestation (second trimester) and 178 followed from 29 to 42 weeks gestation (third trimester). The prevalence in the second and third trimesters of maternal anemia was 41% and 55% and iron deficiency anemia was 3.6% and 5.6% respectively. Infants of pregnant women who were not anemic in the second trimester were heavier, taller and had a larger head circumference compared with infants of anemic pregnant women. Infants of pregnant women who were not anemic in the third trimester had orientation scores higher than infants of women who were anemic. The findings of this study underscore the necessity of alleviating anemia in women in the early stages of gestation.

Menon KC, Ferguson EL, Thomson CD, Gray AR et al. Effects of anemia at different stages of gestation on infant outcomes. *Nutrition.* 2016 Jan; 32(1). 61-5.

http://www.sciencedirect.com/science/article/pii/S0899900715003263

❹ Healthy Diet

Summary: *We recommend that women consume a healthy, preferably organic, balanced diet rich in protein, vegetables, and fruit, starting preconception and continuing throughout their pregnancy. A healthy diet contributes to successful conception, fetal growth and reduces the risk of miscarriage, preterm delivery, neonatal death, birth defects, asthma, allergies, and infections. Consuming artificial sweeteners can increase the risk of preterm birth, and are toxic to neurons and contribute to tumors.*

Scientific Evidence

A. Recommendation of American Dietetic Association: Pregnant women should gain appropriate weight, exercise, consume healthy foods and vitamin/mineral supplements, and avoid harmful substances. It is the position of the American Dietetic Association that women of childbearing ages should maintain good nutritional status through a lifestyle that optimizes maternal health and reduces the risk of birth defects, suboptimal fetal growth and development, and chronic health problems in their children. The key components of a health-promoting lifestyle during pregnancy include appropriate weight gain; appropriate physical activity; consumption of a variety of foods in accordance with the *Dietary Guidelines for Americans 2005*; appropriate and timely vitamin and mineral supplementation; avoidance of alcohol, tobacco, and other harmful substances; and safe food handling.

Kaiser, L., & Allen, L. H. (2008). Position of the American Dietetic Association: nutrition and lifestyle for a healthy pregnancy outcome. *J Am Diet Assoc*, 108(3), 553-561.

http://naldc.nal.usda.gov/naldc/download.xhtml?id=44440&content=PDF

B. Maternal nutrition influences the availability of nutrients for transfer to the fetus and is a major regulator of prenatal growth and health

outcomes later in life for the child. Symposium reviewing current literature and recommendations of maternal nutrition and its impact on fetal weight, blood pressure into adulthood, growth, and other factors are outlined.

Kind, K. L., Moore, V. M., & Davies, M. J. (2006). Diet around conception and during pregnancy–effects on fetal and neonatal outcomes. *Reproductive BioMedicine Online*, 12(5), 532-541.

http://www.rbmojournal.com/article/S1472-6483(10)61178-9/pdf

C. Balanced energy/protein supplementation improves fetal growth and may reduce the risk of fetal and neonatal death. High-protein or balanced-protein supplementation alone is not beneficial and may be harmful to the fetus. A Cochrane review of trials involving nutritional advice, energy and protein supplementation on pregnancy and fetal outcomes. In five trials (1134 women), nutritional advice to increase energy and protein intakes was successful in achieving those goals, but no consistent benefit was observed on pregnancy outcomes. In 13 trials (4665 women), balanced energy/protein supplementation was associated with modest increases in maternal weight gain and in mean birthweight, and a substantial reduction in risk of small-for-gestational-age (SGA) birth. No significant effects were detected on preterm birth, but significantly reduced risks were observed for stillbirth and neonatal death. In two trials (529 women), high-protein supplementation was associated with a small, nonsignificant increase in maternal weight gain. A nonsignificant reduction in mean birthweight, a significantly increased risk of SGA birth, and a nonsignificant increased risk of neonatal death were also found.

Kramer MS, Kakuma R. Energy and protein intake in pregnancy. Cochrane *Database of Systematic Reviews* 2003, Issue 4. Art. No.: CD000032.

http://apps.who.int/rhl/reviews/langs/CD000032.pdf

D. Poor diet quality during pregnancy is associated with increased depressive symptoms at 32 weeks gestation. In a study of 167 pregnant women, diet quality was evaluated. Two dietary patterns were identified: "healthy" (including fruit, vegetables, fish and whole grains) and "unhealthy" (including sweets, refined grains, high-energy drinks and fast foods). The unhealthy diet was associated with depressive symptoms at 32 weeks gestation.

Baskin R, Hill B, Jack FN, O'Neil A, Skouteris H. Antenatal dietary patterns and depressive symptoms during pregnancy and early post-partum. *Maternal and Child Nutrition*. 2016 Jan 3.

http://onlinelibrary.wiley.com/doi/10.1111/mcn.12218/abstract;jsessionid=F66182F6F7F6907A8F37B48F2678F3AD.f02t02?userIsAuthenticated=false&deniedAccessCustomisedMessage=

E. Organic food consumption during pregnancy reduces the prevalence of hypospadias. Hypospadias is a condition in male infants in which the opening of the urethras on the underside of the penis, instead of at the tip. A cohort of 35,107 women who delivered a singleton male infant, were evaluated for the consumption of organically produced foods (vegetables, fruit, bread/cereal, milk/dairy products, eggs and meat) during pregnancy. Seventy-four male newborns were diagnosed with hypospadias. Women who consumed any organic foods during pregnancy were less likely to give birth to a boy with hypospadias compared with women who reported never or seldom consuming organic food. Associations were strongest for vegetables and milk/dairy consumption.

Brantsaeter AL, Torjusen H, Meltzer HM, Papadopoulou E et al. Organic food consumption during pregnancy and hypospadias and cryptorchidism at birth: the Norwegian mother and child cohort study (Moba). *Environmental Health Perspectives*. 2015 Jul 9.

http://www.indiaenvironmentportal.org.in/files/file/Organic%20Food%20Consumption.pdf

F. A Mediterranean diet during pregnancy has a protective effect against asthma-like symptoms and atopy in childhood. Adherence to a Mediterranean diet in the mothers of 460 children from Menorca, Spain was included in the analysis after 6.5 years of follow-up. Maternal dietary intake during pregnancy and children's dietary intake at age 6.5 years were assessed along with prevalence rates of persistent wheeze, atopic wheeze and atopy. A high Mediterranean Diet Score during pregnancy was found to be protective for persistent wheeze, atopic wheeze and atopy (hyperallergic) at age 6.5 years.

Chatzi, L., Torrent, M., Romieu, I., Garcia-Esteban, R., Ferrer, C., Vioque, J., ... & Sunyer, J. (2008). Mediterranean diet in pregnancy is protective for wheeze and atopy in childhood. *Thorax*, 63(6), 507-513.

http://thorax.bmj.com/content/63/6/507.short

G. Daily intake of artificially sweetened soft drinks may increase the risk of preterm delivery. Analyses of 59,334 women from the Danish National Birth Cohort examined the association between intake of artificially sweetened soft drinks and preterm delivery. The study found an association between intake of artificially sweetened carbonated and noncarbonated soft drinks and an increased risk of preterm delivery. A stronger increase in risk was observed for early preterm and moderately preterm delivery than with late-preterm delivery.

Halldorsson, T. I., Strøm, M., Petersen, S. B., & Olsen, S. F. (2010). Intake of artificially sweetened soft drinks and risk of preterm delivery: a prospective cohort study of 59,334 Danish pregnant women. *The American Journal of Clinical Nutrition*, ajcn-28968.

http://ajcn.nutrition.org/content/92/3/626.full

H. Metabolites of aspartame reduce key neurotransmitters, are toxic to neurons, and contribute to the formation of tumors in the CNS. The artificial sweetener aspartame is broken down into phenylalanine (50%), aspartic acid (40%) and methanol (10%) during metabolism in the body. Excess phenylalanine blocks the transport of important amino acids to the brain contributing to reduced levels of dopamine and serotonin. Aspartic acid at high concentrations is a toxin that causes hyperexcitability of neurons and is also a precursor of other excitatory amino acid - glutamates. The methanol metabolites cause CNS depression, vision disorders and other symptoms leading ultimately to metabolic acidosis and coma. The latest studies show that aspartame's metabolite - diketopiperazine - is carcinogenic in the CNS. It contributes to the formation of tumors in the CNS such as gliomas, medulloblastomas and meningiomas.

Rycerz, K., & Jaworska-Adamu, J. E. (2013). Review paper Effects of aspartame metabolites on astrocytes and neurons. *Folia Neuropathologica,* 51(1), 10-17.

http://www.ncbi.nlm.nih.gov/pubmed/23553132

I. This article summarizes the cellular effects of aspartame on the brain. The authors examined what happens on a cellular level during consumption of aspartame. They observed that aspartame disturbs amino acid metabolism, protein structure and metabolism, integrity of nucleic acids, neuronal function, endocrine balances and changes in the brain concentrations of catecholamines. It was also reported that aspartame and its breakdown products cause nerves to fire excessively, which indirectly causes a very high rate of neuron depolarization. The ATP stores in the cells are depleted, indicating that low concentrations of glucose are present in the cells, and this in turn will indirectly decrease the synthesis of acetylcholine, glutamate and GABA. Mitochondria are damaged, which could lead to apoptosis of cells and infertility in men and also a lowered rate of oxidative metabolism are present, thus lowering concentrations of the transmitters glutamate and production of GABA. The cellular walls are destroyed; thus, the cells are more permeable, leading to a compromised BBB. Thus, overall oxidative stress and neurodegeneration are present. From all the adverse effects caused by this product, it is suggested that serious further testing and research be undertaken to eliminate any and all controversies surrounding this product.

Humphries, P., Pretorius, E., & Naude, H. (2008). Direct and indirect cellular effects of aspartame on the brain. *European Journal of Clinical Nutrition*, 62(4), 451-462.

http://www.nature.com/ejcn/journal/v62/n4/pdf/1602866a.pdf

J. Results from this study suggest that a Western-type diet, high in meat and fats and low in fruits and vegetables, is associated with increased odds of induced preterm birth. This study extracts and visualizes dietary patterns from self-reported dietary data collected in mid-pregnancy from nearly 60,000 mother-child pairs who were part of a prospective, longitudinal cohort (Danish National Birth Cohort). A total of seven dietary patterns were extracted by principal component analysis, referred to as: Vegetables/Prudent, Alcohol, Western, Nordic, Seafood, Candy and Rice/Pasta/ Poultry. A consistent dose-response association with preterm birth was only observed for Western diet comparing the highest to the lowest quintile.

Rasmussen, M. A., Maslova, E., Halldorsson, T. I., & Olsen, S. F. (2014). Characterization of dietary patterns in the Danish national birth cohort in relation to preterm birth. *PloS one*, 9(4), e93644.

http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0093644

K. In this review the authors address several different studies which illustrate that an unbalanced diet prior and during pregnancy, regarding the intake of micronutrients of both mother and father, can have long-lasting effects on the health of adult offspring. The research field of fetal programming has developed tremendously over the years and increasing knowledge suggests that both maternal and paternal unbalanced diet can have long-lasting effects on the health of offspring. Studies implicate that macronutrients play an important role in fetal programming, although the importance of micronutrients is also becoming increasingly apparent. Folic acid and vitamins B2, B6 and B12 are essential for one-carbon metabolism and are involved in DNA methylation. They can therefore influence the programming of the off-

spring's epigenome. Also, other micronutrients such as vitamins A and C, iron, chromium, zinc and flavonoids play a role in fetal programming.

Vanhees, K., Vonhögen, I. G., van Schooten, F. J., & Godschalk, R. W. (2014). You are what you eat, and so are your children: the impact of micronutrients on the epigenetic programming of offspring. *Cellular and Molecular Life Sciences*, 71(2), 271-285.

http://link.springer.com/article/10.1007/s00018-013-1427-9#/page-1

❺ Pesticides vs. Organic Foods

Summary: *We recommend avoiding pesticides and eating organic foods, especially during preconception and pregnancy. Consumption of conventional foods, especially fruits and vegetables, is the major source of exposure to pesticides. Increased pesticide levels are associated with an increased risk of ADHD and autism spectrum disorder. Eating organic dairy products results in a decreased risk of eczema over participants who consume conventionally-raised dairy.*

Scientific Evidence

A. Organophosphate exposure, at levels common among US children, may contribute to ADHD prevalence. The National Health and Nutrition Examination Survey (2000-2004) examined the association between urinary concentrations of dialkyl phosphate metabolites of organophosphates and attention-deficit/hyperactivity disorder (ADHD) in 1139 children 8 to 15 years of age. Children with higher urinary dialkyl phosphate concentrations, especially dimethyl alkylphosphate (DMAP) concentrations, were more likely to be diagnosed as having ADHD. For the most-commonly detected DMAP metabolite, children with levels higher than the median of detectable concentrations had twice the rate of ADHD compared with children with undetectable levels.

Bouchard, M. F., Bellinger, D. C., Wright, R. O., & Weisskopf, M. G. (2010). Attention-deficit/hyperactivity disorder and urinary metabolites of organophosphate pesticides. *Pediatrics*, 125(6), e1270-e1277.

http://pediatrics.aappublications.org/content/125/6/e1270.short

B. Exposure to organophosphates comes from a conventional diet. Consuming mostly organic foods greatly reduces or eliminates this exposure. Study measured organophosphate metabolites in 23 school aged children during con-sumption of a conventional diet, then when their diet was replaced by an organic diet, and then after reversal back to conventional diet. During the conventional diet in both phase 1 and 3, they detected urinary metabolites of organophosphates, however these metabolites dropped to almost undetectable levels during the organic diet phase. Once conventional food was re-introduced, the metabolites were detected in high levels again.

Lu, C., Toepel, K., Irish, R., Fenske, R. A., Barr, D. B., & Bravo, R. (2006). Organic diets significantly lower children's dietary exposure to organophosphorus pesticides. *Environmental Health Perspectives*, 260-263.

http://www.jstor.org/stable/3436519?seq=1#page_scan_tab_contents

C. Switching children to an organic diet greatly reduces their pesticide exposures. Urinary pesticide metabolite levels (n=40) in children living in urban and agricultural areas were measured before, during and after introduction of an organic diet. The organic diet significantly reduced levels of organophosphate pesticide metabolites and 2,4-D herbicide levels in the children's urine.

