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COMPENDIUM OF SCIENTIFIC ABSTRACTS

REGARDING

NOVEL COMPONENT OF PRE- AND POSTNATAL NUTRITION

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Introduction

For preconceptional as well as prenatal nutrition, multi-nutrient supply has long been established. Official recommendations comprise folic acid, the vitamins B12 and D and the minerals magnesium, iron and iodine in particular. Also, the supplementation of the omega-3 fatty acid DHA for neuronal and eye development of the fetus and breastfeed infant is strongly recommended.

In addition to these established recommendations, nutritionists are increasingly gaining insight into the importance of choline for prenatal nutrition. Choline is a compound that is a building block for cell membranes (phosphatidylcholine) as well as for neurotransmitter in the brain (acetylcholine). Because of these functions, it plays a central role in the neural development of the unborn child. Even later, after birth, an adequate supply of choline during pregnancy seems to have positive effects. For example, infants from mothers with a high choline intake showed improved learning and memory performance in studies. Good choline supply during pregnancy also seems to have a strong protective effect on fetal brain from various exogenous impacts such as drug abuse or infection.

Choline deficiency - risk factor for neural tube defects

Neural tube defects are the most common malformations of the central nervous system, which consists of the brain and spinal cord. They occur between the 3rd and 4th week of pregnancy, if the embryonic neural tube is incompletely closed. To prevent neural tube defects, the additional intake of folic acid has long been the standard in preconceptional care. However, choline and betaine, a breakdown product of choline, seem to have this protective effect as well. Several studies have shown a significant reduction in the risk of neural tube defects due to high choline intake - despite already existing folic acid supplementation. In line with this, poor choline intake on the other hand was associated with an increased risk of neural tube defects. The mechanism behind this effect is very likely choline's and betain's involvement in the 1 carbon cycle and epigenetic regulation.

Choline deficiency - risk also for the mother-to-be

Because choline is also important for maternal homocysteine breakdown and liver function, a low choline intake during pregnancy can lead to increased homocysteine levels. These in turn are considered to be a risk factor for pregnancy complications such as preeclampsia, prematurity and reduced birth weight. The choline demand is significantly increased during pregnancy and lactation, pregnant women are recommended to take 450 mg daily, breastfeeding women even 550 mg daily. Undersupply of pregnant women and nursing mothers is unfortunately very common, 90% do not achieve the recommended daily intake.

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Inclusion of choline in the official recommendations for prenatal supplements

Recently, international nutrition experts have argued for including choline in preparations for pregnancy and breastfeeding. US health authorities have already included choline in the official recommendations for prenatal supplements, but authorities in Europe are still lagging behind. It is therefore not surprising that there are hardly any products for pregnant and breastfeeding women on the European market that contain choline.

The following collection of abstracts provide an overview over the current state of research.

Impact of prenatal choline on brain and eye development

Perinatal choline influences brain structure and function.

Zeisel SH, Niculescu MD.

Choline is derived not only from the diet, but also from de novo synthesis. It is important for methyl-group metabolism, the formation of membranes, kidney function, and neurotransmission. When deprived of dietary choline, most adult men and postmenopausal women develop signs of organ dysfunction (fatty liver or muscle damage) and have a decreased capacity to convert homocysteine to methionine. Choline is critical during fetal development, when it influences stem cell proliferation and apoptosis, thereby altering brain structure and function (memory is permanently enhanced in rodents exposed to choline during the latter part of gestation).

Nutr Rev. 2006 Apr;64(4):197-203.

Early second trimester maternal plasma choline and betaine are related to measures of early cognitive development in term infants

Brian T F Wu , Roger A Dyer, D Janette King, Kelly J Richardson, Sheila M Innis

Background: The importance of maternal dietary choline for fetal neural development and later cognitive function has been well-documented in experimental studies. Although choline is an essential dietary nutrient for humans, evidence that low maternal choline in pregnancy impacts neurodevelopment in human infants is lacking. We determined potential associations between maternal plasma free choline and its metabolites betaine and dimethylglycine in pregnancy and infant neurodevelopment at 18 months of age.

Methodology: This was a prospective study of healthy pregnant women and their full-term, single birth infants. Maternal blood was collected at 16 and 36 weeks of gestation and infant neurodevelopment was assessed at 18 months of age for 154 mother-infant pairs. Maternal plasma choline, betaine, dimethylglycine, methionine, homocysteine, cysteine, total B12, holotranscobalamin and folate were quantified. Infant neurodevelopment was evaluated

using the Bayley Scales of Infant Development-III. Multivariate regression, adjusting for covariates that impact development, was used to determine the associations between maternal plasma choline, betaine and dimethylglycine and infant neurodevelopment.

Results: The maternal plasma free choline at 16 and 36 weeks gestation was median (interquartile range) 6.70 (5.78-8.03) and 9.40 (8.10-11.3) µmol/L, respectively. Estimated choline intakes were (mean ± SD) 383 ± 98.6 mg/day, and lower than the recommended 450 mg/day. Betaine intakes were 142 ± 70.2 mg/day. Significant positive associations were found between infant cognitive test scores and maternal plasma free choline (B=6.054, SE=2.283, p=0.009) and betaine (B=7.350, SE=1.933, p=0.0002) at 16 weeks of gestation. Maternal folate, total B12, or holotranscobalamin were not related to infant development.

Conclusion: We show that choline status in the first half of pregnancy is associated with cognitive development among healthy term gestation infants. More work is needed on the potential limitation of choline or betaine in the diets of pregnant women.

PLoS One. 2012;7(8):e43448.doi: 10.1371/journal.pone.0043448. Epub 2012 Aug 20.

