

# Choline

## *The Underconsumed and Underappreciated Essential Nutrient*

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Choline has been recognized as an essential nutrient by the Food and Nutrition Board of the National Academies of Medicine since 1998. Its metabolites have structural, metabolic, and regulatory roles within the body. Humans can endogenously produce small amounts of choline via the hepatic phosphatidylethanolamine *N*-methyltransferase pathway. However, the nutrient must be consumed exogenously to prevent signs of deficiency. The Adequate Intake (AI) for choline was calculated at a time when dietary in-

takes across the population were unknown for the nutrient. Unlike the traditional National Academy of Medicine approach of calculating an AI based on observed or experimentally determined approximations or estimates of intake by a group (or groups) of healthy individuals, calculation of the AI for choline was informed in part by a depletion-repletion study in adult men who, upon becoming deficient, developed signs of liver damage. The AI for other gender and life-stage groups was calculated based on standard reference weights, except for infants 0 to 6 months, whose AI reflects the observed mean intake from consuming human breast milk. Recent analyses indicate that large portions of the population (ie, approximately 90% of Americans), including most pregnant and lactating women, are well below the AI for choline. Moreover, the food patterns recommended by the 2015–2020 Dietary Guidelines for Americans are currently insufficient to meet the AI for choline in most age-sex groups. An individual's requirement for choline is dependent on common genetic variants in genes required for choline, folate, and 1-carbon metabolism, potentially increasing more than one-third of the population's susceptibility to organ dysfunction. The American Medical Association and American Academy of Pediatrics have both recently reaffirmed the importance of choline during pregnancy and lactation. New and emerging evidence suggests that maternal choline intake during pregnancy, and possibly lactation, has lasting beneficial neurocognitive effects on the offspring. Because choline is found predominantly in animal-derived foods, vegetarians and vegans may have a greater risk for inadequacy. With the 2020–2025 Dietary Guidelines for Americans recommending expansion of dietary information for pregnant women, and the inclusion of recommendations for infants and toddlers 0 to 2 years, better communication of the role that choline plays, particularly in the area of neurocognitive development, is critical. This narrative review summarizes the peer-reviewed literature and discussions from the 2018 Choline Science Summit, held in Washington, DC, in February 2018. *Nutr Today*. 2018;53(6):240–253

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**C**holine is an essential nutrient needed for proper liver, muscle, and brain functions; lipid metabolism; and cellular membrane composition and repair.<sup>1-4</sup> Humans can produce small amounts of choline via the hepatic phosphatidylethanolamine *N*-methyltransferase pathway; however, most individuals must consume this nutrient through the diet to supplement the endogenously produced amount to prevent deficiency.<sup>1</sup>

The name choline is derived from the Greek term for bile (ie, chole) because it was first isolated from ox bile in 1862. Its nutritional importance was not recognized until the 1930s, when deficiency was demonstrated to cause fatty liver disease in dogs and rats, which resolved when choline was reintroduced to the diet. Over the following decade, consensus emerged around the general essentiality of choline to prevent liver damage in several mammalian species, including the rat, dog, chicken, pig, rhesus monkey, and baboon.<sup>5</sup> Recognition that choline is an essential nutrient for humans was further advanced in the 1980s by studies in men and women on parenteral nutrition who developed liver damage in its absence.<sup>5,6</sup> A dietary requirement for choline was first demonstrated in healthy men participating in a depletion-repletion metabolic study.<sup>7</sup> The Adequate Intake (AI) for choline was established by the Food and Nutrition Board of the National Academy of Medicine (NAM) (formerly the Institute of Medicine) in 1998, at a time when dietary intakes across the population were unknown for the nutrient. Traditionally, the AI reflects an observed or experimentally determined approximation or estimate of intake by a group (or groups) of healthy individuals.<sup>1,5</sup> Adequate Intakes have been used when data to calculate an estimated average requirement (EAR) and recommended dietary allowance (RDA) are not available. Unlike this typical NAM approach, the development of the AI for choline was informed by the previously mentioned depletion-repletion study in adult men, in which deficiency resulted in liver damage.<sup>1,5</sup> The AI for adults was calculated as 7 mg/kg times the reference weight of a man (76 kg) or woman (61 kg), with rounding based on prevention of liver damage. Upward adjustments during pregnancy and lactation were made based on the amount of choline accretion by the fetus and placenta and the amount secreted in human breast milk. For infants aged 0 to 6 months, the AI was set to reflect the observed mean intake of choline from consuming human breast milk (*note*: this value does not take into consideration the higher content of the colostrum) (Table 1).<sup>1</sup> The dietary requirement for choline has not been revisited by NAM since 1998, despite a growing body of scientific literature. There is a need for dose-response studies across various populations to inform revision of the current Dietary Reference Intakes (DRIs) to include an EAR and RDA, so that accurate assessment of the amounts of individuals who are inadequate can be determined.