Bradman A, Quirós-Alcalá L, Castorina R, Aguilar Schall R, Camacho J, Holland NT, Barr DB, Eskenazi B. 2015. Effect of organic diet intervention on pesticide exposures in young children living in low-income urban and agricultural communities. *Environ Health Perspect* 123:1086-1093.

http://dx.doi.org/10.1289/ehp.1408660.

D. Conventionally grown fruits and vegetables are a major source of pesticides in children. According to the National Research Council report from 1993, fruits and vegetables were the most important source of pesticide exposure in children.

National Research Council. *Pesticides in the Diets of Infants and Children*. Washington, DC: The National Academies Press, 1993.

http://www.nap.edu/catalog/2126/pesticides-in-the-diets-of-infants-and-children

E. Typical exposure to pesticides through consumption of conventional produce may lead to a higher rate of ADHD. Previous studies showed a link between high exposure to organophosphate containing pesticides and ADHD in children with high exposure rates such as those from farming communities. A more recent study from the National

Health and Nutrition Examination Survey (NHANES) linked even typical exposure, such as eating fruits and vegetables that contain pesticides to a higher rate of ADHD.

Kuehn BM. Increased Risk of ADHD Associated With Early Exposure to Pesticides, PCBs. *JAMA*. 2010; 304(1):27-28.

http://jama.jamanetwork.com/article.aspx?articleid=186163&resultclick=1

F. Evidence links neurodevelopmental disorders with gestational pesticide exposures. The Childhood Autism Risks from Genetics and Environment (CHARGE) study evaluated whether residential proximity to agricultural pesticides during pregnancy is associated with autism spectrum disorders (ASD) or developmental delay (DD). Proximity to organophosphates at some point during gestation was associated with a 60% increased risk for ASD, especially in the 2nd and 3rd trimester. Children of mothers residing near pyrethroid insecticide applications just before conception or during third trimester were at greater risk for both ASD and DD.

Shelton, J. F., Geraghty, E. M., Tancredi, D. J., Delwiche, L. D., Schmidt, R. J., Ritz, B.,& Hertz-Picciotto, I. (2014). Neurodevelopmental disorders and prenatal residential proximity to agricultural pesticides: the CHARGE study. *Environ Health Perspect*, 122(10), 1103-1109.

http://ehp.niehs.nih.gov/1307044/

G. Organic crops contain more of certain vitamins/minerals and less nitrates and heavy metals than conventionally grown crops. Published comparative measurements of organic and conventional nutrient content were entered into a database for calculation. Organic crops contained significantly more vitamin C, iron, magnesium, and phosphorus and significantly less nitrates than conventional crops. There were nonsignificant trends showing less protein but of a better quality and a higher content of nutritionally significant minerals with lower amounts of some heavy metals in organic crops compared to conventional ones.

Virginia Worthington. Nutritional Quality of Organic Versus Conventional Fruits, Vegetables, and Grains. *The Journal of Alternative and Complementary Medicine*. April 2001, 7(2): 161-173.

http://online.liebertpub.com/doi/abs/10.1089/107555301750164244

H. Choosing organically grown vegetables during pregnancy was associated with a 21% reduced risk of pre-eclampsia. The study examined 28,192 pregnant women, their intake of organic foods and risk for pre-eclampsia. Women who reported to have eaten organic vegetables 'often' or 'mostly' had a 21% lower risk of pre-eclampsia than those who reported 'never/rarely' or 'sometimes'. The lower risk was mostly associated with high organic vegetable consumption, while no associations were found for high intake of organic fruit, cereals, eggs or milk, or a combined index reflecting organic consumption.

Torjusen H, Brantsæter AL, Haugen M, et al. Reduced risk of preeclampsia with organic vegetable consumption: results from the prospective Norwegian Mother and Child Cohort Study. BMJ Open 2014; 4:e006143.

http://bmjopen.bmj.com/content/4/9/e006143.short

I. Consumption of organic dairy products is associated with lower eczema risk. Consumption of organic meat, fruit, vegetables and eggs were not associated with risk. The KOALA Birth Cohort Study in the Netherlands (n=2764) measured organic food consumption, eczema and wheeze in infants until age 2 years. Venous blood samples taken from 815 infants at 2 years of age were analysed for total and specific IgE. Consumption of organic dairy products was associated with lower eczema risk but there was no association of organic meat, fruit, vegetables or eggs, or the pro-portion of organic products within the total diet with the development of eczema, wheeze or atopic sensitisation.

Kummeling, I., Thijs, C., Huber, M., van de Vijver, L. P., Snijders, B. E., Penders, J., & Dagnelie, P. C. (2008). Consumption of organic foods and risk of atopic disease during the first 2 years of life in the Netherlands. *British Journal of Nutrition*, 99(03), 598-605.

http://journals.cambridge.org/action/displayAbstract?fromPage=online&aid=1700496&fileId=S0007114507815844

J. Prenatal pesticide exposure increases the occurrence of otitis media (ear infections) during early childhood. The PELAGIE mother-child cohort enrolled 3421 women at the beginning of pregnancy in Brittany France. At the two-year follow-up, 1505 families completed a self-administered questionnaire, including the domestic use of pesticides and consumption of organic diet during pregnancy and the occurrences of otitis media in the child. Metabolites of triazine herbicides and organophosphate insecticides were measured in the urine collected before the 19th week of gestation in a 248 mothers. Children whose mothers reported an organic diet during pregnancy had a reduced risk of otitis media. The presence in maternal urine of dealkylated triazine metabolites was positively associated with recurrent (3 or more) otitis media.

Buscail C, Chevrier C, Serrano T, Pele F, et al. Prenatal pesticide exposure and otitis media during early childhood in the PELAGIE mother-child cohort. *Occupational and Environmental Medicine*. 2015 Dec;72 (12):837-44.

http://oem.bmj.com/content/early/2015/09/07/oemed-2015-103039.short

❻ Avoid GMOs

Summary: *We recommend avoiding GMO foods as a precaution, especially for pregnant women. GMO foods are banned in 61 countries due to concerns about their safety, as discussed below. Part of the concern is that GMO foods often have increased pesticide levels (see above section), and part of the reason is the changes to the foods themselves as discussed here.*

Scientific Evidence

A. The Institute for Responsible Technology and several key researchers in the area of GMO foods and human health relate genetically modified foods to several conditions that may trigger many of the gluten-related disorders that are affecting 18 million Americans. This report was recently released by the Institute for Responsible Technology (IRT), which is a world leader in educating policy makers and the public about GMO foods and crops. The report uses data from the US Department of Agriculture, US Environmental Protection Agency, medical journal reviews, as well as other independent research. The authors relate GM foods to five conditions that may either trigger or exacerbate gluten-related disorders, including the autoimmune disorder, Celiac Disease: intestinal permeability, imbalanced gut bacteria, immune activation and allergic response, impaired digestion, and damage to the intestinal wall.

The Institute for Responsible Technology Report on GMOs and gluten sensitivities.

http://responsibletechnology.org/media/images/content/Press_Release_Gluten_11_25.pdf

B. The authors evaluate the risk assessment and various studies evaluating the effect of GM foods on human cells. They raise concern that safety studies of these foods have not been properly conducted and that further research is warranted before determining that these foods are safe for human consumption. The risk assessment of genetically modified (GM) crops for human nutrition and health has not been systematic. Evaluations for each GM crop or trait have been conducted using different feeding periods, animal models, and parameters. The most common result is that GM and conventional sources induce similar nutritional performance and growth in animals. However, adverse microscopic and molecular effects of some GM foods in different organs or tissues have been reported. Diversity among the methods and results of the risk assessments reflects the complexity of the subject. While there are currently no standardized methods to evaluate the safety of GM foods, attempts towards harmonization are on the way. More scientific effort is necessary in order to build confidence in the evaluation and acceptance of GM foods.

Magaña-Gómez, J. A., & de la Barca, A. M. C. (2009). Risk assessment of genetically modified crops for nutrition and health. *Nutrition Reviews*, 67(1), 1-16.

http://nutritionreviews.oxfordjournals.org/content/67/1/1.abstract

C. The milk of goat mothers fed non-GE soy was more nutritious, had higher fat, protein and Immunoglobulin G (IgG) I compared to GE fed mothers. This resulted in larger, faster growing goat kids. Pregnant goats fed with genetically engineered (GE) soybeans have offspring who grow more slowly and who are also shorter. The reduced growth of the goat kids was attributed by the researchers to their observation that the milk of the GE-fed mothers was significantly less nutritious and contained less of the IgG antibodies important for early growth. The colostrum from the GE-fed mothers contained only 2/3 of the fat, 1/3 of the protein and close to half of the IgG of the mothers fed the non-GM soy. After both thirty days and sixty days the kids of GE-fed mothers were approximately 20% lower in weight and shorter in stature. The authors noted that low IgG antibody levels in colostrum are correlated in other ruminants with slower growth and also that IgG antibodies are known to have a role in nutrient absorption because they promote gut development in newborns.

R. Tudisco, S. Calabrò, M.I. Cutrignelli, G. Moniello, M. Grossi, V. Mastellone, P. Lombardi, M.E. Pero, F. Infascelli, Genetically modified soybean in a goat diet: Influence on kid performance. *Small Ruminant Research*, Volume 126, Supplement 1, May 2015, Pages 67-74.

http://www.sciencedirect.com/science/article/pii/S0921448815000528

D. The metabolites of specific pesticides are more detectable than their precursors and seem to easily cross the placenta to reach the fetus. There is strong evidence of the potential teratogenic effects of gluphosinate (a pesticide) in humans and increased risk of con-genital malformations with exposure. Blood of 30 pregnant women and 39 non-pregnant women

was studied. The aim of this study was to evaluate the correlation between maternal and fetal exposure, and to determine exposure levels of pesticides associated to genetically modified foods, glyphosate and its metabolites. Glyphosate and gluphosinate were detected in serum of non-pregnant women and not detected in pregnant women. On the other hand, the metabolites for these pesticides were detected in pregnant women, their fetuses and non-pregnant women. One metabolite, 3-MPPA was detected in 100% of maternal and umbilical cord blood samples, and in 67% of the blood samples from non-pregnant women.

Aris, A., & Leblanc, S. (2011). Maternal and fetal exposure to pesticides associated to genetically modified foods in Eastern Townships of Quebec, Canada. *Reproductive Toxicology*, 31(4), 528-533.

http://www.sciencedirect.com/science/article/pii/S0890623811000566

E. The authors explain the documented effects of glyphosate and its ability to induce disease, and show that glyphosate is the "textbook example" of the disruption of homeostasis by environmental toxins. Glyphosate's inhibition of cytochrome P450 (CYP) enzymes is an overlooked component of its toxicity to mammals. CYP enzymes play crucial roles in biology, one of which is t detoxify xenobiotics. Thus, glyphosate enhances the damaging effects of other food borne chemical residues and environmental toxins. Consequences include most of the diseases and conditions associated with a Western diet, which include gastrointestinal disorders, obesity, diabetes, heart disease, depression, autism, infertility, cancer and Alzheimer's disease.

Samsel, A., & Seneff, S. (2013). Glyphosate's suppression of cytochrome P450 enzymes and amino acid biosynthesis by the gut microbiome: pathways to modern diseases. *Entropy*, 15(4), 1416-1463.

http://www.mdpi.com/1099-4300/15/4/1416

F. The presence of glyphosate residues in both humans and animals could shift the entire population towards numerous health hazards. Studying the impact of glyphosate residues on health is warranted and the global regulations for the use of glyphosate may have to be re-evaluated. In the present study glyphosate residues were tested in urine and different organs of dairy cows as well as in urine of hares, rabbits and humans. Cows kept in genetically modified free area had significantly lower glyphosate concentrations in urine than conventional cows. Also glyphosate was detected in different organs of slaughtered cows such as the intestine, liver, muscles, spleen and kidney. Fattening rabbits showed significantly higher glyphosate residues in urine than hares. Moreover, glyphosate was significantly higher in urine of humans with conventional feeding, and chronically ill humans showed significantly higher glyphosate residues in urine than found in the healthy population.

Krüger, M., Schledorn, P., Schrödl, W., Hoppe, H. W., Lutz, W., & Shehata, A. A. (2014). Detection of glyphosate residues in animals and humans. *J Environ Anal Toxicol*, 4(210), 2161-0525.

http://www.omicsonline.org/open-access/detection-of-glyphosate-residues-in-animals-and-humans-2161-0525.1000210.pdf

G. A recent study showed that a commonly used regulatory sequence has resulted in contaminant viral DNA (cauliflower mosaic virus) and is found in 54 of the 86 genetically modified commercial preparation in the US. GM organisms are produced by introducing genes from entirely unrelated organisms into the DNA of another organism. With the completion of the Human Genome Project, the theory that one gene codes for one protein was disproven, as we have around 21,000 genes which code for at least 100,000 different proteins. So, a gene may code for many proteins. The hazards or consequences of this contaminant viral DNA have not yet been identified.

Podevin, N., & du Jardin, P. (2012). Possible consequences of the overlap between the CaMV 35S promoter regions in plant transformation vectors used and the viral gene VI in transgenic plants. *GM Crops & Food,* 3(4), 296-300.

http://www.tandfonline.com/doi/abs/10.4161/gmcr.21406#.VpfJL4-cHIU

H. A full lifespan study of rats exposed to GM maize with and without Roundup pesticide showed liver and kidney damage, increased tumor incidence, and shortened life spans as compared to control rats fed GM-free maize. This study, published, then retracted one year later on no identified scientific or ethical grounds, was republished by a second journal after rigorous peer review. It differs from previous safety studies, in that the rats were followed for two years, and that the Roundup group received the commercial form of this pesticide (containing adjuvant chemicals of uncertain safety), rather than the pure glyphosate active ingredient tested in other studies. It is noteworthy that the above described conditions and reduced lifespan occurred in rats on the GM-only diet at the same rates as in rats on the GM plus Roundup diet. Also, these pathologic responses occurred at similar rates in the low dose groups as in the high dose groups, best explained by endocrine disruptive effects, which often have a non-monotonic (nonlinear) dose-response curve.