Choline intake during pregnancy and child cognition at age 7 years.

Boeke CE, Gillman MW, Hughes MD, Rifas-Shiman SL, Villamor E, Oken E.

Animal models indicate that exposure to choline in utero improves visual memory through cholinergic transmission and/or epigenetic mechanisms. Among 895 mothers in Project Viva (eastern Massachusetts, 1999-2002 to 2008-2011), we estimated the associations between intakes of choline, vitamin B12, betaine, and folate during the first and second trimesters of pregnancy and offspring visual memory (measured by the Wide Range Assessment of Memory and Learning, Second Edition (WRAML2), Design and Picture Memory subtests) and intelligence (measured using the Kaufman Brief Intelligence Test, Second Edition (KBIT-2)) at age 7 years. Mean second-trimester intakes were 328 (standard deviation (SD), 63) mg/day for choline, 10.5 (SD, 5.1) µg/day for vitamin B12, 240 (SD, 104) mg/day for betaine, and 1,268 (SD, 381) µg/day for folate. Mean age 7 test scores were 17.2 (SD, 4.4) points on the WRAML 2 Design and Picture Memory subtests, 114.3 (SD, 13.9) points on the verbal KBIT-2, and 107.8 (SD, 16.5) points on the nonverbal KBIT-2. In a model adjusting for maternal characteristics, the other nutrients, and child's age and sex, the top quartile of second-trimester choline intake was associated with a child WRAML2 score 1.4 points higher (95% confidence interval: 0.5, 2.4) than the bottom quartile (P-trend = 0.003). Results for first-trimester intake were in the same direction but weaker. Intake of the other nutrients was not associated with the cognitive tests administered. Higher gestational choline intake was associated with modestly better child visual memory at age 7 years.

Am J Epidemiol. 2013 Jun 15;177(12):1338-47. doi: 10.1093/aje/kws395. Epub 2013 Feb 20.

Racial/ethnic and sociodemographic factors associated with micronutrient intakes and inadequacies among pregnant women in an urban US population.

Brunst KJ, Wright RO, DiGioia K, Enlow MB, Fernandez H, Wright RJ, Kannan S.

OBJECTIVE:

To assess sociodemographic correlates of micronutrient intakes from food and dietary supplements in an urban, ethnically diverse sample of pregnant women in the USA.
DESIGN:
Cross-sectional analyses of data collected using a validated semi-quantitative FFQ. Associations between racial, ethnic and sociodemographic factors and micronutrient intakes were examined using logistic regression controlling for pre-pregnancy BMI, maternal age and smoking status.
SETTING:
Prenatal clinics, Boston, MA, USA.
SUBJECTS:
Analyses included pregnant women (n 274) in the PRogramming of Intergenerational Stress Mechanisms (PRISM) study, an urban longitudinal cohort designed to examine how stress influences respiratory health in children when controlling for other environmental exposures (chemical stressors, nutrition).
RESULTS:
High frequencies of vitamin E (52 %), Mg (38 %), Fe (57 %) and vitamin D (77 %) inadequacies as well as suboptimal intakes of choline (95 %) and K (99 %) were observed. Factors associated with multiple antioxidant inadequacies included being Hispanic or African American, lower education and self-reported economic-related food insecurity. Hispanics had a higher prevalence of multiple methyl-nutrient inadequacies compared with African Americans; both had suboptimal betaine intakes and higher odds for vitamin B_6 and Fe inadequacies compared with Caucasians. Nearly all women (98 %) reported Na intakes above the tolerable upper limit; excessive intakes of Mg (35 %), folate (37 %) and niacin (38 %) were also observed. Women reporting excessive intakes of these nutrients were more likely Caucasian or Hispanic, more highly educated, US-born and did not report food insecurity.
CONCLUSIONS:
Racial/ethnic and other sociodemographic factors should be considered when tailoring periconceptional dietary interventions for urban ethnic women in the USA.
Public Health Nutr. 2014 Sep;17(9):1960-70. doi: 10.1017/S1368980013003224. Epub 2013 Dec 13.

Advocacy for Improving Nutrition in the First 1000 Days to Support Childhood Development and Adult Health.

Schwarzenberg SJ, Georgieff MK; COMMITTEE ON NUTRITION.

Maternal prenatal nutrition and the child's nutrition in the first 2 years of life (1000 days) are crucial factors in a child's neurodevelopment and lifelong mental health. Child and adult health risks, including obesity, hypertension, and diabetes, may be programmed by nutritional status during this period. Calories are essential for growth of both fetus and child but are not sufficient for normal brain development. Although all nutrients are necessary for brain growth, key nutrients that support neurodevelopment include protein; zinc; iron; choline; folate; iodine; vitamins A, D, B6, and B12; and long-chain polyunsaturated fatty acids. Failure to provide key nutrients during this critical period of brain development may result in lifelong deficits in brain function despite subsequent nutrient repletion. Understanding the complex interplay of micro- and macronutrients and neurodevelopment is key to moving beyond simply recommending a "good diet" to optimizing nutrient delivery for the developing child. Leaders in pediatric health and policy makers must be aware of this research given its implications for public policy at the federal and state level. Pediatricians should refer to existing services for nutrition support for pregnant and breastfeeding women, infants, and toddlers. Finally, all providers caring for children can advocate for healthy diets for mothers, infants, and young children in the first 1000 days. Prioritizing public policies that ensure the provision of adequate

nutrients and healthy eating during this crucial time would ensure that all children have an early foundation for optimal neurodevelopment, a key factor in long-term health.
Pediatrics. 2018 Feb;141(2). pii: e20173716. doi: 10.1542/peds.2017-3716. Epub 2018 Jan 22.