The American Academy of Pediatrics (AAP) (1985) and the US Food and Drug Administration recommend that infant formulas contain at least 7 mg of choline per 100 kcal.<sup>5,9</sup> The AAP recently stated that “although all nutrients are necessary for brain growth, key nutrients that support neurodevelopment include protein; zinc; iron; choline; folate; iodine; vitamins A, D, B<sub>6</sub> and B<sub>12</sub> and long-chain polyunsaturated fatty acids. Failure to provide these key nutrients during this critical period of brain development may result in lifelong deficits in brain function despite subsequent nutrient repletion.”<sup>9</sup> The American Medical Association has also recently reinforced the importance of choline for fetal and infant development by recommending the nutrient as a component of all prenatal vitamin supplements.<sup>10</sup>

In February 2018, a second Choline Science Summit was held in Washington, DC, bringing together government, academic, and industry scientists along with leaders of several nongovernmental associations. The symposium addressed the latest science on choline that had accumulated since the 2009 Choline Science Summit<sup>4</sup> and gathered insights for helping raise awareness and intake of this essential nutrient, particularly among vulnerable subpopulations. It included discussions on the role of choline in human health and development throughout the lifecycle, the role of genetics in influencing the dietary requirement, and a closer look at the gaps in choline requirements compared with actual dietary intakes in the US population. Participants also discussed future research needs and strategies for accurately communicating the importance of choline in future public health education efforts. The highlights of the 2018 Choline Science Summit, including call-to-action items, are presented in this manuscript.

## CHOLINE CONTENT OF FOODS

The most common forms of choline in foods are fat-soluble phosphatidylcholine and sphingomyelin, as well as water-soluble phosphocholine, glycerophosphocholine, and free choline<sup>11</sup> (Figure 1). Animal-derived products typically contain higher amounts of choline than certain plant foods do. Foods naturally containing choline include chicken liver (3 oz; 247 mg), salmon (3 oz; 187 mg), eggs (1 large egg with yolk; 147 mg), shitake mushrooms (1/2 cup; 58 mg), chicken broilers or fryers (3 oz; 56 mg), beef grass-fed strip steak (3 oz; 55 mg), wheat germ (1 oz toasted; 51 mg), milk (8 oz; 38 mg), Brussels sprouts (1/2 cup; 32 mg), and almonds (1 oz; 15 mg). Certain plant foods like cruciferous vegetables and certain beans are good sources of choline and contribute approximately 10% of the daily requirement.<sup>2</sup>

## CURRENT DIETARY INTAKES OF CHOLINE IN THE UNITED STATES

When the AI for choline was established by the NAM Food and Nutrition Board in 1998, dietary intakes of choline at



the population level were unknown. A depletion-repletion metabolic study assessing liver damage in healthy men<sup>7</sup> significantly informed the development of the current AIs.<sup>1,2</sup> However, since then, studies showing significant variations in the dietary requirement for choline due to common genetic polymorphisms have become available. It is now generally accepted that choline has an impact on cell structure, neurotransmitter synthesis, atherosclerosis, and possibly neurological disorders. It has shown to be potentially critical during pregnancy, lactation, and early childhood.<sup>2-4</sup>