Séralini, G. E., Clair, E., Mesnage, R., Gress, S., Defarge, N., Malatesta, M., ... & de Vendômois, J. S. (2014). Republished study: long-term toxicity of a Roundup herbicide and a Roundup-tolerant genetically modified maize. *Environmental Sciences Europe*, 26(1), 14.

http://www.enveurope.com/content/26/1/14/abstract

I. A study in mice found significant alterations in white blood cells, platelets, and red blood cells with commonly used pesticide bacterium (Bt or Bacillus Thuringiensis), which has been extensively incorporated into GM foods, and also cotton. One of these toxins, CRY1AB, which caused anemia in treated mice, has been found in the blood of pregnant women and fetuses in Canada. While Bt has been used for four decades in integrative pest management and organic farming, and is generally recognized as safe, the introduction of genes coding for some of its more toxic CRY endotoxins into GM corn and cotton may substantially increase their toxic effects. The authors concluded their paper: "Taking into account the increased risk of human and animal exposures to significant levels of these toxins, especially through diet, our results suggest that further studies are required to clarify the mechanism involved in the hematotoxicity found in mice, and to establish the toxicological risks to non-target organisms, especially mammals, before concluding that these microbiological control agents are safe for mammals."

Mezzomo BP, Miranda-Vilela AL, Freire IdS, Barbosa LCP, Portilho FA, et al (2013)Hematotoxicity of Bacillus thuringiensis as Spore-crystal Strains Cry1Aa, Cry1Ab, Cry1Ac or Cry2Aa in Swiss Albino Mice. *J Hematol Thromb* Dis 1: 104.

http://foodrecap.net/wp-content/uploads/2013/05/nailing-cry-toxin-harmful-to-mice.pdf

J. This review addresses some major concerns about the safety, environmental and ecological risks and health hazards involved with GM foods and recombinant technology.

Bawa AS, Anilakumar KR. Genetically modified foods: safety, risks and public concerns-a review. *J Food Sci Technol*. 2013 Dec; 50(6):1035-46.

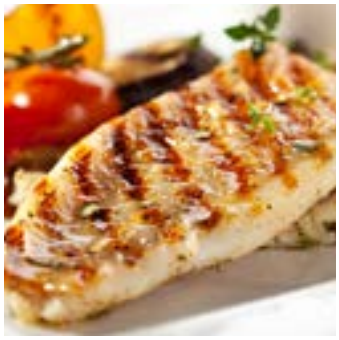
http://link.springer.com/article/10.1007/s13197-012-0899-1

K. Additional reading on GMO health concerns:

http://www.globalresearch.ca/ten-scientific-studies-proving-gmos-can-be-harmful-to-human-health/5377054

❼ Consume Low-Mercury Seafood

Summary: *We recommend consuming low mercury seafood 2 or more times per week during pregnancy and breastfeeding. Consuming low-mercury seafood (2 or more servings per week) is associated with better cognition in infants, and a decreased risk of depression in mothers. However, consumption of high-mercury seafood is associated with worse cognition, so limit consumption to low-mercury seafood.*



Scientific Evidence

A. Children of mothers who consumed a greater number of fish servings per week of low mercury fish performed better on cognitive tests at 3 years of age. Using data from a prospective cohort study of 341 mother-child pairs, the authors studied associations of maternal second-trimester fish intake and erythrocyte mercury levels with children's scores on the Peabody Picture Vocabulary Test (PPVT) and Wide Range Assessment of Visual Motor Abilities (WRAVMA) at age 3 years. Higher fish intake (>2 servings per week) was associated with better child cognitive test performance, and higher mercury levels with poorer test scores.

Oken E, Radesky JS, Wright RO, et al. Maternal fish intake during pregnancy, blood mercury levels, and child cognition at age 3 years in a US cohort. *Am J Epidemiology* 2008; 167:1171–81.

http://aje.oxfordjournals.org/content/167/10/1171.full.pdf+html

B. Docosahexaenoic acid (DHA) fatty acid supplementation of breastfeeding mothers results in higher infant plasma phospholipid DHA contents during supplementation and a higher Bayley Psychomotor Development Index at 30 months of age. The researchers measured the plasma lipid levels, visual function, and neurodevelopmental status of 160 infants whose breastfeeding mothers who were given either a high DHA supplement, or placebo pill containing vegetable oils. When infants were tested 4 months after delivery, those in the supplement group had a 35% greater content of DHA in infant plasma phospholipids then the placebo group. Infants whose mothers received DHA had an 8.4-point higher Psychomotor Development on the Bayley Scales of Infant Development at 30 mo of age. There was no significant difference on measures of visual acuity or mental development between groups.

Jensen, C. L., Voigt, R. G., Prager, T. C., Zou, Y. L., Fraley, J. K., Rozelle, J. C., ... & Heird, W. C. (2005). Effects of maternal docosahexaenoic acid intake on visual function and neurodevelopment in breastfed term infants. *American Journal of Clinical Nutrition,* 82(1), 125-132.

http://ajcn.nutrition.org/content/82/1/125.full.pdf+html

C. Consuming more low mercury fish during pregnancy resulted in better visual development in the children. A study examined fish intake during pregnancy, along with hair and cord mercury levels of 135 mothers. As fish consumption increased, so did a measure of infant cognition on visual recognition memory (VRM) at 6 months of age. For each additional fish serving above the mean of 1.2 per week, scores on the VRM test increased by 4 points. However as mercury levels increased, cognition decreased. Infant cognition was highest in mothers who consumed the highest amount of low mercury fish.

Oken, E., Wright, R. O., Kleinman, K. P., Bellinger, D., Amarasiriwardena, C. J., Hu, H., & Gillman, M. W. (2005). Maternal fish consumption, hair mercury, and infant cognition in a US cohort. *Environmental Health Perspectives*, 1376-1380.

http://www.jstor.org/stable/3436105

D. Eating seafood during pregnancy may have beneficial effects on depression. In a study of 14,541 women in England, at 32 weeks' gestation, the mother completed a questionnaire that included symptoms of depression and a food frequency questionnaire from which the amount of omega-3 fatty acids from fish was calculated. Analyses showed lower maternal intake of omega-3 from seafood was associated with high levels of depressive symptoms. Compared with women consuming more than 1.5 g omega-3 from seafood per week, those consuming none were more likely to have high levels of depressive symptoms at 32 weeks' gestation.

Golding, J., Steer, C., Emmett, P., Davis, J. M., & Hibbeln, J. R. (2009). High levels of depressive symptoms in pregnancy with low omega-3 fatty acid intake from fish. *Epidemiology*, 20(4), 598-603.

http://journals.lww.com/epidem/Fulltext/2009/07000/High_Levels_of_Depressive_Symptoms_in_Pregnancy.20.aspx

E. Fish consumption and omega-3 fatty acid consumption is recommended in pregnant women. This review discusses the benefits of omega-3 fatty acid consumption during pregnancy and provides guidelines for obstetricians advising patients. The most biologically active forms of omega-3 fatty acids are docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), which are primarily derived from marine sources such as seafood and algae. Recent surveys indicate that many pregnant women avoid eating seafood, primarily due to concern about the adverse effects of mercury and other contaminants on the developing fetus. This limits the amount of omega 3 fatty acids pregnant women derive from their diet.

Coletta, J. M., Bell, S. J., & Roman, A. S. (2010). Omega-3 fatty acids and pregnancy. *Reviews in Obstetrics and Gynecology*, 3(4), 163.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3046737/

F. Higher fish intake by pregnant mothers and their children was associated with better cognitive performance in children. Fish intake by mothers during pregnancy, and by the infant postnatally was measured in 7421 participants. The child's cognitive development was assessed using the MacArthur Communicative Development Inventory at 15 months of age and the Denver Developmental Screening Test at 18 months of age. Adjusted mean MacArthur comprehension scores for children whose mothers consumed fish 4 or more times per week was significantly higher than those whose mothers did not consume fish.

Daniels, J. L., Longnecker, M. P., Rowland, A. S., Golding, J., & the ALSPAC Study, T. (2004). Fish intake during pregnancy and early cognitive development of offspring. *Epidemiology*, 15 (4), 394 - 402.

http://journals.lww.com/epidem/Fulltext/2004/07000/Fish_Intake_During_Pregnancy_and_Early_Cognitive.4.aspx

G. The Food and Drug Administration (FDA) and the Environmental Protection Agency (EPA) have issued revised advice encouraging pregnant women, those who might become pregnant, breastfeeding mothers and young children to eat more fish—and to eat a variety of fish lower in mercury. The latest science shows that eating fish low in mercury during pregnancy and in early childhood can help with growth and neurodevelopment.

"New Advice: Some Women and Children Should Eat More Fish." Published June 2014 by FDA.gov.

file:///F:/prevention/fish/New%20Advice_Some%20Women%20and%20Children%20Should%20Eat%20More%20Fish_0614.pdf

H. Consumption of large fatty fish during pregnancy presents moderate child neuropsychological benefits, including improvements in cognitive functioning and some protection from autism-spectrum traits. This study evaluated 1,892 and 1,589 mother-child pairs at the ages of 14 months and 5 years, respectively, in a population-based Spanish birth cohort. Bayley and McCarthy scales and the Childhood Asperger Syndrome Test were used to assess neuropsychological development. Overall, consumption of seafood above the recommended limit of 340 g/week was associated with 10-g/week increments in neuropsychological

scores. By subtype, in addition to lean fish, consumption of large fatty fish showed a positive association; offspring of persons within the highest quantile (>238 g/week) had an adjusted increase of 2.29 points in McCarthy general cognitive score. Similar findings were observed for the Childhood Asperger Syndrome Test.

Julvez, J., Méndez, M., Fernandez-Barres, S., Romaguera, D., Vioque, J., Llop, S., ... & Riaño, I. (2016). Maternal Consumption of Seafood in Pregnancy and Child Neuropsychological Development: A Longitudinal Study Based on a Population With High Consumption Levels. *American Journal of Epidemiology,* kwv195.

http://aje.oxfordjournals.org/content/early/2016/01/05/aje.kwv195.abstract

Additional reading about seafood consumption in pregnancy:

I. 7 Important Things To Know About Omega-3 Fatty Acids from the National Centers for Complementary and Alternative Health, a branch within the National Institutes of Health.

https://nccih.nih.gov/health/tips/omega

8 Probiotics

Summary: *We recommend taking a probiotic supplement for pregnant and breastfeeding mothers, as well as infants and young children. Maternal use of probiotics during pregnancy seemed to help reduce risk of allergic disease in their children. Certain probiotics seemed to be helpful in treating mastitis. One study found that probiotics decreased colic in infants, but another study found that they did not help with severe colic. Pre-term infants were found to benefit from probiotics with reduced risk of both necrotizing enterocolitis and mortality. A meta-analysis of seventeen studies found that risk of allergic eczema was significantly reduced in infants given probiotics.*

Scientific Evidence

A. At 2 years old children of mothers who were given a probiotic milk during pregnancy and breastfeeding had a 50% reduction in allergic disease (AD) than controls. There was no significant effects on asthma or atopy (hyperallergic). In a randomized double-blind study, 415 pregnant women received either pro-biotic milk or placebo from 36 weeks of pregnancy to 3 months postnatally. The probiotic milk contained 5 billion CFU of *Lactobacillus rhamnosus* GG, and 50 billion CFU of *L. acidophilus* La-5 and *Bifidobacterium animalis* subsp. lactis Bb-12. Children with an itchy rash for more than 4 weeks were assessed for AD. At 2 years of age, all children were assessed for atopic sensitization, AD, asthma and allergic sinus infection. At 2 years, 138 and 140 children in the probiotic and the placebo groups, respectively, were assessed. There was a 50% reduction in allergic disease, but no significant effects on asthma or atopy.

Dotterud CK, Storro O, Johnsen R, Oien T. Probiotics in pregnant women to prevent allergic disease: a randomized, double-blind trial. *Br J Dermatol.* 2010; 163: 616-23.

http://www.ncbi.nlm.nih.gov/pubmed/20545688?dopt=Abstract&holding=f1000,f1000m,isrctn

B. Probiotic supplementation had a protective effect against allergic sensitization in infants with a high hereditary risk due to maternal allergies. Atopic eczema was less likely in the probiotic group then the placebo group. This study examined whether a probiotic supplement given to allergic mothers from the first trimester until the end of exclusive breastfeeding had an effect on infant sensitization. Altogether, 171 mother–infant pairs received either the probiotics *Lactobacillus rhamnosus* strain GG and *Bifidobacterium lactis* Bb12 10 billion CFU/day or placebo in addition to dietary counseling. Mother's breast milk was tested for cytokine levels, and both mother and infant had skin prick tests (SPT) to determine presence of allergies. Probiotic supplementation had a significant protective effect against sensitization in a subgroup of infants with a high hereditary risk due to maternal sensitization: 26% of the infants in the probiotic group vs. 50% in the placebo group tested SPT-positive when the mother was SPT-positive. When the mother had allergic disease, 29.3% of the infants in the probiotic group and 35.8% in the placebo group tested SPT-positive at the age of 12 months. Atopic eczema was diagnosed at the age of 12 months in 13.6% of the infants: 9.7% in the probiotic and 17.6% in the placebo group.

Huurre A, Laitinen K, Rautava S, Korkeamaki M, Isolauri E. Impact of maternal atopy and probiotic supplementation during pregnancy on infant sensitization: A double-blind placebo-controlled study. *Clin Exp Allergy*. 2008; 38:1342-8.

http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2222.2008.03008.x/abstract

C. This review article demonstrates that use of probiotic supplements during pregnancy and/or during infancy creates a statistically significant decline in the incidence of infant/childhood eczema. The authors reviewed articles from MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, and PubMed to search for trials regarding probiotic usage and eczema development from 1945 to 2013. Participants were 7 years old or younger with probiotic exposure in utero or below 6 months of age and who were not diagnosed previously with eczema. 27 publications assessing 10 probiotics in 2,797 participants met the criterion. The pooled relative risk of all the studies indicated that probiotic supplementation in the first several years of life did have a significant impact on development of eczema.