Low availability of choline in utero disrupts development and function of the retina

Isis Trujillo-Gonzalez , Walter B Friday , Carolyn A Munson, Amelia Bachleda, Ellen R Weiss, Nazia M Alam , Wei Sha , Steven H Zeisel, Natalia Surzenko

Adequate supply of choline, an essential nutrient, is necessary to support proper brain development. Whether prenatal choline availability plays a role in development of the visual system is currently unknown. In this study, we addressed the role of in utero choline supply for the development and later function of the retina in a mouse model. We lowered choline availability in the maternal diet during pregnancy and assessed proliferative and differentiation properties of retinal progenitor cells (RPCs) in the developing prenatal retina, as well as visual function in adult offspring. We report that low choline availability during retinogenesis leads to persistent retinal cytoarchitectural defects, ranging from focal lesions with displacement of retinal neurons into subretinal space to severe hypocellularity and ultrastructural defects in photoreceptor organization. We further show that low choline availability impairs timely differentiation of retinal neuronal cells, such that the densities of early-born retinal ganglion cells, amacrine and horizontal cells, as well as cone photoreceptor precursors, are reduced in low choline embryonic d 17.5 retinas. Maintenance of higher proportions of RPCs that fail to exit the cell cycle underlies aberrant neuronal differentiation in low choline embryos. Increased RPC cell cycle length, and associated reduction in neurofibromin 2/Merlin protein, an upstream regulator of the Hippo signaling pathway, at least in part, explain aberrant neurogenesis in low choline retinas. Furthermore, we find that animals exposed to low choline diet in utero exhibit a significant degree of intraindividual variation in vision, characterized by marked functional discrepancy between the 2 eyes in individual animals. Together, our findings demonstrate, for the first time, that choline availability plays an essential role in the regulation of temporal progression of retinogenesis and provide evidence for the importance of adequate supply of choline for proper development of the visual system.-Trujillo-Gonzalez, I., Friday, W. B., Munson, C. A., Bachleda, A., Weiss, E. R., Alam, N. M., Sha, W., Zeisel, S. H., Surzenko, N. Low availability of choline in utero disrupts development and function of the retina.
FASEB J. 2019 Aug;33(8):9194-9209. doi: 10.1096/fj.201900444R. Epub 2019 May 15.

Choline and DHA in Maternal and Infant Nutrition: Synergistic Implications in Brain and Eye Health.

Mun JG, Legette LL, Ikonte CJ, Mitmesser SH.

The aim of this review is to highlight current insights into the roles of choline and docosahexaenoic acid (DHA) in maternal and infant nutrition, with special emphasis on dietary recommendations, gaps in dietary intake, and synergistic implications of both nutrients in infant brain and eye development. Adequate choline and DHA intakes are not being met by the vast majority of US adults, and even more so by women of child-bearing age. Choline and DHA play a significant role in infant brain and eye development, with inadequate intakes leading to visual and neurocognitive deficits. Emerging findings illustrate synergistic interactions between choline and DHA, indicating that insufficient intakes of one or both could have lifelong deleterious impacts on both maternal and infant health.
Nutrients. 2019 May 21;11(5). pii: E1125. doi: 10.3390/nu11051125.

Nutritional Factors in Fetal and Infant Brain Development

Carol L Cheatham

Fetal and infant brain development determine the trajectory of the organism across the lifespan. Optimal maternal and infant nutrition during the period of rapid brain development is vital to the integrity of the neural substrate for subsequent lifelong functions. The goal of this review is to educate the reader on the effects of fetal and infant nutrition on the developing human brain. A review of the literature reveals 6 nutrients that have been studied with respect to maternal nutrition and subsequent offspring brain development: folate, iodine, iron, vitamin D, choline, and docosahexaenoic acid (DHA; 22:6n-3). The research is discussed with a focus on the timing of nutrient needs (preconception, prenatally, and postnatally) as well as potential confounding and unobserved variables.

Ann Nutr Metab. 2019;75 Suppl 1:20-32. doi: 10.1159/000508052. Epub 2020 Jun 19.

Choline: Exploring the Growing Science on Its Benefits for Moms and Babies

Hunter W. Korsmo, Xinyin Jiang, and Marie A. Caudill3,

The importance of ensuring adequate choline intakes during pregnancy is increasingly recognized. Choline is critical for a number of physiological processes during the prenatal period with roles in membrane biosynthesis and tissue expansion, neurotransmission and brain development, and methyl group donation and gene expression. Studies in animals and humans have shown that supplementing the maternal diet with additional choline improves several pregnancy outcomes and protects against certain neural and metabolic insults. Most pregnant women in the U.S. are not achieving choline intake recommendations of 450 mg/day and would likely benefit from boosting their choline intakes through dietary and/or supplemental approaches.

Nutrients. 2019 Aug; 11(8): 1823.Published online 2019 Aug 7. doi: 10.3390/nu11081823

Choline, Neurological Development and Brain Function: A Systematic Review Focusing on the First 1000 Days

Emma Derbyshire and Rima Obeid

The foundations of neurodevelopment across an individual's lifespan are established in the first 1000 days of life (2 years). During this period an adequate supply of nutrients are essential for proper neurodevelopment and lifelong brain function. Of these, evidence for choline has been building but has not been widely collated using systematic approaches. Therefore, a systematic review was performed to identify the animal and human studies looking at interrelationships between choline, neurological development, and brain function during the first 1000 days of life. The database PubMed was used, and reference lists were searched. In total, 813 publications were subject to the title/abstract review, and 38 animal and 16 human studies were included after evaluation. Findings suggest that supplementing the maternal or child's diet with choline over the first 1000 days of life could subsequently: (1) support normal brain development (animal and human evidence), (2) protect against neural and metabolic insults, particularly when the fetus is exposed to alcohol (animal and human evidence), and (3) improve neural and cognitive functioning (animal evidence). Overall, most offspring would benefit from increased choline supply during the first 1000 days of life, particularly in relation to helping facilitate normal brain development. Health policies and guidelines should consider re-evaluation to help communicate and impart potential choline benefits through diet and/or supplementation approaches across this critical life stage.