In 2004, the US Department of Agriculture (USDA), in collaboration with the University of North Carolina, released the first provisional USDA Database for the Choline Content of Common Foods. This database was updated in 2008 and it can be used to estimate the choline content of more than 630 food items.<sup>11</sup> Using this USDA database along with consumption data from the National Health and Nutrition Examination Survey, researchers have estimated usual choline intakes in the United States to be just over 300 mg/d for nonpregnant, nonlactating individuals.<sup>8,13,14</sup> Only about 10% of Americans and 8% of pregnant women currently meet their gender- and life-stage-specific AI for choline<sup>8,13,14</sup>; again, those cutoffs are based on prevention of liver damage (ie, it is not based on the typical mean intake of the healthy population like the AI for other nutrients). Table 1 shows the average usual intakes, as well as the percentage of the US population above the AI and upper intake level (UL) for choline, grouped by gender and life stage. Young children are more likely to meet the AI for choline, although the DRIs for this population are extrapolated downward from studies in adults based on body mass. Premenopausal adult women are the least likely gender and life-stage subpopulation to meet the AI: the average usual intake of choline in this subpopulation is  $319 \pm 6$  mg/d, which is only approximately 71% of the AI. The 25th percentile in this subpopulation has a usual intake of  $254 \pm 11$  mg/d, which is roughly 60% of the AI.<sup>14</sup> Vegetarians have the lowest intakes among the US population, estimated at  $192 \pm 7$  mg/d.<sup>15</sup> Choline intakes have been shown to be driven by egg intake and, secondarily, protein foods (ie, meat, poultry, and seafood) intake.<sup>14</sup> Incorporating 1 to 2 eggs per day as a substitution for processed and/or red meat in the Healthy US-Style 2000 Kcal Pattern increases choline intakes to current recommended levels, without altering other essential nutrients and maintaining cholesterol intakes within a safe range for healthy individuals.<sup>14</sup> Dietary supplements provide less than 5% of dietary choline in relation to recommended intakes because choline salts are bulky and vastly increase the size of the supplemental product.<sup>14</sup> Current intakes cannot be deemed inadequate based upon the AI value alone. Although AIs may be useful in guiding individual dietary plans, by definition, they are established when the evidence is insufficient to calculate an EAR. Therefore, it is

not possible to conclusively assess the risk of inadequacy in a population.<sup>16</sup> Future research will be critical for establishing an EAR to assess the risk for inadequacy within subgroups of the population.

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*Only about 10% of Americans and 8% of pregnant women currently meet their gender- and life-stage-specific AI for choline.*

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## CONSEQUENCES OF DEFICIENCY AND EXCESS

The risk of deficiency and excess intake of choline varies depending on a number of modifiable and nonmodifiable factors; current DRIs for nutrients take into account the impact of sex, age, and reproductive life-stage on nutrient needs and tolerable upper limits. For choline, it is worth noting that, in addition to the variables considered by the DRIs, significant additional variation in nutrient needs still remains due in part to genetic variants. For dietary choline, a large and growing body of research has supported the notion that common genetic variants in genes required for choline, folate, and 1-carbon metabolism influence dietary choline requirements.<sup>2,3,5,17</sup> Several single-nucleotide polymorphisms have been shown to predict the likelihood of developing signs of choline deficiency in controlled laboratory settings where dietary intake is low, and they also influence the metabolic fate of dietary choline when intakes are adequate, as recently reviewed by Ganz et al.<sup>17</sup> While further research is needed to define the precise contribution of genetic variants to dietary choline needs, clinicians working with patients/clients should remain aware of this evidence, particularly as the market for genotype-based diets continues to grow and questions will likely arise.