Mansfield, J. A., Bergin, S. W., Cooper, J. R., & Olsen, C. H. (2014). Comparative Probiotic Strain Efficacy in the Prevention of Eczema in Infants and Children: A Systematic Review and Meta-Analysis. *Military Medicine,* 179(6), 580-592.

http://publications.amsus.org/doi/abs/10.7205/MILMED-D-13-00546

D. In this study of probiotic supplementation vs. placebo early in life, 17% of the placebo group were later diagnosed with attention deficit hyperactivity disorder (ADHD) or Asperger syndrome (AS), vs. none in the probiotic group. 75 infants who were randomized to receive *Lactobacillus rhamnosus* GG or placebo during the first 6 months of life were followed-up for 13 years. Gut microbiota was assessed at the age of 3 week, 3, 6, 12, 18, 24 months, and 13 years. The diagnoses of ADHD and Asperger syndrome (AS) by a child neurologist or psychiatrist were based on ICD-10 diagnostic criteria. At the age of 13 years, ADHD or AS was diagnosed in 6/35 (17.1%) children in the placebo and none in the probiotic group. The mean (SD) numbers of Bifidobacterium species bacteria in feces during the first 6 months of life was lower in affected children than in healthy children. Early probiotic supplementation may reduce the risk of neuropsychiatric disorder development later in childhood possible by mechanisms not limited to gut microbiota composition.

Pärtty, A., Kalliomäki, M., Wacklin, P., Salminen, S., & Isolauri, E. (2015). A possible link between early probiotic intervention and the risk of neuropsychiatric disorders later in childhood: a randomized trial. *Pediatric Research*, 77(6), 823-828.

http://www.nature.com/pr/journal/v77/n6/abs/pr201551a.html

E. Mothers with mastitis who took a probiotic supplement had less breast pain, recovered more quickly and had lower rates of recurrence than those taking antibiotics. Certain probiotic strains have been found to be helpful in the treatment of mastitis, a bacterial infection which can cause painful breast inflammation and redness in nursing mothers, and a common cause of premature weaning. A study of 352 breastfeeding mothers with mastitis found that those who took a daily probiotic (a capsule containing 90 billion cells of either *Lactobacillus fermentum* CECT5716 or *Lactobacillus salivarius* CECT5713 — both being strains found in breast milk) for 21 days had significantly less breast pain, lower total bacterial counts and greater rates of complete recovery (88% and 85%, respectively) than women taking an antibiotic (29%). Women taking either strain of probiotic also had lower rates of recurrence of infection (10.5% and 7.1%, respectively) compared to women who took an antibiotic (30.7%).

Arroyo, R., Martín, V., Maldonado, A., Jiménez, E., Fernández, L., & Rodríguez, J. M. (2010). Treatment of infectious mastitis during lactation: antibiotics versus oral administration of Lactobacilli isolated from breast milk. *Clinical Infectious Diseases*, 50(12), 1551-1558.

http://cid.oxfordjournals.org/content/50/12/1551.full

F. Colicky infants given a probiotic supplement cried less, had less episodes of regurgitation and an increased frequency in stools than those given placebo. They also had less emergency room visits for colic and needed fewer use of other treatments for abdominal discomfort. *Lactobacillus reuteri* DSM 17938 has also shown benefit in reducing colic in some infants. A 3-month, multi-site study of 589 healthy newborns given 100 million cells per day (from 5 drops of an oil formulation sold as Gerber Soothe Colic Drops) found that, compared to placebo, infants receiving the probiotic drops had a significant decrease in crying time (38 minutes vs. 71 minutes per day), regurgitation (2.9 vs. 4.6 times per day) and an increase in frequency of stools (4.2 vs. 3.6 times per day). The declines in crying time and regurgitation were significant within the first month of treatment. Treated infants also had significantly fewer visits to emergency rooms for colic, fewer lost working days among parents, and lower use of other treatments for abdominal discomfort.

Indrio F, Di Mauro A, Riezzo G, et al. Prophylactic Use of a Probiotic in the Prevention of Colic, Regurgitation, and Functional Constipation: A Randomized Clinical Trial. *JAMA Pediatrics* 2014; 168(3):228-233.

http://archpedi.jamanetwork.com/article.aspx?articleid=1812293

G. A study in infants with colic severe enough for parents to seek emergency care found

that the same probiotic, given for one month, provided no more benefit than placebo. In this study 127 infants were given the same probiotic, *Lactobacillus reuteri* DSM 17938 as the previous study above, or placebo for one month. Although daily duration of cry or fuss decreased over the study period in both groups, the decline by 1 month was greater in the placebo group than probiotic group, with a mean difference in reduction of 46 minutes. Similarly, laboratory analyses of fecal samples at 1 month (treatment group n=31, placebo group n=34) showed no differences between groups in fecal microbial diversity, calprotectin levels, or E coli load. Additional studies are underway that may help determine which subgroups of infants are most likely to benefit from probiotics.

Sung Valerie, Hiscock Harriet, Tang Mimi L K, Mensah Fiona K, Nation Monica, Satzke Catherine et al. Treating infant colic with the probiotic *Lactobacillus reuteri*: double blind, placebo controlled randomised trial. *BMJ*, 2014; 348g: 2107.

http://www.bmj.com/content/348/bmj.g2107

H. A meta-analysis of twelve studies found that probiotic administration to pre-term infants reduced the risk of both necrotizing enterocolitis (NEC) and overall mortality. The study included 10,000 premature neonates with 5,144 in the probiotic supplemented group and 5,656 in the control group. Probiotic supplementation reduced the risk of NEC by 45% and the risk of mortality by 28%. There was no significant difference in sepsis among the two groups.

Olsen R, Greisen G, Schrøder M, Brok J. Prophylactic Probiotics for Preterm Infants: A Systematic Review and Meta-Analysis of Observational Studies. *Neonatology.* 2015 Dec 2;109(2): 105-112.

http://www.karger.com/Article/FullText/441274

I. A meta-analysis of seventeen studies found that supplementation of infants with probiotics significantly reduced the risk of allergic eczema. The seventeen studies included 4755 children with 2381 in the probiotic group and 2374 in the control group. The relative risk of infant eczema was reduced by 22% in children who received any probiotics and by 46% in infants who were supplemented with a mixture of probiotics. The added benefit of probiotic mixtures is consistent with results from other human and lab animal studies.

Zuccotti G, Meneghin F, Aceti A, Barone G, Callegari ML, Di Mauro A, Fantini MP, Gori D, Indrio F, Maggio L, Morelli L, Corvaglia L; Italian Society of Neonatology. Probiotics for prevention of atopic diseases in infants: systematic review and meta-analysis. *Allergy.* 2015 Nov; 70 (11):1356-71.

http://onlinelibrary.wiley.com/doi/10.1111/all.12700/abstract;jsessionid=5748838421236182 31FE0129242533EA.f03t01

⑨ Clean Water

Summary: *We recommend drinking pure, filtered water to avoid harmful chemicals that are often present in typical drinking water. Pesticides, toxic metals, and water disinfection chemicals are present in the general water supply and are associated with increased rates of fertility problems, miscarriages, birth defects, intellectual disability, and autism. Purification of water for drinking, cooking, bathing, and showering is recommended.*

Scientific Evidence

A. The CDC Advisory Committee on Childhood Lead Poisoning Prevention recommends to reduce or eliminate lead sources for children before they are exposed and to reduce lead concentrations in drinking water as much as possible. For the many children living in housing built before 1978, lead hazard sources include lead paint as well as lead in plumbing components and fixtures. Children can still be exposed to tap water with lead levels of ≥15 ppb if they live in older homes that are more likely to have lead water pipes or fixtures. When investigating cases of children with blood lead levels (BLLs) at or above the reference value established as the 97.5 percentile of the distribution of BLLs in U.S. children aged 1–5 years, drinking water should be considered as a source.

Brown, M. J., & Margolis, S. (2012). *Lead in drinking water and human blood lead levels in the United States.* US Department of Health and Human Services, Centers for Disease Control and Prevention.

http://www.cdc.gov/mmWR/preview/mmwrhtml/su6104a1.htm

B. Prenatal lead exposure at modest levels has measurable adverse effects on maternal and infant health, such as fertility, hypertension, and infant neurodevelopment. In 2004, 143,000 deaths and a loss of 8,977,000 disease-adjusted life years were attributed to lead exposure worldwide,

primarily from lead-associated adult cardiovascular disease and mild intellectual disability in children. Children represent approximately 80% of the disease impact attributed to lead, with an estimated 600,000 new cases of childhood intellectual disabilities each year resulting from blood lead levels ≥10 µg/dL.

Velleman Y, Mason E, Graham W, Benova L, Chopra M, Campbell OMR, et al. (2014) From Joint Thinking to Joint Action: A Call to Action on Improving Water, Sanitation, and Hygiene for Maternal and Newborn Health. *PLoS Med* 11(12): e1001771.

http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1001771

C. Atrazine is an endocrine disrupter present in some public water supplies and can be avoided by drinking purified water and eating an all organic diet. Although the European Union banned the pesticide in 2004, atrazine (a weed killer) is still widely used in the United States, especially on corn crops. More than 90 percent of the samples taken in 139 water systems in the US had measurable levels of atrazine in both 2003 and 2004. It is present in 75% of streams.

Wu, M., Quirindongo, M., Sass, J., & Wetzler, A. (2009). Poisoning the well. *Natural Resources Defense Council*, 1-25.

https://www.nrdc.org/health/atrazine/files/atrazine.pdf

D. Exposure to manganese at levels common in groundwater is associated with intellectual impairment in children. Manganese is an essential nutrient, but in excess it can be neurotoxic. This cross-sectional study included 362 children 6–13 years of age living in communities supplied by groundwater. Manganese concentration was measured in home tap water (MnW) and children's hair (MnH). Higher MnW and MnH were significantly associated with lower IQ scores.

Bouchard, M. F., Sauvé, S., Barbeau, B., Legrand, M., Brodeur, M. È., Bouffard, T., ... & Mergler, D. (2010). Intellectual impairment in school-age children exposed to manganese from drinking water. *Environmental health perspectives*, 119(1), 138-143.

http://ehp.niehs.nih.gov/1002321/

E. Disinfection by-products (DBPs) in drinking water are hazardous and can also be inhaled or absorbed through the skin during showering, bathing, and swimming in chlorinated swimming pools. Drinking water DBPs are an unintended consequence of using chemical disinfectants to kill harmful pathogens in water. Potential health risks of DBPs from drinking water include bladder cancer, early-term miscarriage, and birth defects. Risks from swimming pool DBP exposures include asthma and other respiratory effects.

Richardson, S.D., & Postigo, C. (2011). Drinking water disinfection by-products. *Emerging Organic Contaminants and Human Health*, 20, 93-137.

http://link.springer.com/chapter/10.1007/698_2011_125

F. National Research Council reviews current scientific literature on health effects of the addition of fluoride to public drinking water. They raise great concerns due to the links between fluoride and a large number of serious health conditions.

Goal, M. C. L. (2006). Fluoride in drinking water: a scientific review of EPA's standards.

http://www.actionpa.org/fluoride/nrc/NRC-2006.pdf

G. Health warning with cited studies urging parents to avoid fluoride (including fluoridated drinking water) in infants less than 1 year old. Health risks include: enamel fluorosis (32% of American children), endocrine disruption and bone cancer.

http://fluoridealert.org/articles/50-reasons/

Scientific Evidence

A. A recent review of the latest epidemiological studies found that exposure to ambient air pollution during early child development has a negative impact on the neuropsychological development of children. The evidence is particularly relevant to fine particulate matter. The authors conclude that the public health impact of air pollutants cannot be ignored and the precautionary principle should be applied to protect children.

⑩ Clean Air

Summary: *We recommend airing out your home at least once per week and avoiding high pollution areas when possible. Use a HEPA filter to purify air. Air pollution (including smoking and second-hand smoke) adversely affects fertility, miscarriage rates, preterm births, birth defects, sudden infant death, and autism.*

Suades-González, E., Gascon, M., Guxens, M., & Sunyer, J. (2015). Air pollution and neuropsychological development: a review of the latest evidence. *Endocrinology*, 156(10), 3473-3482.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4588818/

B. A review of many studies found that exposure to air pollution during the prenatal period significantly increased the risk of autism. Mercury, toxic metals, and particulates were the primary risk factors.

Lyall K, Schmidt RJ, and Hertz-Picciotto I. Maternal lifestyle and environmental risk factors for autism spectrum disorders. *International Journal of Epidemiology*, 2014, 443–464

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3997376/

C. Air pollution has a significant effect on miscarriage and clinical pregnancy rates, especially on patients with fertility problems. Ten studies were included and divided into animal studies and human epidemiological studies including the general population as well as women undergoing in vitro fertilization and embryo transfer (IVF/ET). Results from this systematic review suggest a significant impact of air pollution on miscarriage and clinical pregnancy rates in the general population, whereas among subfertile patients certain air pollutants seem to exert a greater impact on fertility outcomes, including miscarriage and live birth rates.

Frutos, V., Gonzalez-Comadran, M., Sola, I., Jacquemin, B., Carreras, R. & Checa, M.A. (2015). Impact of air pollution on fertility: a systematic review. *Gynecological Endocrinology*, 31(1), 7-13.

http://www.tandfonline.com/doi/pdf/10.3109/09513590.2014.958992

D. Maternal exposure to particulate pollution was associated with low birth weight (LBW). This study aimed to quantify the association between maternal exposure to particulate air pollution and term birth weight and LBW across 14 centers from 9 countries. In meta-analyses, term LBW was positively associated with an increase in particulate matter found in the air.

Dadvand, Parker, J., Bell, M.L., Bonzini, M., Brauer, M., Darrow, L.A., … & Woodruff, T.J. (2013). Maternal exposure to particulate air pollution and term birth weight: a multi-country evaluation of effect and heterogeneity. *Environmental Health Perspectives*, 121(3), 267-273.

https://dash.harvard.edu/bitstream/handle/1/11365872/3621183.pdf?sequence=1

E. The American College of Preventive Medicine recommends reducing exposure to secondhand smoke due to serious health risks, especially for children and pregnant women. Secondhand smoke exposure contributes to poor birth weight, congenital anomalies, and sudden infant deaths and sudden unexplained infant deaths. Second hand smoke is estimated to contribute to heart attacks in nonsmokers and nearly 53,800 deaths in the U.S. annually.