Nutrients. 2020 Jun; 12(6): 1731.Published online 2020 Jun 10. doi: 10.3390/nu12061731

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Choline's role in epigenetic regulation

Maternal choline intake alters the epigenetic state of fetal cortisol-regulating genes in humans

Xinyin Jiang , Jian Yan, Allyson A West, Cydne A Perry, Olga V Malysheva, Srisatish Devapatla, Eva Pressman, Francoise Vermeylen, Marie A Caudill

The in utero availability of methyl donors, such as choline, may modify fetal epigenetic marks and lead to sustainable functional alterations throughout the life course. The hypothalamic-pituitary-adrenal (HPA) axis regulates cortisol production and is sensitive to perinatal epigenetic programming. As an extension of a 12-wk dose-response choline feeding study conducted in third-trimester pregnant women, we investigated the effect of maternal choline intake (930 vs. 480 mg/d) on the epigenetic state of cortisol-regulating genes, and their expression, in placenta and cord venous blood. The higher maternal choline intake yielded higher placental promoter methylation of the cortisol-regulating genes, corticotropin releasing hormone (CRH; P=0.05) and glucocorticoid receptor (NR3C1; P=0.002); lower placental CRH transcript abundance (P=0.04); lower cord blood leukocyte promoter methylation of CRH (P=0.05) and NR3C1 (P=0.04); and 33% lower (P=0.07) cord plasma cortisol. In addition, placental global DNA methylation and dimethylated histone H3 at lysine 9 (H3K9me2) were higher (P=0.02) in the 930 mg choline/d group, as was the expression of select placental methyltransferases. These data collectively suggest that maternal choline intake in humans modulates the epigenetic state of genes that regulate fetal HPA axis reactivity as well as the epigenomic status of fetal derived tissues.

FASEB J. 2012 Aug;26(8):3563-74. doi: 10.1096/fj.12-207894. Epub 2012 May 1.

Considering maternal dietary modulators for epigenetic regulation and programming of the fetal epigenome.

Chango A, Pogribny IP.

Fetal life is characterized by a tremendous plasticity and ability to respond to various environmental and lifestyle factors, including maternal nutrition. Identification of the role of dietary factors that can modulate and reshape the cellular epigenome during development, including methyl group donors (e.g., folate, choline) and bioactive compounds (e.g., polyphenols) is of great importance; however, there is insufficient knowledge of a particular effect of each type of modulator and/or their combination on fetal life. To enhance the quality and safety of food products for proper fetal health and disease prevention in later life, a better understanding of the underlying mechanisms of dietary epigenetic modulators during the critical prenatal period is necessary. This review focuses on the influence of maternal dietary components on DNA methylation, histone modification, and microRNAs, and summarizes current knowledge of the effect and importance of dietary components on epigenetic mechanisms that control the proper expression of genetic information. Evidence reveals that some components in the maternal diet can directly or indirectly affect epigenetic mechanisms. Understanding the underlying mechanisms of how early-life nutritional environment affects the epigenome during development is of great importance for the successful prevention of adult chronic diseases through optimal maternal nutrition.

Nutrients. 2015 Apr 14;7(4):2748-70. doi: 10.3390/nu7042748.

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Nutrition, One-Carbon Metabolism and Neural Tube Defects: A Review.

Li K, Wahlqvist ML, Li D.

Neural tube defects (NTDs) are a group of severe congenital malformations, induced by the combined effects of genes and the environment. The most valuable finding so far has been the protective effect of folic acid supplementation against NTDs. However, many women do not take folic acid supplements until they are pregnant, which is too late to prevent NTDs effectively. Long-term intake of folic acid-fortified food is a good choice to solve this problem, and mandatory folic acid fortification should be further promoted, especially in Europe, Asia and Africa. Vitamin B2, vitamin B-6, vitamin B-12, choline, betaine and n-3 polyunsaturated fatty acids (PUFAs) can also reduce the NTD risk by interacting with the one-carbon metabolism pathway. This suggest that multivitamin B combined with choline, betaine and n-3 PUFAs supplementation may have a better protective effect against NTDs than folic acid alone. Genetic polymorphisms involved in one-carbon metabolism are associated with NTD risk, and gene screening for women of childbearing age prior to pregnancy may help prevent NTDs induced by the risk allele. In addition, the consumption of alcohol, tea and coffee, and low intakes of fruit and vegetable are also associated with the increased risk of NTDs, and should be avoided by women of childbearing age.

Nutrients. 2016 Nov 23;8(11). pii: E741.