### Deficiency

Choline deficiency causes clinically evident disease in humans. Healthy men and women with normal folate and vitamin B<sub>12</sub> status who were fed a choline-deficient diet develop fatty liver disease, characterized by elevated liver enzymes in the blood, as well as muscle damage as indicated by increased circulating creatine phosphokinase concentrations, which resolve when choline is restored to the diet.<sup>7,18</sup> Phosphatidylcholine, which can be derived from the diet and synthesized in small quantities by the body, is essential for normal assembly and secretion of very-low-density lipoproteins that transport triglycerides out of the liver; hepatic steatosis during deficiency results in the accumulation of triglycerides and resultant liver damage.<sup>19</sup>

The susceptibility to develop liver damage has been shown to be related to polymorphisms of the gene phosphatidylethanolamine *N*-methyltransferase,<sup>20</sup> as well as polymorphisms in other enzymes involved in choline metabolism.<sup>21,22</sup> Only about 44% of premenopausal women develop liver damage when they are choline deficient.<sup>21</sup> The remaining 56% of premenopausal women who do not have these genetic polymorphisms produce endogenous choline sufficient to evade signs of liver damage. Choline production is enhanced by increased estrogen production. During pregnancy, estrogen concentrations increase dramatically (~60 times) at term<sup>23,24</sup>; despite the potential enhanced capacity for the body to synthesize choline, data from animal models suggest that fetal and infant demand is so high that maternal stores are depleted during pregnancy and lactation.<sup>2</sup> Low maternal choline intakes during pregnancy have been shown to increase the risk of both neural tube defects and cleft palates.<sup>25–27</sup> This risk is related to common genetic variations that alter one's dietary choline requirement.<sup>28</sup> A very common genetic variant in folate metabolism that has been linked to an increase risk of neural tube defects is the 5, 10-methylenetetrahydrofolate dehydrogenase (*MTHFD1*) 1958A allele (rs2236225), and premenopausal women carrying this allele have additionally been shown to be 15-times more likely to develop signs of clinical deficiency on a low choline diet.<sup>29</sup>

## Toxicity

High intakes of choline are associated with a fishy body odor, vomiting, excessive sweating and salivation, hypotension, and liver toxicity.<sup>1</sup> The NAM defined a 3500 mg choline per day tolerable UL for adults based on a study in 7 patients with Alzheimer's disease, where oral administration of 7.5 g/d of choline resulted in a hypotensive effect accompanied by nausea and diarrhea.<sup>30</sup> Similar gastrointestinal effects and a fishy body odor were observed in studies administering doses of 8 to 20 g/d of choline.<sup>31–33</sup> The NAM considered 7.5 g/d of choline as the Lowest Observed Adverse Effect Level and, after application of an uncertainty factor of 2 and rounding, set a UL of 3.5 g/d for adults. The NAM was unable to establish ULs for infants because of the lack of data on adverse effects in this age group and the ULs for children were derived from the adult value by scaling according to reference body weight<sup>1</sup> (Table 1). The European Food Safety Authority Panel on Dietetic Products, Nutrition, and Allergies did not define a UL for choline in 2016<sup>34</sup>

Consumption of choline has been shown to increase the production of trimethylamine *N*-oxide (TMAO), a gut-derived metabolite, which has recently emerged as a candidate risk factor for cardiovascular diseases (CVDs).<sup>35,36</sup> The choline-TMAO connection is not yet established. Microbes metabolize choline, betaine, and carnitine to trimethylamine (TMA), which is oxidized to TMAO in the host