Jacobs, M., Alonso, A.M., SHerin, K.M., Koh, Y., Dhamija, A. & Lowe, A.L. (2013). Policies to restrict secondhand smoke exposure: American college of preventive medicine position statement. *American Journal of Preventative Medicine*, 45(3), 360-367.

http://www.sciencedirect.com/science/article/pii/S0749379713003218

F. Exposure of pregnant rats to diesel exhaust reduces progesterone, which is required for maintenance of normal pregnancy in mammals, and stimulates the function of the adrenal cortex, suggesting a risk of spontaneous abortion associated with maternal hormonal changes. Nanoparticles in diesel exhaust potentially have profound impact on fetal development and maternal endocrine function during pregnancy due to their ability to penetrate deeply into the body. To investigate the effects of nanoparticle-rich diesel exhaust (NR-DE) on pregnancy, pregnant rats were exposed to NR-DE, filtered diesel exhaust (F-DE) or clean air for 19 days of gestation. The serum concentration of maternal progesterone was significantly lower, while those of luteinizing hormone (LH) and corticosterone were significantly higher in the NR-DE and F-DE groups than those in the control group. The serum concentration of estradiol was significantly higher in the F-DE group. In fetuses, body weight was greater and crown-rump length was shorter in the NR-DE and F-DE groups than those in the control group.

ChunMei, L.I., Xuezheng, L.I., Suzuki, A.K., Fujitani, Y., Nagaoka, K., Watanabe, G., Taya, K. (2012). Effects of exposure to nanoparticle-rich diesel exhaust on pregnancy in rats. *The Journal of Reproduction and Development*, 59(2), 145-150.

http://europepmc.org/articles/pmc3934203

G. Living in areas with higher levels of air pollution during pregnancy was associated with increased risk of autism. Air pollution contains many toxicants known to have adverse effects on the fetus. Researchers conducted a population based case–control study of 217 cases of ASD in southwestern Pennsylvania to estimate the association between ASD and levels for 30 neurotoxicants from air pollution. The study noted a significantly higher number of cases of ASD when comparing the lowest and highest exposure rates of several of the pollutants studied.

Talbott, E.O., Marshall, L.P., Rager, J.R., Arena, V.C., Sharma, R.K., & Stacy, S.L. (2015). Air toxics and the risk of autism spectrum disorder: the results of a population based case-control study in southwestern Pennsylvania. *Environmental Health*, 14(80).

http://www.ehjournal.net/content/14/1/80

H. Exposure to fine particulate matter in the air increases the rate of preterm birth (PTB). Exposures to toxic air particulates beginning around the time of implantation and near birth appeared to be more strongly associated with PTB than exposures during other time periods. Exposures during the week of birth and the 2 weeks before birth also were positively associated with all PTB categories.

Rappazzo KM, Daniels JL, Messer LC, Poole C, Lobdell DT. 2014. Exposure to fine particulate matter during pregnancy and risk of preterm birth among women in New Jersey, Ohio, and Pennsylvania, 2000–2005. *Environ Health Perspect* (122), 992–997.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4154214/pdf/ehp.1307456.pdf

I. Exposure to traffic-related air pollution during pregnancy and the first year of life was associated with a 3-fold increase in risk for autism. Examination of hazardous pollutants has suggested the importance of traffic related pollutants in autism etiology. This study includes data on 279 autism cases and 245 typically developing controls enrolled in the Childhood Autism Risks from Genetics and the Environment (CHARGE) Study in California. Autism cases were 3 times more likely to live at residences in the highest quartile traffic related pollution exposure during pregnancy and the first year of life compared to controls living in the areas with the lowest pollution rates.

Volk, H. E., Lurmann, F., Penfold, B., Hertz-Picciotto, I., & McConnell, R. (2013). Traffic Related Air Pollution, Particulate Matter, and Autism. *JAMA Psychiatry,* 70(1), 71–77.

http://doi.org/10.1001/jamapsychiatry.2013.266

J. Short-term decreases in air pollution late in pregnancy in Beijing during the 2008 Summer Olympics, a normally heavily polluted city, were associated with higher birth weight. Using 83,672 term births to mothers residing in four urban districts of Beijing, this study estimated the difference in birth weight associated with having individual months of pregnancy during the 2008 Olympics (8 August–24 September 2008) compared with the same dates in 2007 and 2009. Babies whose 8th month of gestation occurred during the 2008 Olympics were, on average, 23 g larger than babies whose 8th month occurred during the same calendar dates in 2007 or 2009.

Rich, D. Q., Liu, K., Zhang, J., Thurston S.W., …, & Zhang, J. (2015). Differences in birth weight associated with the 2008 Beijing Olympics air pollution reduction: results from a natural experiment. *Environmental Health Perspectives*, 123(9), 880-887.

http://ehp.niehs.nih.gov/wp-content/uploads/123/9/ehp.1408795.alt.pdf

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11 Reducing Exposure to Toxic Chemicals and Toxic Metals

Summary: *We recommend reducing exposure to toxic chemicals such as plastics, paints, cleaning products and beauty products. Exposure to toxic chemicals and toxic metals is associated with lower birth weight, lower scores in memory and IQ, and increased risk of ADHD, autism spectrum disorder, birth defects, and infant death.*

Scientific Evidence

A. A comprehensive review summarizes various sources of wide spread environment toxic exposures and their known adverse effects on child development. These exposures include tobacco smoke, ethanol (alcohol), solvents, heavy metals, volatile organic compounds, persistent organic pollutants, and pesticides. Various prevention strategies for each exposure are offered that are relevant to the precautionary principal.

Falck AJ; Mooney S; Kapoor SS; White KM; Bearer C; El Metwally D. Developmental Exposure to Environmental Toxicants. [Review] *Pediatric Clinics of North America*. 62(5):1173-97, 2015 Oct.

http://www.ncbi.nlm.nih.gov/pubmed/26318946

B. Prenatal exposure to chlorpyrifos is associated with deficits in Working Memory Index and Full-Scale IQ at 7 years of age. In a sample of 265 children in a prospective study of air pollution, this study measured prenatal chlorpyrifos (CPF) exposure using umbilical cord blood and 7-year neurodevelopment using the Wechsler Intelligence Scale for Children, 4th edition (WISC-IV). On average, for each standard deviation increase in CPF exposure, Full-Scale intelligence quotient (IQ) declined by 1.4% and Working Memory declined by 2.8%.

Rauh, V., Arunajadai, S., Horton, M., Perera, F., Hoepner, L., Barr, D.B., & Whyatt, R. Seven-year neurodevelopmental scores and prenatal exposure to chlorpyrifos, a common agricultural pesticide. *Environmental Health Perspectives* 2011; 119, 1196-1201.

http://ehp.niehs.nih.gov/1003160/

C. The results of this experiment support an association between even low-level prenatal organochlorine exposure and ADHD-like behaviors in childhood. Organochlorines are environmentally persistent contaminants that readily cross the placenta, posing a potential risk to the developing fetus. The authors examined 607 children between the ages of 7-11 years old and found higher risk for ADHD-like behaviors assessed with the Conner's Rating Scale for Teachers at higher levels of PCBs, dioxin like PCBs and p,p′-DDE, which are all environmental contaminants. Across the 3 exposures, risk of ADHD-like behaviors increased by 26%–92% for the highest quartiles of exposure versus the lowest quartiles.

Sagiv, S.K., Thurston, S.W., Bellinger, D.C., Tolbert, P.E., Altshul, L.M., & Korrick, S.A. (2009). Prenatal organochlorine exposure and behaviors associated with attention deficit hyperactivity disorder in school-aged children. *American Journal of Epidemiology*, 171(5), 593-601.

http://aje.oxfordjournals.org/content/171/5/593.full

D. Lipids and lipid signaling pathways, such as prostaglandin E2 (PGE2), are crucial in the development of the brain. Toxic air pollutants, pesticides and consumer products are shown to disrupt signaling of this important lipid mediator causing disruptions in key areas of brain development and gene expression. The lipid mediator PGE2 is crucial in brain development and function. Exposure to environmental chemicals such as toxic air pollutants, pesticides and consumer products have been shown to cross the blood brain barrier in the developing fetus. These chemicals increase inflammation, oxidative stress, and cause permanent changes in the PGE2 signaling in the brain. Research shows that these products disrupt neuronal development, cognitive and behavioral abnormalities and alter gene expression.

Wong, C. T., Wais, J., Crawford, D. A. (2015). Prenatal exposure to common environmental factors affects brain lipids and increases risk of developing autism spectrum disorders. *European Journal of Neuroscience*, 42: 2742-2760.

http://onlinelibrary.wiley.com/doi/10.1111/ejn.13028/abstract;jsessionid=12D932732E10F7A09DFD4228A5DFFB6E.f02t01

E. Exposure to high levels of residential insecticides impaired fetal growth. Findings support recent regulatory action to phase out residential uses of the insecticides. This study of 314 mother–newborn pairs measured exposure of insecticide chemicals chlorpyrifos and diazinon in maternal personal air during pregnancy as well as in umbilical cord plasma at delivery. For each unit increase in cord plasma chlorpyrifos levels, birth weight decreased by 42.6 g and birth length decreased by 0.24 cm. Combined measures of cord plasma chlorpyrifos and diazinon were also inversely associated with birth weight and length. Birth weight averaged 186.3 g less among newborns with the highest, compared with lowest exposure levels. Results indicate that prenatal chlorpyrifos exposures

have impaired fetal growth among this cohort and that diazinon exposures may have contributed to the effects.

Whyatt, R. M., Rauh, V., Barr, D. B., Camann, D. E., Andrews, H. F., Garfinkel, R., Perera, F. P. (2004). Prenatal Insecticide Exposures and Birth Weight and Length among an Urban Minority Cohort. *Environmental Health Perspectives*, 112(10), 1125–1132.

http://doi.org/10.1289/ehp.6641

F. Review of 37 articles examining exposure to environmental toxins at various stages of development, potential genetic susceptibilities to these toxicants and risk for autism spectrum disorder. Findings suggest that the etiology of ASD involve a complex interaction between genetic factors and environmental toxicants in a subset of children. The authors examined publications investigating potential associations between environmental toxicants and ASD. Within studies examining exposure to environmental toxicants during critical periods of development, 92% of studies reported an association between toxic exposure in the environment and ASD, especially in regards to pesticides, phthalates, polychlorinated biphenyls (PCBs), solvents, toxic waste sites, air pollutants and heavy metals, with the strongest evidence found for air pollutants and pesticides. In studies examining biomarkers or toxicants there were mixed findings, with only 47% reporting higher concentrations of heavy metals in blood, urine, hair, brain or teeth of children with ASD. Other biomarker studies reported that solvent, phthalate and pesticide levels were associated with ASD, whereas PCB studies were mixed. Regarding studies investigating potential genetic susceptibilities to toxicants, 10 unique studies examined polymorphisms in genes associated with increased susceptibilities to toxicants, with 8 studies reporting that such polymorphisms were more common in ASD. Notably, many of the reviewed studies had significant limitations, including lack of replication, limited sample sizes, retrospective design, recall and publication biases, inadequate matching of cases and controls, and the use of nonstandard tools to diagnose ASD. The findings suggest that the etiology of ASD may involve complex interactions between genetic factors and certain environmental toxicants that may act synergistically in a manner that increases the likelihood of developing ASD.

Rossignol, D. A., Genuis, S. J., & Frye, R. E. (2014). Environmental toxicants and autism spectrum disorders: a systematic review. *Translational Psychiatry*, 4(2), e360.

http://www.nature.com/tp/journal/v4/n2/full/tp20144a.html

G. Review of 60 articles focusing on exposure to pesticides, heavy metals, PCBs, and Manganese and the risk of developing ADHD. Five major studies have investigated organophosphate pesticides (OP) and ADHD. OP exposure has been associated with symptoms consistent with ADHD, particularly hyperactivity. OP pesticides inhibit acetylcholinesterase levels and alter the levels of other neurotransmitters and growth factors. OPs also adversely affect motor development. Recent studies have shown that some genetic variations render the mother and child more susceptible to the effects of OP pesticides. There are few human studies on the effects of organochlorines including DDT and PCBs; however, several rodent and primate studies indicate ADHD-like behavior following exposure. PCBs are known to alter dopamine levels and children with ADHD have been shown to have lower cellular dopamine levels. This may be one possible mechanism underlying organochlorine toxicity, nevertheless, there are insufficient studies to determine the exact biological mechanisms. PCBs have been associated with decreased concentration as well as verbal, pictorial and working memory. Impulsivity and problems with attention have also been correlated with PCB exposure. Some studies have shown correlations with mercury exposure and hyperactivity and attention problems, however other studies have shown conflicting results. The link between ADHD and lead exposure is well-established. Eleven studies report ADHD symptoms associated with lead, with several showing deficits at levels below the safety threshold established by the World Health Organization.

Only two studies have examined the association of manganese exposure and ADHD. Both studies showed positive associations with ADHD.

Polanska K, Jurewicz J, Hanke W. Review of current evidence on the impact of pesticides, polychlorinated biphenyls and selected metals on attention deficit / hyperactivity disorder in children. *Int J Occup Med Environ Health* 2013; 26(1):16–38.

http://ijomeh.eu/Review-of-current-evidence-on-the-impact-of-pesticides-polychlorinated-biphenyls-and-selected-metals-on-attention-deficit-hyperactivity-disorder-in-children,2211,0,2.html

H. Paints release PCBs, indicating widespread contamination of homes, offices and schools with a previously unknown source of banned PCBs. Thirty-three commercial paints purchased from three stores tested positive for PCB contamination. Fifty PCB congeners were detected in two paint pigments widely used in the paint industry. These pigments are also found ink, textiles, paper, cosmetics, leather, plastics, food and other materials. PCB exposure has been linked to birth defects and numerous other adverse health conditions.