Choline, Other Methyl-Donors and Epigenetics

Steven Zeisel

Choline dietary intake varies such that many people do not achieve adequate intakes. Diet intake of choline can modulate methylation because, via betaine homocysteine methyltransferase (BHMT), this nutrient (and its metabolite, betaine) regulate the concentrations of S-adenosylhomocysteine and S-adenosylmethionine. Some of the epigenetic mechanisms that modify gene expression without modifying the genetic code depend on the methylation of DNA or of histones; and diet availability of choline and other methyl-group donors influences both of these methylations. Examples of methyl-donor mediated epigenetic effects include the changes in coat color and body weight in offspring when pregnant agouti mice are fed high choline, high methyl diets; the changes in tail kinking in offspring when pregnant Axin(Fu) mice are fed high choline, high methyl diets; the changes in Cdkn3 methylation and altered brain development that occurs in offspring when pregnant rodents are fed low choline diets. When choline metabolism is disrupted by deleting the gene Bhmt, DNA methylation is affected (especially in a region of chromosome 13), expression of specific genes is suppressed, and liver cancers develop. Better understanding of how nutrients such as choline and methyl-donors influence epigenetic programs has importance for our understanding of not only developmental abnormalities but also for understanding the origins of chronic diseases.

Nutrients. 2017 Apr 29;9(5):445. doi: 10.3390/nu9050445.

Effect of supplementation with methyl-donor nutrients on neurodevelopment and cognition: considerations for future research.

McKee SE, Reyes TM.

Pregnancy represents a critical period in fetal development, such that the prenatal environment can, in part, establish a lifelong trajectory of health or disease for the offspring. Poor nutrition (macro- or micronutrient deficiencies) can adversely affect brain development and significantly increase offspring risk for metabolic and neurological disease development. The

concentration of dietary methyl-donor nutrients is known to alter DNA methylation in the brain, and alterations in DNA methylation can have long-lasting effects on gene expression and neuronal function. The decreased availability of methyl-donor nutrients to the developing fetus in models of poor maternal nutrition is one mechanism hypothesized to link maternal malnutrition and disease risk in offspring. Animal studies indicate that supplementation of both maternal and postnatal (early- and later-life) diets with methyl-donor nutrients can attenuate disease risk in offspring; however, clinical research is more equivocal. The objective of this review is to summarize how specific methyl-donor nutrient deficiencies and excesses during pre- and postnatal life alter neurodevelopment and cognition. Emphasis is placed on reviewing the current literature, highlighting challenges within nutrient supplementation research, and considering potential strategies to ensure robust findings

Nutr Rev. 2018 Jul 1;76(7):497-511. doi: 10.1093/nutrit/nuy007.

Choline as protective factor

Higher gestational choline levels protect fetal brain development in maternal infection

Robert Freedman, Sharon K. Hunter, Amanda J Law, Brandie D. Wagner, PhD6, Angelo D'Alessandro, Uwe Christians, , Kathlen Noonan, MSW1, Anna Wyrwa,, M. Camille Hoffman,

—To assess whether choline decreases effects of maternal infections on fetal brain circuit development and on expression of infant behavior at 3 months of age. Study Design—A case-control study was conducted in a public hospital obstetrics and midwifery service, with prenatal assessments of maternal infection, C-Reactive Protein (CRP), and choline levels and postnatal assessments of cerebral neuronal inhibition in 162 newborns. At 3 months, 136 parents completed reports of their child's behavior. Results—Maternal infection at 16 weeks gestation, experienced by 41% of mothers, raised mean maternal CRP (d' = 0.47, P = 0.002) and decreased the development of cerebral inhibition of auditory response at 1 month of age (d' = 0.39, P

J Pediatr. 2019 May; 208: 198–206.e2. Published online 2019 Mar 14. doi: 10.1016/j.jpeds.2018.12.010

Interaction of maternal choline levels and prenatal Marijuana's effects on the offspring

M Camille Hoffman, Sharon K Hunter , Angelo D'Alessandro, Kathleen Noonan , Anna Wyrwa , Robert Freedman

Background: This study investigated whether higher maternal choline levels mitigate effects of marijuana on fetal brain development. Choline transported into the amniotic fluid from the mother activates a7-nicotinic acetylcholine receptors on fetal cerebro-cortical inhibitory neurons, whose development is impeded by cannabis blockade of their cannabinoid-1(CB1) receptors.

Methods: Marijuana use was assessed during pregnancy from women who later brought their newborns for study. Mothers were informed about choline and other nutrients, but not specifically for marijuana use. Maternal serum choline was measured at 16 weeks gestation.

Results: Marijuana use for the first 10 weeks gestation or more by 15% of mothers decreased newborns' inhibition of evoked potentials to repeated sounds (d' = 0.55, $p < 0.05$). This effect was ameliorated if women had higher gestational choline (rs = -0.50, p = 0.011). At 3 months

of age, children whose mothers continued marijuana use through their 10th gestational week or more had poorer self-regulation (d' = -0.79, p < 0.05). This effect was also ameliorated if mothers had higher gestational choline (rs = 0.54, p = 0.013). Maternal choline levels correlated with the children's improved duration of attention, cuddliness, and bonding with parents. **Conclusions:** Prenatal marijuana use adversely affects fetal brain development and subsequent behavioral self-regulation, a precursor to later, more serious problems in childhood. Stopping marijuana use before 10 weeks gestational age prevented these effects. Many mothers refuse to cease use because of familiarity with marijuana and belief in its safety. Higher maternal choline mitigates some of marijuana's adverse effects on the fetus.
Psychol Med. 2020 Jul;50(10):1716-1726.doi: 10.1017/S003329171900179X. Epub 2019 Jul 31.