liver by the insulin-regulated enzyme flavin-containing monooxygenase 3. Significant preclinical evidence has been generated suggesting that high levels of TMAO exhibit proatherogenic and prothrombotic effects. Supporting this is a growing body of observational evidence associating high fasting TMAO levels with CVD.<sup>37</sup> This evolving body of literature has suggested that dietary choline, betaine, and carnitine may increase the risk of CVDs. However, randomized clinical trial evidence to assess the relationship of TMAO to CVD in humans is limited, and ethical considerations preclude the likelihood of such studies. Current epidemiological studies do not show a link between dietary choline intakes and CVD.<sup>38</sup> Of note, not all animal models have supported the relationship between TMAO and atherogenesis,<sup>39</sup> and the evidence amassed from epidemiological cohorts has not adequately addressed the potential for reverse causality and/or confounding (ie, high TMAO levels could result from the impact of disease on kidney function and the microbiome). The available evidence at present leaves substantial uncertainty regarding the impact of efforts to reduce dietary choline to reduce TMAO levels and cardiovascular outcomes. Efforts to modify circulating TMAO concentrations with diet may additionally have unintended consequences, as choline exhibits pleiotropic effects beyond its impact on circulating TMAO levels (such as choline's role in supporting hepatic function), and foods that contain additional cardioprotective nutrition, such as omega-3 fatty acid-rich fish, contain substantial quantities of preformed TMAs that can be converted to TMAO in the liver. A recent crossover feeding trial in healthy young men consuming meals containing TMAO (fish, cod), its dietary precursors, choline (eggs), and carnitine (beef) versus a fruit control showed that fish consumption yielded higher blood and urinary concentrations of TMAO (42–62 times) than did eggs, beef, or the fruit control.<sup>40</sup> High TMAO producers were found to have a higher ratio of the microbial phyla Firmicutes to Bacteroidetes and a less diverse gut microbiome<sup>40</sup>; this is consistent with previous reports that suggest that TMAO is produced by Firmicutes but not Bacteroidetes.<sup>41</sup> Notably, a greater ratio of Firmicutes to Bacteroidetes has previously been associated with an increased risk of obesity and metabolic syndrome.<sup>42</sup> This research highlights the important role of gut microbial composition in determining TMAO production and bolsters the notion that higher circulating concentrations of TMAO in a diseased versus nondiseased state may reflect differences in gut microbe composition owing to the disease itself or other lifestyle factors, rather than indicating a causative role of TMAO itself in the disease process.<sup>40,43</sup>

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***The choline-TMAO connection is not yet established.***

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## CHOLINE IN HUMAN HEALTH

Choline's role in human health begins prenatally and extends into adulthood and old age. Its functions are complex and include but are not limited to neurotransmitter synthesis (acetylcholine), cell membrane signaling (phospholipids), lipid transport (lipoproteins), and methyl-group metabolism (homocysteine conversion to methionine). Lactation increases the maternal demand for choline because human milk is rich in choline. More detailed reviews of the health effects of choline across the lifespan have been published elsewhere.<sup>2,3,44</sup> The following is an overview of new research that was presented at the 2018 Choline Science Summit.

### Placental Health

Increasing evidence demonstrates that the placenta is also sensitive to choline supply throughout pregnancy. Optimal development and functioning of the placenta result in both maternal and fetal health, and impairments result in maternal disease, such as preeclampsia, and undesirable fetal outcomes, including growth restriction. In a recent randomized, controlled feeding trial of 480 versus 930 mg/d of choline intakes, placentas from third-trimester pregnant women consuming higher amounts of dietary choline exhibited significant changes in the expression of genes regulating placental vascularization, angiogenesis, and stress reactivity. Higher maternal choline intakes decrease placental expression of the antiangiogenic factor Fms-like tyrosine kinase-1, a preeclampsia risk factor,<sup>45</sup> and infant plasma cortisol,<sup>46</sup> which may reduce the risk of stress-related diseases in later life. In vitro studies have demonstrated that lower choline availability induces inflammation<sup>47</sup> and that this may impair early placental development and the arterial remodeling required for placental perfusion and nutrient transfer to the fetus. These effects in cultured cells have been largely recapitulated in rodent models, whereby higher dietary choline intakes influence markers of inflammation and angiogenesis and help to facilitate transport of nutrients, including docosahexaenoic acid, across the placenta to the fetus.<sup>48,49</sup>