Hu D, Hornbuckle KC. Inadvertent polychlorinated biphenyls in commercial paint pigments. Environ Sci Technol. 2010 Apr 15; 44(8):2822-7.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2853905/

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I. Review article on neurodevelopmental disabilities and industrial chemicals that are known to injure developing brains. Neurodevelopmental disabilities, including autism, attention-deficit hyperactivity disorder, dyslexia, and other cognitive impairments, affect millions of children worldwide, and some diagnoses seem to be increasing in frequency. Industrial chemicals that injure the developing brain are among the known causes for this rise in prevalence. In 2006, the authors did a systematic review and identified five industrial chemicals as developmental neurotoxicants: lead, methylmercury, polychlorinated biphenyls, arsenic, and toluene. Since 2006, epidemiological studies have documented six additional developmental neurotoxicants manganese, fluoride, chlorpyrifos, dichlorodiphenyltrichloroethane, tetrachloroethylene, and the polybrominated diphenyl ethers. The authors postulate that even more neurotoxicants remain undiscovered.

Grandjean, P., & Landrigan, P. J. (2014). Neurobehavioural effects of developmental toxicity. *The Lancet Neurology*, 13(3), 330-338.

http://www.sciencedirect.com/science/article/pii/S1474442213702783

J. Areas of the country with the highest acreage of durum wheat, which is heavily sprayed with particular herbicides, showed significant increases in birth malformations and infant death from congenital defects. Most of the spring and durum wheat produced in the United States is grown in Minnesota, Montana, North Dakota, and South Dakota, with more than 85% of the acreage treated with chlorophenoxy herbicides such as 2,4-dichlorophenoxyacetic acid (2,4-D) and 4-chloro-2-methylphenoxyacetic acid (MCPA). Rates of adverse birth outcomes in rural, agricultural counties of these states during 1995-1997 were studied. Significant increases in birth malformations were observed for the circulatory/respiratory category for combined sexes. In addition, infants conceived during April-June—the time of herbicide application—had an increased chance of being diagnosed with circulatory/respiratory (excluding heart) malformations compared with births conceived during other months of the. Musculoskeletal/integumental anomalies increased for combined sexes in the high-wheat counties. Infant death from congenital anomalies significantly increased in high-wheat counties for males but not for females. These results are especially of concern because of widespread use of chlorophenoxy herbicides.

Schreinemachers, D. M. (2003). Birth malformations and other adverse perinatal outcomes in four US Wheat-producing states. *Environmental Health Perspectives*, 111(9), 1259.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1241584/

K. Maternal acetaminophen use during pregnancy is associated with a higher risk for HKDs and ADHD-like behaviors in children. Study of 64,322 live-born children and mothers enrolled in the Danish National Birth Cohort during 1996-2002. Children whose mothers used acetaminophen during pregnancy were at higher risk for receiving a hospital diagnosis of HKD (hazard ratio = 1.37; 95% CI, 1.19-1.59), use of ADHD medications (hazard ratio = 1.29; 95% CI, 1.15-1.44), or having ADHD-like behaviors at age 7 years (risk ratio = 1.13; 95% CI, 1.01-1.27). Stronger associations were observed with use in more than 1 trimester during pregnancy, and exposure response trends were found with increasing frequency of acetaminophen use during gestation for all outcomes.

Liew, Z., Ritz, B., Rebordosa, C., Lee, P. C., & Olsen, J. (2014). Acetaminophen use during pregnancy, behavioral problems, and hyperkinetic disorders. *JAMA Pediatrics*, 168(4), 313-320.

http://archpedi.jamanetwork.com/article.aspx?articleid=1833486&mrefcanalimliberoit

Additional reading on toxic chemicals:

L. Great resource for reducing toxic exposure from beauty products:

http://www.healthychild.org/when-looking-good-is-bad-for-baby/

⓬ Avoiding Endocrine Disruptors

Summary: *We recommend avoiding products that contain endocrine disruptors including plastics and many beauty products, and instead choosing glass containers and natural products whenever possible. Studies suggest that endocrine disruptors may increase the risk of autism spectrum disorders, miscarriages, and developmental disabilities. Even some "BPA-free" products often contain replacement chemicals with estrogenic activity, but some BPA-free PC-replacement products (made from glycol-modified polyethylene terephthalate or cyclic olefin polymer) did not release chemicals with detectable EA under any conditions tested.*

Scientific Evidence

A. Reducing exposure to endocrine disrupters during pregnancy can improve fetal survival and growth, and prevent some chronic diseases in offspring. This review focuses on endocrine disrupters that prevent development of uterine glands to negatively impact fertility, as well as the importance of the uterus in providing mechanisms for transport of nutrients. Key events affecting the ability of mammals to reproduce begin in utero with differentiation of the gonads and male and female reproductive systems. However, full differentiation of the female reproductive system is a unique postnatal event in mammals that is vulnerable to endocrine disrupters such as environmental estrogens and progestins that render the uterus nonfunctional.

Bazer, F.W., Wu, G., Johnson, G.A., & Xiaqiu, W. (2014). Environmental factors affecting pregnancy: Endocrine disrupters, nutrients and metabolic pathways. Molecular and Cellular Endocrinology, 398(1-2), 53-68.

http://www.ncbi.nlm.nih.gov/pubmed/25224489

B. Early-life exposure to endocrine disrupting chemicals (EDCs) impairs immune function elevating the risk of unresolving inflammation and chronic diseases. A recent review of immunotoxicity following exposure to EDCs identifies misregulated inflammation as a common adverse immune outcome. Persistent unresolving inflammation paired with immune dysfunction elevated the risk of several chronic diseases.

Dietert, R.R. (2012). Misregulated inflammation as an outcome of early-life exposure to endocrine-disrupting chemicals. *Reviews in Environmental Health*, 27(2-3):117-31.

http://www.degruyter.com/view/j/reveh.2012.27.issue-2-3/reveh-2012-0020/reveh-2012-0020.xml

C. Prenatal exposure to phthalates was associated with worse behavioral and attention deficit problems. The Mount Sinai Children's Environmental Health Study enrolled a multiethnic prenatal population of 404 mothers in New York City. Third-trimester maternal urines were collected and analyzed for phthalate metabolites, and children were assessed for cognitive and behav-ioral development between the ages of 4 and 9 years. Increased concentrations of phthalate metabolites were associated with poorer scores on the aggression, conduct problems, attention problems, and depression clinical scales; and externalizing problems and behavioral symptom index composite scales.

Engel, S.M., Miodovnik, A., Canfield, R.L., Zhu, C., Silva, M.J., Calafat, A.M., & Wolff, M.S. (2010). Prenatal phthalate exposure is associated with childhood behavior and executive functioning. *Environmental Health Perspectives*, 118(4), 565-571.

http://www.ncbi.nlm.nih.gov/pubmed/20106747

D. Higher serum MEHP, DEHP, and BPA (known endocrine disruptors) were found in the autism spectrum disorder group compared to healthy controls suggesting that endocrine disruptors may have a role in the development of autism spectrum disorders. The aim of this study was to investigate the relationship between autism spectrum disorders development and exposure to the endocrine disruptors: MEHP, DEHP, BPA, and phthalates. The study included 48 children with autism spectrum disorder and 41 healthy controls. Children with autism spectrum disorder had significantly increased serum MEHP, DEHP, and BPA concentrations compared to healthy control subjects.

Kardas, F., Bayram, A.K., Demirc, I E., Akin, L., Ozmen, S., Kendirci, M., Canpolat, M., Oztop, D.B., Narin, F., Gumus, H., Kumandas, S., & Per, H. (2015). Increased Serum Phthalates (MEHP, DEHP) and Bisphenol A Concentrations in Children with Autism Spectrum Disorder: The role of endocrine disruptors in Autism etiopathogenesis. *Journal of Child Neurology*, published before print.

http://jcn.sagepub.com/content/early/2015/10/07/0883073815609150.abstract

E. This study shows a correlation between environmental exposure to BPA and fetal malformations in humans. There were 151 pregnant women enrolled and divided into two groups: women with established diagnosis of developmental defect, and the control group of pregnant women with normally developed fetus. In case of chromosomal malformations, the average value of free BPA appears

to be nearly three times greater than that of the controls.

Guida, M., Troisi, J., Ciccone, C., Granozio, G., Cosimato, C., Di, A., Sardo, S., Ferrara, C., Guida, M., Nappi, C., Zullo, F., & Di Carlo, C. (2015). Bisphenol A and congenital developmental defects in humans. *Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis*, 774 (April 2015), 33-39.

http://www.sciencedirect.com/science/article/pii/S0027510715000470

F. In response to concern about chemicals leaching from plastic children's products containing BPA, many companies have created BPA free products. This study demonstrates that many of these new products continue to leach endocrine disrupting chemicals and may not be any better than the products they are replacing. This study tested newer products that are meant to replace BPA free children's toys, sippy cups and plates to determine whether they are safer than the toys made with BPA. They found that many unstressed and stressed, BPA free PC-replacement-products made from acrylic, polystyrene, polyethersulfone, and Tritan™ resins leached chemicals with Estrogenic Activity (EA), including products made for use by babies. Exposure to various forms of UV radiation often increased the leaching of chemicals with EA. In contrast, some BPA-free PC-replacement products made from glycol-modified polyethylene terephthalate or cyclic olefin polymer or co-polymer resins did not release chemicals with detectable EA under any conditions tested.

Bittner, G. D., Yang, C. Z., & Stoner, M. A. (2014). Estrogenic chemicals often leach from BPA-free plastic products that are replacements for BPA-containing polycarbonate products. *Environmental Health*, 13, 41.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4063249/pdf/1476-069X-13-41.pdf

G. Maternal prenatal exposure to phthalates are associated with deficits in children's intellectual development, including a 7 point lower IQ score at age 7 years. In a follow up of 328 inner-city mothers and their children, this study measured prenatal urinary metabolites of several phthalates in late pregnancy. The Wechsler Intelligence Scale for Children, 4th edition was administered at child age 7 years and evaluates four areas of cognitive function associated with overall intelligence quotient (IQ). The Child full-scale IQ was inversely associated with prenatal urinary metabolite concentrations of 2 specific phthalates. In children of mothers with the highest versus lowest quartile metabolite concentrations, IQ was 6.7 and 7.6 points lower, respectively. Significant associations were also seen between maternal prenatal metabolite concentrations and child processing speed, perceptual reasoning and working memory. These results indicate that phthalate exposure is common and significantly damaging at typical exposure levels.

Factor-Litvak, P., Insel, B., Calafat, A. M., Liu, X., Perera, F., Rauh, V. A., & Whyatt, R. M. (2014). Persistent Associations between Maternal Prenatal Exposure to Phthalates on Child IQ at Age 7 Years. *PloS one*, 9(12), e114003.

http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0114003

13 Prenatal Care and Medical Testing

Summary: *We recommend regular prenatal check-ups, including a preconception consult. Proper prenatal care and medical testing yield significant benefits for post-partum maternal health, lead to better outcomes in hypertensive disorders of pregnancy, and allow for healthier pregnancy outcomes. Using various tests for chromosomal abnormalities can detect fetal abnormalities in a large number of pregnancies.*

Scientific Evidence

A. Complete prenatal care is associated with better maternal and fetal outcomes in hypertensive disorders of pregnancy. Hypertensive disorders in pregnancy in 1501 women were classified according to usual definitions as chronic hypertension, preeclampsia, eclampsia, and preeclampsia/eclampsia superimposed on chronic hypertension. Adverse maternal and fetal outcomes included maternal death and near miss fetal outcomes documented as stillbirth, neonatal death and newborn respiratory complication. Prenatal care was classified as complete ('6 visits), incomplete (<6 visits) or not done. Women who had incomplete prenatal care or had not done prenatal care had higher mortality rates and greater frequency of near miss cases, and their children had higher mortality rates.

Barbosa, I. R. C., Silva, W. B. M., Cerqueira, G. S. G., Novo, N. F., Almeida, F. A., & Novo, J. L. V. G. (2015). Maternal and fetal outcome in women with hypertensive disorders of pregnancy: the impact of prenatal care. *Therapeutic Advances in Cardiovascular Disease*, 9(4)140-146.

http://tak.sagepub.com/content/9/4/140.short

B. Timely and adequate prenatal care not only creates a positive impact on infant health, but also yields significant benefits for post-partum maternal health. This study examines the impact of adequate prenatal care on the probability of post-partum maternal hospitalization during the first 6 months after birth. The results show that sufficient prenatal care significantly reduces the probability of post-partum maternal hospitalization among women who have had vaginal delivery by 43.8%.

Liu, T.C., Chen, B., Chan, Y.S., & Chen, C.S. (2015). Does prenatal care benefit maternal health? A study of post-partum maternal care use. *Health Policy,* 119(10), 1382-1389.

http://www.ncbi.nlm.nih.gov/pubmed/26189913

C. The rate of occurrence of caesarian section in an area where women do not have high access to prenatal care visits is well above what The World Health Organization recommends. An association is present between social disadvantage and inappropriate access to prenatal care, low number of prenatal medical visits (below 4) and late timing of first visit (after more than 12 gestational weeks). The average rate of cesarean section observed in the sample was 28.2%. This value was higher than expected; The World Health Organization recommends that the caesarean section rate should not be higher than 10% to 15%.

Minelli, L., Pasquini, R., & Chiavarini, M. (2015). The care of pregnant women and their babies: empirical data from Umbria region. *Annali Di Igiene*, 27(3), 539-545.

http://www.ncbi.nlm.nih.gov/pubmed/26152540

D. Newborn screening provides a population-wide safety net for early diagnosis of critical congenital heart defects. In 2011, statewide newborn screening programs for critical congenital heart defects began in the United States, and subsequently screening has been widely implemented. This review focuses on data reports and collection efforts related to both prenatal diagnosis and newborn screening. Defect-specific, maternal, and geographic factors are associated with variations in prenatal detection, so newborn screenings should be used to ensure early diagnosis.