Neuroprotective immunity by essential nutrient "Choline" for the prevention of SARS CoV2 infections: An in silico study by molecular dynamics approach

Papia Chowdhury, Pustak Pathak

Prenatal COVID infection is one of the worst affected and least attended aspects of the COVID-19 disease. Like other coronaviruses, CoV2 infection is anticipated to affect fetal development by maternal inflammatory response on the fetus and placenta. Studies showed that higher prenatal choline level in mother's body can safeguard the developing brain of the fetus from the adverse effects of CoV2 infection. Choline is commonly used as food supplement. By virtual screening, molecular docking and molecular dynamics techniques, we have established a strong inhibitory possibility of choline for SARS 3CLpro protease which may provide a lead for prenatal COVID-19 treatment.
Chem Phys Lett. 2020 Dec 16;761:138057.doi: 10.1016/j.cplett.2020.138057. Epub 2020 Oct 3.

Prospects for improving future mental health of children through prenatal maternal micronutrient supplementation in China

Ying Li , Robert Freedman

Prenatal micronutrients in pregnant women's diets, including supplements, have an essential role in fetal brain development and may reduce the risk of mental disorders in offspring. Folic acid, vitamin D, omega-3 fatty acids, and choline have been investigated for this purpose. Folic acid supplementation throughout pregnancy has well-established positive effects. Vitamin D, administered to the mother before birth or to the newborn, has also been shown to reduce the risk of neurodevelopmental disorders. Omega-3 fatty acids during pregnancy have a more uncertain role, with recent trials questioning a beneficial effect on cognition and attention deficit disorder, despite positive effects on prematurity and neonatal wheezing prevention. Choline supplementation is associated with positive effects on cognition and behavior, including early behaviors associated with the development of autism and schizophrenia. There is no experience yet with COVID-19, but adverse effects on fetal brain development of most common coronaviruses are mitigated by higher choline levels. Maternal dietary supplementation of nutrients is a benign and inexpensive intervention in pregnancy to prevent life-long disability from mental illness. Use of dietary supplements in poorer, rural areas of China is below recommendations. Physicians, midwives, and public health officials in China

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can promote prenatal nutrient supplementation to reduce the future burden of mental illnesses that might be prevented before birth.
Pediatr Investig. 2020 Jun 24;4(2):118-126. doi: 10.1002/ped4.12199. eCollection 2020 Jun.

Maternal choline and respiratory coronavirus effects on fetal brain development

Robert Freedman, Sharon K Hunter, Amanda J Law, Angelo D'Alessandro, Kathleen Noonan, Anna Wyrwa, M Camille Hoffman

Prenatal COVID-19 infection is anticipated by the U.S. Centers for Disease Control to affect fetal development similarly to other common respiratory coronaviruses through effects of the maternal inflammatory response on the fetus and placenta. Plasma choline levels were measured at 16 weeks gestation in 43 mothers who had contracted common respiratory viruses during the first 6-16 weeks of pregnancy and 53 mothers who had not. When their infants reached 3 months of age, mothers completed the Infant Behavior Questionnaire-Revised (IBQ-R), which assesses their infants' level of activity (Surgency), their fearfulness and sadness (Negativity), and their ability to maintain attention and bond to their parents and caretakers (Regulation). Infants of mothers who had contracted a moderately severe respiratory virus infection and had higher gestational choline serum levels (≥7.5 mM consistent with U.S. Food and Drug Administration dietary recommendations) had significantly increased development of their ability to maintain attention and to bond with their parents (Regulation), compared to infants whose mothers had contracted an infection but had lower choline levels (<7.5 mM). For infants of mothers with choline levels ≥7.5 µM, there was no effect of viral infection on infant IBQ-R Regulation, compared to infants of mothers who were not infected. Higher choline levels obtained through diet or supplements may protect fetal development and support infant early behavioral development even if the mother contracts a viral infection in early gestation when the brain is first being formed.
J Psychiatr Res. 2020 Sep;128:1-4. doi: 10.1016/j.jpsychires.2020.05.019. Epub 2020 May 25.

Choline and homocysteine

Effects of methyl-deficient diets on methionine and homocysteine metabolism in the pregnant rat

Fiona A Wilson , Grietje Holtrop, A Graham Calder, Susan E Anderson, Gerald E Lobley, William D Rees

Although the importance of methyl metabolism in fetal development is well recognized, there is limited information on the dynamics of methionine flow through maternal and fetal tissues and on how this is related to circulating total homocysteine concentrations. Rates of homocysteine remethylation in maternal and fetal tissues on days 11, 19, and 21 of gestation were measured in pregnant rats fed diets with limiting or surplus amounts of folic acid and choline at two levels of methionine and then infused with L-[1-(13)C,(2)H(3)-methyl]methionine. The rate of homocysteine remethylation was highest in maternal liver and declined as gestation progressed. Diets deficient in folic acid and choline reduced the production of methionine from homocysteine in maternal liver only in the animals fed a methionine-limited diet. Throughout gestation, the pancreas exported homocysteine for methylation

within other tissues. Little or no methionine cycle activity was detected in the placenta at days 19 and 21 of gestation, but, during this period, fetal tissues, especially the liver, synthesized methionine from homocysteine. Greater enrichment of homocysteine in maternal plasma than placenta, even in animals fed the most-deficient diets, shows that the placenta did not contribute homocysteine to maternal plasma. Methionine synthesis from homocysteine in fetal tissues was maintained or increased when the dams were fed folate- and choline-deficient methionine-restricted diets. This study shows that methyl-deficient diets decrease the remethylation of homocysteine within maternal tissues but that these rates are protected to some extent within fetal tissues.

Am J Physiol Endocrinol Metab. 2012 Jun 15;302(12):E1531-40. doi: 10.1152/ajpendo.00668.2011. Epub 2012 Mar 27.