### Infant and Child Neurocognitive Development

High choline intake during the perinatal period has been demonstrated to have a lasting neuroprotective effect in both animal and human studies. Caudill and others (2017) most recently reported the beneficial effects of a higher third-trimester maternal choline intake (930 vs 480 mg/d) on infant processing speed at 4, 7, 10, and 13 months of age (n = 24). Intriguingly, in the lower maternal choline intake group (ie, 480 mg/d), infants born to mothers who were enrolled for a greater duration of pregnancy consuming the study diet exhibited faster reaction times,

suggesting that even modest increases in prenatal choline intake (usually between 300 and 350 mg/d), in the context of a nutritionally complete diet, may produce cognitive benefits in humans.<sup>50</sup> In humans, the hippocampus continues to develop after birth, resembling the adult structure by 4 years of age. To evaluate the persistence of these cognitive benefits, Strupp and colleagues recently conducted a follow-up study of the 24 children enrolled in the Caudill et al 2017 cohort at 7 years of age. Results of the cognitive assessment revealed lasting benefits of the higher maternal choline intake on child attention, memory, and problem solving, providing the first randomized controlled trial evidence that higher maternal choline intake has benefits that last into the school-age years.<sup>51</sup> Although these findings require confirmation in a larger sample, they provide compelling evidence that maternal choline intake during pregnancy has lasting effects on a child's cognitive function. Data from observational studies are somewhat mixed but tend to also support that higher choline intakes during pregnancy enhance cognitive outcomes of the offspring.<sup>52-55</sup> Consistent with the findings from the Caudill and Strupp laboratories, observational data obtained from Project Viva in Massachusetts demonstrated that maternal choline intake within the AI range during pregnancy was associated with better memory function in children 7 years of age as compared with children of mothers whose consumption was approximately 50% of the AI.<sup>53</sup> A narrative review by McCann and others (2006) highlighted 34 rodent studies that examined the relationship of choline during early development and suggested that supplementation during pregnancy may strongly contribute to changes in neurological function in the fetus, as well as improvement in postnatal cognitive behavioral tests across the lifespan.<sup>56</sup>

### Adult Neurocognitive Function and Protection

The mechanisms and clinical evidence with regard to the neurodevelopmental and neuroprotective actions of choline have recently been extensively reviewed by Blusztajn and others<sup>57</sup> and Wallace.<sup>3</sup> High choline intakes during gestation and early childhood have been shown to enhance cognition across the lifespan in multiple animal models,<sup>2,3,57</sup> but this has yet to be confirmed in human studies. Several challenge studies in both younger and older adults provide mixed results.<sup>3</sup> The most compelling short-duration challenge study showed supplementation with choline bitartrate to decrease pupil size, a widely accepted biomarker of cholinergic function, within 70 minutes. Healthy younger adults treated with choline bitartrate in this study had greater precision at rapidly hitting centers of targets as compared with those on the placebo (*note*: participant baseline choline intake or blood status not assessed).<sup>58</sup> Human observational studies assessing protection from cognitive decline in older adults also report inconsistent results. However, studies in rodents

provide evidence of lasting effects of increased maternal intakes that become more pronounced with aging.<sup>3</sup>

A recent Cochrane systematic review and meta-analysis of cytidinediphosphocholine-choline supplementation reported improvements in memory and behavior deficits among elderly subjects with chronic cerebral disorders, although only 1 study lasted longer than 3 months. Evidence on global impression was also strong but limited by the duration of studies.<sup>59</sup> Higher choline intake has been inversely correlated with white-matter hyperintensity volume among participants in the Framingham Offspring Cohort (average baseline intake, ~320 mg/d),<sup>60</sup> a fairly well-accepted marker for Alzheimer's disease and age-related cognitive decline. The strongest evidence for neuroprotection in humans stems from a case control study of individuals with diagnosed cognitive decline, in which patients with Alzheimer's disease were shown to exhibit lower levels of 8 choline-containing phospholipids (and 2 non-choline-containing species) as compared with healthy controls. It should be noted that other causes may have been responsible for the disease state, and this study was not designed to assess causality. These 10 lipids derived from peripheral blood have been validated to predict mild cognitive impairment or Alzheimer's disease within a 2- to 3-year timeframe with over 90% accuracy.<sup>61</sup> Although no animal model of age-related cognitive decline fully imitates the human disease state, supplementation has been shown to influence Alzheimer's disease through modulating the accumulation of amyloid plaques in mice.<sup>57</sup>