Olney, R.S., Ailes, E.C., & Sontaq, M.K. (2015). Detection of critical congenital heart defects: Review of contributions from prenatal and newborn screening. *Seminars in Perinatology*, 39(3), 230-237.

http://www.ncbi.nlm.nih.gov/pubmed/25979782

E. First trimester screening using a combination of sonography and maternal serum testing can correctly identify 97% of Down's syndrome cases. There is extensive evidence that effective screening for major chromosomal abnormalities can be provided in the first trimester of pregnancy. Prospective studies in a total of 200,868 pregnancies, including 871 fetuses with trisomy 21 (Down's syndrome), have demonstrated that increased nuchal translucency can identify 76.8% of fetuses with trisomy 21, which represents a false-positive rate of 4.2%. When fetal nuchal translucency was combined with maternal serum free–B human chorionic gonadotropin and pregnancy-associated plasma protein-A in prospective studies in a total of 44,613 pregnancies, including 215 fetuses with trisomy 21, the detection rate was 87.0% for a false-positive rate of 5.0%. Studies from specialist centers with 15,822 pregnancies, which included 397 fetuses with trisomy 21, have demonstrated that the absence of the nasal bone can identify 69.0% of trisomy 21 fetuses, which represents a false-positive rate of 1.4%. It has been estimated that first-trimester screening by a combination of sonography and maternal serum testing can identify 97% of trisomy 21 fetuses, which represents a false-positive rate of 5%, or that the detection rate can be 91%, which represents a false-positive rate of 0.5%.

Nicolaides, K. H. (2004). Nuchal translucency and other first-trimester sonographic markers of chromosomal abnormalities. *American Journal of Obstetrics and Gynecology,* 191(1), 45-67.

http://www.ajog.org/article/S0002-9378(04)00339-4/pdf

F. A review of data from over 33,000 pregnancies identifies numerous associations between biomarkers on a maternal screening test called the Quad Screen, and adverse outcomes. The goal was to estimate the effect of second-trimester levels of maternal serum alpha-fetoprotein (AFP), human chorionic gonadotrophin (hCG), unconjugated estriol (uE3), and inhibin A (the quad screen) on obstetric complications by using a large, prospectively collected database (the FASTER database). As part of this trial, patients had a quad screen drawn at 15–18 6/7 weeks. The authors identified numerous associations between the quad screen markers and preterm birth, intrauterine growth restriction, preeclampsia, and fetal loss. The risk of having an adverse outcome increased significantly if a patient had 2 or more abnormal markers. The sensitivity and positive predictive values using combinations of markers is relatively low, although superior to using individual markers.

Dugoff, L., Hobbins, J. C., Malone, F. D., Vidaver, J., Sullivan, L., Canick, J. A., ... & FASTER Trial Research Consortium. (2005). Quad screen as a predictor of adverse pregnancy outcome. *Obstetrics & Gynecology*, 106(2), 260-267.

http://journals.lww.com/greenjournal/Abstract/2005/08000/Quad_Screen_as_a_Predictor_of_Adverse_Pregnancy.9.aspx

14 Exercise

Summary: *We recommend 150 minutes per week of moderate-intensity exercise (or 75 minutes of high-intensity exercise) and strength-building activities during preconception and throughout pregnancy to improve maternal health, fetal outcomes, and an easier birth. A regular and moderate physical exercise program throughout pregnancy is not a risk to maternal and fetal well-being, and has shown to help to control excessive weight gain, improve levels of maternal glucose tolerance, and improve cognitive functioning of offspring.*

Scientific Evidence

A. The American College of Obstetricians and Gynecologists recommends that women with low-risk pregnancies participate in moderate-intensity physical activity during their pregnancy. In this article, the authors provide a critical review of the literature examining the effect of exercise on preeclampsia, gestational diabetes, weight gain, labor and birth, and other issues associated with pregnancy. Overall, the evidence indicates that exercise during pregnancy is safe and perhaps even reduces the risk of preeclampsia and gestational diabetes.

Lewis, B., Avery, M., Jennings, E., Sherwood, N., Martinson, B. & Crain, L.A. (2008). The effect of exercise during pregnancy on maternal outcomes: practical implications for practice. *American Journal of Lifetime Medicine*, 2 (5), 441-445.

http://ajl.sagepub.com/content/2/5/441.abstract

B. Physical activity during pregnancy may modify the brain's functional maturation and determine its lifelong reliability. Research on humans has demonstrated improvement in cognitive performance in the children of women who exercised regularly throughout pregnancy and in individuals who were physically active during childhood and adolescence. Investigations using animal models have also reported that physical activity improves the cognitive function of developing rats. In this review the neurobiological mechanisms of such effects are presented.

Gomes da Silva, S., & Arida, R. M. (2015). Physical activity and brain development. *Expert Review of Neurotherapeutics*, 15(9), 1041-1051.

http://www.tandfonline.com/doi/abs/10.1586/14737175.2015.1077115#.VpgAL4-cHlU

C. Physical activity is beneficial for women during pregnancy and also in the postpartum period; it is not associated with risks for the newborn and can lead to changes in lifestyle that imply long-term benefits. This review aims to provide an update on the recent evidence concerning exercise during pregnancy including effects for mother and fetus and the types, frequency, intensity, duration and rate of progression of exercise performed. Exercises during pregnancy are associated with higher cardiorespiratory fitness, prevention of urinary incontinence and low back pain, reduced symptoms of depression, gestational weight gain control, and for cases of gestational diabetes, reduced number of women who required insulin.

Nascimento, S.L., Surita, F.G., & Cecatti, J.G. (2012). Physical exercise during pregnancy: a systematic review. *Current Opinion in Obstetrics & Gynecology*, 24(6), 387-394.

http://www.ncbi.nlm.nih.gov/pubmed/23014142

D. A moderate physical activity program performed during pregnancy improved levels of maternal glucose tolerance. A physical activity (PA, land/aquatic activities) program during the entire pregnancy (three sessions per week) was conducted by a qualified instructor. 83 healthy pregnant women were randomly assigned to either an exercise group (EG) or a control group (CG). Significant differences were found between study groups on the maternal glucose screen; Values corresponding to the EG were better than those of the CG.

Barakat, R., Cordero, Y., Coteron, J., Luacees, M. & Montejo, R. (2011). Exercise during pregnancy improves maternal glucose screen at 24–28 weeks: A Randomized Controlled Trial. *British Journal of Sports Medicine*, 46(9), 656-661.

http://www.ncbi.nlm.nih.gov/pubmed/21948120

E. A regular and moderate physical activity program throughout pregnancy is not a risk to maternal and fetal well-being, and it helps to control excessive weight gain. Women in the experimental group participated in a physical conditioning program throughout pregnancy, which included a total of 55- to 60-minute weekly sessions, 3 days per week. There were significantly more pregnant women in the control group who gained excessive weight during their pregnancies than in the exercise group. (35.6% vs. 21.2%).

Barakat, R., Perales, M., Bacchi, M., Coteron, J. & Refoyo, I. (2014). A program of exercise throughout pregnancy. Is it safe to mother and newborn? *American Journal of Health Promotion*, 29(1), 2-8.

http://www.ncbi.nlm.nih.gov/pubmed/24200335

F. Review of current literature on exercise in pregnancy concludes marked benefits for mother and fetus. Maternal benefits include improved cardiovascular function, limited pregnancy weight gain, decreased musculoskeletal discomfort, reduced incidence of muscle cramps and lower limb edema, mood stability, attenuation of gestational diabetes mellitus and gestational hypertension. Fetal benefits include decreased fat mass, improved stress tolerance, and advanced neurobehavioral maturation.

Poyatos'León, R., García'Hermoso, A., Sanabria'Martínez, G., Álvarez'Bueno, C., Sánchez'López, M., & Martínez–Vizcaíno, V. (2015). Effects of exercise during pregnancy on mode of delivery: a meta'analysis. *Acta Obstetricia et Gynecologica Scandinavica*.

http://www.ncbi.nlm.nih.gov/pubmed/20524714

G. Exercise performed during pregnancy can help to reduce the prevalence of gestational diabetes mellitus. This study assessed the effectiveness of an exercise program consisting of land and aquatic activities using both aerobic and muscular conditioning on the development of gestational diabetes mellitus (GDM). Three hundred and forty-two pregnant women from Spain without obstetric contraindications were recruited and randomized to the intervention group or the standard care group. The intervention group participated in 50-60 minutes of land and water activities three times per week. The prevalence of GDM was 1% in the intervention group as compared to 8.8% in the control group. The researchers concluded that exercise program reduced the prevalence of GDM by preserving glucose tolerance.

Cordero, Y., Mottola, M., Vargas, J., Blanco, M., & Barakat, R. (2015). Exercise is associated with a reduction in gestational diabetes mellitus. *Medicine & Science in Sports & Exercise*, 47(7), 1328-1333.

http://europepmc.org/abstract/med/25333246

⓯ Waiting between Pregnancies

Summary: *We recommend waiting a minimum of 18 months between the end of one pregnancy and the start of another. Short inter-pregnancy intervals are associated with preterm birth, low birthweight, and an increased risk of autism spectrum disorder. Highest risks in these studies are associated with pregnancies spaced <6 months apart, <1 year apart, and <18 months apart, respectively. A spacing of 18-23 months seems ideal.*

Scientific Evidence

A. Interpregnancy intervals shorter than 18 months and longer than 59 months are significantly associated with increased risk of adverse perinatal outcomes. In this meta-analysis, Interpregnancy intervals (IPI) shorter than 18 months are significantly associated with increased risk of adverse perinatal outcomes including pre-term birth and low birthweight. The authors find this issue relevant to public health and clinical practice because if short IPI are found to be independently associated with a higher risk of adverse perinatal outcomes, a type of intervention could be instated.

Conde-Agudelo, A., Rosas-Bermudez, A., & Kafury-Goeta, A.C. (2006). Birth spacing and risk of adverse perinatal outcomes, A Meta-analysis. *The Journal of the American Medical Association*, 295 (15), 1809-1823.

http://www.ncbi.nlm.nih.gov/pubmed/16622143

B. Children born at short intervals between pregnancies are at increased risk of developing autism; the highest risk was associated with pregnancies spaced <1 year apart. The purpose of this study was to determine whether or not the interpregnancy interval (IPI) would have an effect on the risk of autism in successive births. Results suggest that children born after shorter intervals between pregnancies are at increased risk of developing autism. Also, the highest risk was associated with pregnancies spaced less than 12 months apart. In addition, second-born children were at increased risk of autism relative to their firstborn siblings only in pairs with short IPIs.

Cheslack-Postava, K., Liu, K. & Bearman, P.S. (2011). Closely spaced pregnancies are associated with increased odds of autism in California sibling births. *Pediatrics*, 127(2), 246-253.

http://pediatrics.aappublications.org/content/early/2011/01/10/peds.2010-2371

C. The risk of pre-term birth and its recurrence increases with short inter-pregnancy intervals, even after adjustment for coexisting risk factors. The purpose of this study was to test the hypothesis that short interpregnancy intervals (IPIs) increase the risk for preterm birth (PTB), recurrence

of PTB, and delivery at early extremes of gestational age. The authors performed a population-based cohort study of 156,330 women who had 2 births. The shortest IPIs (<6 months) increased the risk of extreme PTB, IPIs of <6 months and 6-12 months increased the overall risk of PTB, and PTB recurrence.

DeFranco, E.A., Stamilio, D.M., Boslaugh, S.E., Gross, G.A., & Muglia, L.J. (2007). A short interpregnancy interval is a risk factor for preterm birth and its recurrence. *American Journal of Obstetrics and Gynecology*, 197(3), e1-246.

http://www.ncbi.nlm.nih.gov/pubmed/17826413

D. This study discusses that birth spacing is an important, feasible and practical intervention and should be included in developing country health programs. This editorial summarizes evidence on birth spacing and newborn, infant, child and maternal health. Included studies suggest that for infants and children under five years of age, births spaced at least 36 months apart are associated with the lowest mortality risk, birth to conception intervals of less than 6 months are associated with an increased risk of pre-term birth, low birthweight, and small for gestational age, and birth to conception intervals of less than 6 months are associated with increased risk of maternal mortality and morbidity.

Norton, M. (2005). New evidence on birth spacing: promising findings for improving newborn, infant, child, and maternal health, *International Journal of Gynecology & Obstetrics*, 89 (1), S1-S6.

http://www.ncbi.nlm.nih.gov/pubmed/15820364

E. Risk for adverse birth outcomes was lowest when the interpregnancy interval was 18-23 months and increased when the interval deterred from 18-23 months. The increase in adverse birth outcomes was most significant when IPI was shorter than 6 months. Findings from three recent studies, reviewed in this article, show results that support the hypothesis that short interpregnancy intervals (IPI) leads to adverse outcomes. It was found that the risk for adverse birth outcomes was lowest when the interpregnancy interval was 18-23 months and increased when the interval deterred from 18-23 months. The increase in adverse birth outcomes was most significant when IPI was shorter than 6 months.

Zhu, B.P. (2005). Effect of interpregnancy interval on birth outcomes: findings from three recent US studies. *International Journal of Gynecology & Obstetrics*, 89(1), S25-S33.

http://www.ncbi.nlm.nih.gov/pubmed/15820365

F. Shorter Interpregnancy intervals (18 months or less) significantly increases the risk for neonatal infant mortality. This study of over 3,400 infant births examined interpregnancy intervals (IPIs) of various lengths and infant mortality. Logistic regression models were utilized to assess the odds for infant mortality at monthly interpregnancy intervals while adjusting for established predictors of infant mortality (i.e., preterm birth, low birth weight, and small for gestational age), and other potential confounders. Unadjusted analysis showed greater clustering at extreme IPIs of <6 months and ≥60 months for infants that died (32%) compared to infants that survived (24.7 %). Shorter IPI (i.e., <6-17 months) compared to 'ideal' IPI (i.e., 18–23 months), were associated with infant mortality even after adjusting for confounders. Short intervals were significantly associated with neonatal deaths.

Hussaini, K. S., Ritenour, D., & Coonrod, D. V. (2013). Interpregnancy intervals and the risk for infant mortality: a case control study of Arizona infants 2003–2007. *Maternal and child health journal*, 17(4), 6.

http://link.springer.com/article/10.1007/s10995-012-1041-846-653.

G. Children born after shorter intervals between pregnancies are at increased risk of developing autism; the highest risk was associated with pregnancies spaced 1 year apart. 662,730 second-born children were observed. In particular, interpregnancy intervals (IPIs) of <12 months were associated with a 3 times greater risk for autism. 12 to 23 months and 24 to 35 months were associated with an increased risk relative to IPIs of ≥36 months. The association was not mediated by preterm birth or low birth weight and persisted across categories of sociodemographic characteristics, with some attenuation in the oldest and youngest parents. Second-born children were at increased risk of autism relative to their firstborn siblings only in pairs with short IPIs.