Sex differences in hepatic one-carbon metabolism

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Background: **There are large differences between men and women of child-bearing age in the expression level of 5 key enzymes in one-carbon metabolism almost certainly caused by the sex hormones. These male-female differences in one-carbon metabolism are greatly accentuated during pregnancy. Thus, understanding the origin and consequences of sex differences in one-carbon metabolism is important for precision medicine.**

Results: **We have created a mathematical model of hepatic one-carbon metabolism based on the underlying physiology and biochemistry. We use the model to investigate the consequences of sex differences in gene expression. We give a mechanistic understanding of observed concentration differences in one-carbon metabolism and explain why women have lower S-andenosylmethionine, lower homocysteine, and higher choline and betaine. We give a new explanation of the well known phenomenon that folate supplementation lowers homocysteine and we show how to use the model to investigate the effects of vitamin deficiencies, gene polymorphisms, and nutrient input changes.**

Conclusions: **Our model of hepatic one-carbon metabolism is a useful platform for investigating the mechanistic reasons that underlie known associations between metabolites. In particular, we explain how gene expression differences lead to metabolic differences between males and females.**

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Maternal choline supplementation alters vitamin B-12 status in human and murine pregnancy

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Despite participation in overlapping metabolic pathways, the relationship between choline and vitamin B-12 has not been well characterized especially during pregnancy. We sought to determine the effects of maternal choline supplementation on vitamin B-12 status biomarkers in human and mouse pregnancy, hypothesizing that increased choline intake would improve vitamin B-12 status. Associations between common genetic variants in choline-metabolizing genes and vitamin B-12 status biomarkers were also explored in humans. Healthy third-trimester pregnant women (n=26) consumed either 480 or 930 mg choline/day as part of a

12-week controlled feeding study. Wild-type NSA and Dlx3 heterozygous (Dlx3+/-) mice, which display placental insufficiency, consumed a 1×, 2× or 4× choline diet and were sacrificed at gestational days 15.5 and 18.5. Serum vitamin B-12, methylmalonic acid (MMA) and homocysteine were measured in all samples; holotranscobalamin (in humans) and hepatic vitamin B-12 (in mice) were also measured. The 2× choline supplementation for 12 weeks in pregnant women yielded higher serum concentrations of holotranscobalamin, the bioactive form of vitamin B-12 (~24%, P=.01). Women with genetic variants in choline dehydrogenase (CHDH) and betaine-homocysteine S-methyltransferase (BHMT) had higher serum MMA concentrations (~31%, P=.03) and lower serum holotranscobalamin concentrations (~34%, P=.03), respectively. The 4× choline dose decreased serum homocysteine concentrations in both NSA and Dlx3+/- mice (~36% and~43% respectively, P≤.015). In conclusion, differences in choline supply due to supplementation or genetic variation modulate vitamin B-12 status during pregnancy, supporting a functional relationship between these nutrients.

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Maternal Choline Supplementation Modulates Placental Markers of Inflammation, Angiogenesis, and Apoptosis in a Mouse Model of Placental Insufficiency

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Dlx3 (distal-less homeobox 3) haploinsufficiency in mice has been shown to result in restricted fetal growth and placental defects. We previously showed that maternal choline supplementation (4X versus 1X choline) in the Dlx3+/- mouse increased fetal and placental growth in mid-gestation. The current study sought to test the hypothesis that prenatal choline would modulate indicators of placenta function and development. Pregnant Dlx3+/- mice consuming 1X (control), 2X, or 4X choline from conception were sacrificed at embryonic (E) days E10.5, E12.5, E15.5, and E18.5, and placentas and embryos were harvested. Data were analyzed separately for each gestational day controlling for litter size, fetal genotype (except for models including only +/- pups), and fetal sex (except when data were stratified by this variable). 4X choline tended to increase ($p < 0.1$) placental labyrinth size at E10.5 and decrease ($p < 0.05$) placental apoptosis at E12.5. Choline supplementation decreased ($p < 0.05$) expression of pro-angiogenic genes Eng (E10.5, E12.5, and E15.5), and Vegf (E12.5, E15.5); and pro-inflammatory genes Il1b (at E15.5 and 18.5), Tnfa (at E12.5) and Nfκb (at E15.5) in a fetal sex-dependent manner. These findings provide support for a modulatory effect of maternal choline supplementation on biomarkers of placental function and development in a mouse model of placental insufficiency.

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Associations between folate and choline intake, homocysteine metabolism, and genetic polymorphism of MTHFR, BHMT and PEMT in healthy pregnant Polish women

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Aim: Physiological homocysteine (Hcy) concentrations depend on several factors, both dietary (including folate and choline intake) and biological (such as polymorphism of the genes involved in Hcy metabolism). This study aimed to thus test the associations between genes functionally linked with Hcy metabolism (MTHFR, BHMT and PEMT), folate and choline intakes, and total Hcy (tHcy) concentrations of healthy pregnant women.

Methods: One hundred and three healthy Polish women aged 18-44 years, in the third trimester of pregnancy, were enrolled.

Results: Mean blood tHcy and glutathione (GSH) concentrations were 8.08 ± 3.25 μM and 4.84 ± 1.21 μM, respectively. Concentrations of tHcy were found to be lower in the women who were taking folic acid supplements than in those who did not take these supplements (7.42 ± 1.78 μM vs 9.28 ± 4.42 μM, $P < 0.05$). There were no associations found between the examined parameters and BHMT (rs7356530), MTHFR (rs1801133) and PEMT (rs12325817) alone. However, blood tHcy concentrations differed in the PEMT genotype subgroups when choline and folate intakes were considered: respectively, 25% and 20% lower levels were observed in the C allele carriers who met their needs of choline or folate than in those who did not take enough these nutrients ($P < 0.05$ for both associations).