Cheslack-Postava, K., Liu, K., & Bearman, P. S. (2011). Closely spaced pregnancies are associated with increased odds of autism in California sibling births. *Pediatrics*, 127(2), 246-253.

http://pediatrics.aappublications.org/content/early/2011/01/10/peds.2010-2371.full.pdf+html

⓰ Reducing Stress During Pregnancy

Summary: *We recommend participation in stress-reducing activities during pregnancy. High stress levels during pregnancy pose a risk for short- and long-term fetal and maternal outcomes. Yoga, massage therapy, mindfulness meditation, and psychosocial support have been shown to decrease levels of depression, stress, and anxiety in women. Other positive outcomes include more vaginal births and better coping after birth. Childbirth education classes and prenatal care providers should discuss these stress-reducing practices.*

Scientific Evidence

A. Social stress during early pregnancy is associated with pregnancy loss while stress later in pregnancy is associated with lower birth weight. Prenatal stress can lead to activation of the maternal and fetal hypothalamic-pituitary-adrenal axis, long-term changes in the brain, and how the mother and her offspring respond to stress. This article reviews animal and human studies the neuroendocrine and behavioral responses to stress in the animal and human pregnancies. In addition to explaining the mechanism underlying changes in the hypothalamic-pituitary-adrenal axis responses, the author explains when offspring are particularly sensitive to fetal programming by prenatal stress and linkages to increased anxiety behaviors and the suggestion of permanent changes in the offspring's brain.

Brunton, P.J. (2013). Effects of maternal exposure to social stress during pregnancy: Consequences for mother and offspring. *Reproduction*, 146(5), R175-189.

http://www.ncbi.nlm.nih.gov/pubmed/23901130

B. Training in mindfulness-based cognitive therapy has been shown to decrease feelings of depression, stress, and anxiety in a small group of pregnant women. This pilot study explored the effects of an 8-week mindfulness-based cognitive therapy group on psychological distress and well-being among pregnant women living in Australia. There were 10 intervention and 9 control participants. Participants reported a decline in depression, stress, and anxiety scores at the end of the intervention with improvement continuing through 6 weeks after birth. Increases in mindfulness and self-compassion scores were also observed over time. Themes identified from interviews describing the experience of participants were: 'stop and think', 'prior experience or expectations', 'embracing the present', 'acceptance' and 'shared experience'.

Dunn, C., Hanieh, E., Roberta, R., & Powrie, R. (2012). Mindful pregnancy and childbirth: Effects of a mindfulness-based intervention on women's psychological distress and well-being in the perinatal period. *Archives of Women's Mental Health*, 15(2), 139-143.

http://www.ncbi.nlm.nih.gov/pubmed/22382281

C. Depressed pregnant women who participated in yoga and massage therapy reported a greater decrease on depression, anxiety, and back and leg pain scores and a greater increase in their partner/spouse relationship scores compared to those who did not participate. Eighty-four prenatally depressed women were randomly assigned to yoga, massage therapy, or standard prenatal care control groups to determine the relative effects of yoga and massage therapy on prenatal depression and neonatal outcomes. Following 12 weeks of 20-minute twice weekly yoga or massage therapy sessions, both therapy groups had a greater decrease in depression, anxiety, and back and leg pain scores and a greater increase in their partner/spouse relationship scores as compared with the control group. In addition, the yoga and massage therapy groups did not differ on neonatal outcomes of gestational age at birth and birth weight, and those groups, in turn, had greater gestational age at birth and birth weight than those of the control group.

Field, T., Diego, M., Hernandez-Reif, M., Medina, L., Delgado, J., & Hernandez, A. (2012). Yoga and massage therapy reduce prenatal depression and prematurity. *Journal of Bodywork and Movement Therapies*, 16(2), 204-209.

http://www.ncbi.nlm.nih.gov/pubmed/22464118

D. Mindfulness Yoga may be an effective treatment alternative or augmentation to pharmacotherapy for pregnant women at high risk for psychopathology. Prenatal psychopathology may have an adverse impact on mother and baby, and few women receive treatment. This study offered a 10-week mindfulness yoga (M-Yoga) intervention to psychiatrically high-risk pregnant women as an alternative to pharmacological treatment. Findings suggest that M-Yoga was feasible to implement, acceptable to women, and effective. Symptoms of depression were significantly reduced, while mindfulness and maternal-fetal attachment were significantly increased. Overall, this pilot study is the first to demonstrate that M-Yoga may be an effective treatment alternative or augmentation to pharmacotherapy for pregnant women at high risk for psychopathology.

Muzik, M., Hamilton, S.E., Rosenblum, L.K., Waxler, E., & Hadi, Z. (2012). Mindfulness yoga during pregnancy for psychiatrically at-risk women: Preliminary results from a pilot feasibility study. *Complementary Therapies in Clinical Practice*, 18(4), 235-240.

http://www.ncbi.nlm.nih.gov/pubmed/23059438

E. Adequate sleep may be of health benefit during pregnancy. Although the optimal amount is still unknown, studies show that 7-9 hours of sleep per night is the minimum needed to optimize health outcomes, and during pregnancy this may benefit the developing child. The quality of the intrauterine environment influences maternal-fetal health and the developing child's predisposition to obesity and cardiometabolic disease later in life. Many longitudinal studies with adults suggest that short sleep duration is a risk factor for the development of impaired glycemia and obesity. Reports note disrupted and poorer quality of sleep during pregnancy and highlight an association between reduced sleep and increased risk of gestational diabetes mellitus. This review summarizes current evidence which suggests that incorporating recommendations for adequate sleep and time management strategies that encourage a healthful night's sleep in to prenatal care may improve the health of the mom and her baby.

Ferraro, Z.M., Chaput, J.P., Gruslin, A., & Adamo, K.B. (2014). The potential value of sleep hygiene for a healthy pregnancy: A brief review. *ISRN Family Medicine, 2014*(928293), 1-7.

http://www.hindawi.com/journals/isrn/2014/928293/

F. Comprehensive psychosocial support during pregnancy, including home visiting conducted by nurses, achieves benefits such as higher rates of vaginal delivery, maternal health, and maternal coping. A randomized controlled trial of sustained nurse home visiting in an area of socioeconomic disadvantage in Western Sydney between 2005–2008 was conducted. The intervention focused on improving the transition to parenting by supporting mothers through pregnancy. Health and service use outcome data was analyzed for 208 women (n = 111 intervention; n = 97 comparison receiving usual care). Five nurses provided information, psychosocial support, and health promoting activities for families. Intervention mothers had a higher rate of unassisted vaginal births than the general population. Intervention mothers at 4–6 weeks after birth reported better general health and felt significantly more enabled to cope with and understand their babies and to care for themselves and their babies than did mothers in the usual care group.

Kemp, L., Harris, E., McMahon, C., Matthey, S., Vimpani, G., Anderson, T., Schmied, V., & Aslam, H. (2013). Benefits of psychosocial intervention and continuity of care by child and family health nurses in the pre- and postnatal period: Process evaluation. *Journal of Advanced Nursing*, 69(8), 1850-1861.

http://onlinelibrary.wiley.com/doi/10.1111/jan.12052/abstract?userIsAuthenticated=false&deniedAccessCustomisedMessage=

17 Maintaining Optimal Weight Throughout Pregnancy

Summary: *Women who enter pregnancy overweight or obese and those who gain excessive weight during pregnancy increase risk of adverse pregnancy and birth outcomes, including gestational diabetes, hypertension, cesarean section, macrosomia, and stillbirth. Conversely, women who gain less than the appropriate recommended amount of weight put the developing fetus at risk for low birth weight, preterm birth, and possible release of organic pollutants from maternal body stores. Physical activity, nutritional intervention, and adequate social support have been shown to assist in maintaining a healthy weight before and during pregnancy.*

Scientific Evidence

A. A lifestyle intervention with exercise and dietary counseling during pregnancy increased physical activity, improved dietary habits, and reduced excessive weight gain in urban-living. Participants in the intervention group were provided with community-based group exercise sessions, instructed home exercise, and dietary counselling between 20 and 36 weeks of gestation. At 2 months after beginning the study, intervention group participants had a decreased daily intake of calories, fats, saturated fats, and cholesterol as compared with the control group as well as higher physical activity levels. There was a reduced prevalence of excessive gestational weight gain according to the Institute of Medicine guidelines for the lifestyle intervention group as compared with the control group.

Hui, A., Back, L., Ludwig, S., Gardiner, P., Sevenhuysen, G., Dean, H., et al. Shen, G.X. (2011). Lifestyle intervention on diet and exercise reduced excessive gestational weight gain in pregnant women under a randomized controlled trial. *General Obstetrics*, 119(1), 70-77.

http://www.ncbi.nlm.nih.gov/pubmed/22017967

B. High-quality evidence indicates that diet or exercise, or both, during pregnancy can reduce the risk of excessive weight gain. Excessive weight gain during pregnancy is associated with poor maternal and neonatal outcomes including gestational diabetes, hypertension, caesarean section, macrosomia, and stillbirth. Other benefits may include a lower risk of caesarean delivery, macrosomia, and neonatal respiratory morbidity, particularly for high-risk women receiving combined diet and exercise interventions. Maternal hypertension may also be reduced. Exercise appears to be an important part of controlling weight gain in pregnancy and more research is needed to establish safe guidelines.

Muktabhant, B., Lawrie, T.A., Lumbiganon, P., & Laopaiboon, M. (2015). Diet or exercise, or both, for preventing excessive weight gain in pregnancy. *Cochrane Database of Systematic Reviews*, 6.

http://www.ncbi.nlm.nih.gov/pubmed/26068707

C. On average, neonates of women with healthy, recommended gestational weight gain (GWG) have lower persistent organic pollutants (POP) concentrations than do neonates of mothers with inadequate (too little) GWG. This study measured levels of 14 organochlorine pesticides, 7 polychlorobiphenyls (PCBs), and 14 polybrominated diphenyl ethers (PBDEs) in 325 cord serum samples from a Spanish birth cohort. The authors examined the association of GWG with cord serum POPs concentrations. Results show that women who had inadequate (too little) GWG had higher concentrations of POPs than both the excessive and adequate GWG groups.

Vizcaino, E., Grimalt, J. O., Glomstad, B., Fernández-Somoano, A., & Tardón, A. (2014). Gestational weight gain and exposure of newborns to persistent organic pollutants. *Environmental Health Perspectives*, 122(8), 873.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4123021/

D. Gestational weight gain above recommended guidelines was associated with low Apgar scores, seizures, hypoglycemia, polycythemia, meconium aspiration syndrome and large gestational age, while gestational weight gain far below guidelines was associated with seizure, longer hospital stay and small for gestational age. This was a retrospective cohort study of 20,465 nondiabetic, term, singleton births examining the associations between gestational weight gain and neonatal outcomes. In analyses, gestational weight gain above guidelines was associated with a low 5-minute Apgar score, seizure, hypoglycemia, polycythemia, meconium aspiration syndrome, and large for gestational age compared with women within weight gain guidelines. Gestational weight gain below guidelines was associated with decreased odds of neonatal intensive care unit admission and increased odds of small for gestational age (SGA). Gestational weight gain less than 7 kg was associated with increased risk of seizure, hospital stay more than 5 days, and SGA.

Stotland, N. E., Cheng, Y. W., Hopkins, L. M., & Caughey, A. B. (2006). Gestational weight gain and adverse neonatal outcome among term infants. *Obstetrics & Gynecology*, 108(3, Part 1), 635-643.

http://journals.lww.com/greenjournal/Abstract/2006/09000/Gestational_Weight_Gain_and_Adverse_Neonatal.24.aspx

E. Prenatal exercise and nutrition intervention prevented excessive weight gain and decreased weight retention at 2 months postpartum in women with normal pre-pregnancy weight. This study evaluated the effect of an exercise program of two different intensities, with nutritional control, on gestational weight gain (GWG), infant birth weight, and maternal weight retention at 2 months postpartum. The exercise program consisted of walking sessions three to four times per week, and gradually increasing exercise time from 25 to 40 minutes per session. Results suggest that a prenatal nutrition and exercise program regardless of exercise intensity, reduced excessive GWG and decreased weight retention in women of normal weight before pregnancy.

Ruchat, S.M., Davenport, M.H., Giroux, I., Hillier, M., Batada, A., & Sopper, M.M. (2012). Nutrition and exercise reduce excessive weight gain in normal-weight pregnant women. *American College of Sports Medicine*, 44(8), 1419-1426.

https://www.researchgate.net/publication/221978236_Nutrition_and_Exercise_Reduce_Excessive_Weight_Gain_in_Normal-Weight_Pregnant_Women

F. A walking intervention increased overweight and obese women's moderate-intensity physical activity during pregnancy, with trends toward more favorable maternal and neonatal birth outcomes. Overweight and obese women were recruited during the first trimester of pregnancy to participate in a pilot randomized controlled trial of an unsupervised walking intervention. Moderate-intensity walking was defined as a cadence of at least 80 steps per minute for at least 8 minute bouts. Intervention group participants had significantly more moderate-intensity bouts of walking, with trends toward more favorable maternal and neonatal birth outcomes.

Kong, K., Campbell, C., Foster, R., Peterson, A., Lanningham-Foster, L. (2014). A pilot walking program promotes moderate-intensity physical activity during pregnancy. *Medicine & Science in Sports & Exercise*, 46(3), 462–471.

http://www.ncbi.nlm.nih.gov/pubmed/24002348

G. Additional global reading recommendations:

Berger, D. (2012). From preconception to infancy: environmental and nutritional strategies for lowering the risk of autism. *Autism Science Digest*, 1(4), 17-25.

http://preconception.webs.com/Berger_ASD04%20(2)-1.pdf

Lane, M., Robker, R. L., & Robertson, S. A. (2014). Parenting from before conception. *Science*, 345(6198), 756-760.

http://science.sciencemag.org/content/345/6198/756.short

Pregnancy Kitchen

Science To Table

Pregnancy Kitchen was developed by NHF and is a companion program to be used in conjunction with *The Healthy Child Guide*

BEYOND ORGANIC

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