Conclusions: This study suggests that choline and folate intakes might interact with MTHFR, BHMT and PEMT polymorphisms to determine tHcy and GSH blood concentrations in healthy pregnant women.

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Choline in food

Food and Nutrition Board, Institute of Medicine: Dietary reference intakes: thiamin, riboflavin, Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B 6, Folate, Vitamin B 12, Pantothenic Acid, Biotin, and Choline

Institute of Medicine (US) Standing Committee on the Scientific Evaluation of Dietary Reference Intakes and its Panel on Folate, Other B Vitamins, and Choline

This report is the second in a series that presents a comprehensive set of reference values for nutrient intakes for healthy U.S and Canadian populations. It is a product of the Food and Nutrition Board of the Institute of Medicine (IOM) working in cooperation with scientists from Canada.

The report establishes a set of reference values for the B vitamins and choline to replace previously published Recommended Dietary Allowances (RDAs) for the United States and Recommended Nutrient Intakes (RNIs) for Canada. It considers evidence concerning the prevention of disease and developmental disorders along with more traditional evidence of sufficient nutrient intake; and examines data about choline, a food component that in the past has not been considered essential in the human diet. Although the reference values are based on data, the data were often scanty or drawn from studies that had limitations in addressing the question. Thus, scientific judgment was required in setting the reference values. The reasoning used is described for each nutrient in Chapters 4 through 12. Evidence concerning the use of these nutrients for the amelioration or cure of disease or disability was not considered because that was beyond the project's scope of work.

Washington (DC): National Academies Press (US); 1998.

Concentrations of choline-containing compounds and betaine in common foods

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Choline is important for normal membrane function, acetylcholine synthesis and methyl group metabolism; the choline requirement for humans is 550 mg/d for men (Adequate Intake). Betaine, a choline derivative, is important because of its role in the donation of methyl groups to homocysteine to form methionine. In tissues and foods, there are multiple choline compounds that contribute to total choline concentration (choline, glycerophosphocholine, phosphocholine, phosphatidylcholine and sphingomyelin). In this study, we collected representative food samples and analyzed the choline concentration of 145 common foods using liquid chromatography-mass spectrometry. Foods with the highest total choline concentration (mg/100 g) were: beef liver (418), chicken liver (290), eggs (251), wheat germ (152), bacon (125), dried soybeans (116) and pork (103). The foods with the highest betaine concentration (mg/100 g) were: wheat bran (1339), wheat germ (1241), spinach (645), pretzels (237), shrimp (218) and wheat bread (201). A number of epidemiologic studies have examined the relationship between dietary folic acid and cancer or heart disease. It may be helpful to also consider choline intake as a confounding factor because folate and choline methyl donation can be interchangeable.

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Dietary intake and food sources of choline in European populations

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Choline is an important nutrient for humans. Choline intake of the European population was assessed considering the European Food Safety Authority European Comprehensive Food Consumption Database and the United States Department of Agriculture Nutrient Database. Average choline intake ranges were 151-210 mg/d among toddlers (1 to ≤3 years old), 177-304 mg/d among other children (3 to ≤10 years old), 244-373 mg/d among adolescents (10 to ≤18 years old), 291-468 mg/d among adults (18 to ≤65 years old), 284-450 mg/d among elderly people (65 to ≤75 years old) and 269-444 mg/d among very elderly people (≥75 years old). The intakes were higher among males compared with females, mainly due to larger quantities of food consumed per day. In most of the population groups considered, the average choline intake was below the adequate intake (AI) set by the Institute of Medicine in the USA. The main food groups contributing to choline intake were meat, milk, grain, egg and their derived products, composite dishes and fish. The main limitations of this study are related to the absence of choline composition data of foods consumed by the European population and the subsequent assumption made to assess their intake levels. Given the definition of AI, no conclusion on the adequacy of choline intake can be drawn for most European population groups. Such results improve the knowledge on choline intake in Europe that could be further refined by the collection of choline composition data for foods as consumed in Europe.

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Dietary Reference Values for choline

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)

Following a request from the European Commission, the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) derives Dietary Reference Values (DRVs) for choline. In this Opinion, the Panel considers dietary choline including choline compounds (e.g. glycerophosphocholine, phosphocholine, phosphatidylcholine, sphingomyelin). The Panel considers that none of the biomarkers of choline intake or status is suitable to derive DRVs for choline. The Panel considers that Average Requirements and Population Reference Intakes for choline cannot be derived for adults, infants and children, and therefore defines Adequate Intakes (AIs). For all adults, the Panel sets an AI at 400 mg/day based on the average observed choline intake in healthy populations in the European Union and in consideration of the amounts of choline needed to replete about 70% of depleted subjects who showed signs of organ dysfunction in a depletion/repletion study. For all infants aged 7–11 months, the Panel proposes an AI of 160 mg/day, based on upwards extrapolation from the estimated choline intake of exclusively breast-fed infants from birth to 6 months. For all children aged 1–17 years, the Panel proposes AIs, based on downwards extrapolation from the adult AI, applying growth factors. These AIs range from 140 mg/day (1–3 years) to 400 mg/day (15–17 years). For pregnant women, the Panel derives an AI of 480 mg/day, calculated by extrapolation from the AI for non-pregnant women and the mean gestational increase in body weight. For lactating women, the amount of choline secreted per day in human milk during the first 6 months of exclusive breastfeeding (120 mg/day) is added to the AI for non-lactating women and an AI of 520 mg/day is set.

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