## **THERE IS A CRITICAL NEED TO INCREASE AWARENESS AND INTAKE OF CHOLINE THROUGH PUBLIC AND PROFESSIONAL EDUCATION**

With only an estimated 10% of the US population achieving the AIs and no indication of excessive intakes above the ULs that were set in 1998, coupled with compelling evidence of negative health outcomes associated with lower choline intakes and the absence of harm, the summit participants agreed that there is a need to increase public and health professional awareness of choline by providing education on foods rich in choline. Among health professionals, including registered dietitians and physicians, awareness and knowledge of the importance of choline remain low. Choline has been shown to be ranked last among common nutrients as a nutrient to recommend for a healthy diet, and only about 10% of health professionals indicate moderate familiarity with choline. Among obstetricians and gynecologists, only 6% report they are likely to recommend choline-rich foods to pregnant women.<sup>62</sup> Enlisting the support of professional societies to increase the number of feature articles in journals, e-blasts, magazines, toolkits, webinars, conference presentations, and other con-

tinuing education programs will likely help increase the awareness of the importance of the importance of choline in human health. Targeted education to the obstetrics and gynecology communities is a good start; however, all health professionals need to be aware of food sources of choline.

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## ***Health professionals need to be aware of food sources of choline.***

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Continuing to highlight government tools such as MyPlate that assist Americans in selecting nutrient-dense foods that are within daily calorie goals is essential to helping increase intakes of all shortfall nutrients, including choline. Data indicate that increasing consumption of plant foods may offer health benefits; however, this means that there is a need to include more plant foods in the diet, but not necessarily eliminate nutrient-dense animal-derived foods such as eggs, lean meat, and milk products that contain choline. Some participants urged that the National Institutes of Health sponsor a workshop to encourage health professionals outside of the nutrition space to educate themselves on choline. The food industry will be instrumental in developing new product innovations and formulations that are targeted to the needs of the individual consumer. To facilitate these changes, specific recommendations in future iterations of the Dietary Guidelines for Americans for pregnant and lactating women to increase consumption of choline-rich foods with supplementation to fill any dietary gaps are an important step toward bringing attention and awareness for this essential nutrient. Tables 2 to 5 provide menu models for helping patients meet the AIs for choline, based on a 2000-calorie diet and the dietary patterns based on recommendations from the 2015–2020 Dietary Guidelines for Americans.<sup>63</sup>

## **CALL TO ACTION: CONCLUSIONS FROM THE 2018 CHOLINE SCIENCE SUMMIT**

Our knowledge and understanding of choline have increased exponentially from the time when the DRIs were developed in 1998<sup>1</sup> and since the previous 2009 Choline Science Summit.<sup>4</sup> Recognition of the growing evidence relating inadequate intakes to health consequences, coupled to evidence of suboptimal intakes in high-risk populations, warrants a need for improved public health recommendations for choline. Choline seems to be a critical nutrient involved with neurocognitive development during gestation and lactation, with lasting effects in children, although studies elucidating the dietary requirement for choline or whether it has lasting effects

**TABLE 2 Menu Model for a Choline-Focused Mediterranean-Style Diet<sup>a</sup>**

|           | Mediterranean-Style Diet   | Choline-Focused Mediterranean-Style Diet   |
|-----------|--|--|
| Breakfast | 2/3 cup oats   | <b>1 egg</b>   |
|           | 1 large banana   | 1/2 avocado (about 1/3 cup)  |
|           | 1 tablespoon honey   | 1 slice whole grain bread  |
|           | 1/2 oz roasted, unsalted almonds (about 11 almonds)  | 1 large orange   |
|           | 1 cup soy milk   | 1 cup soy milk   |
| Snack     | 1/2 cup plain, nonfat Greek yogurt   | 1/2 oz roasted, unsalted almonds (about 11 almonds)  |
|           | 1/4 cup low-fat granola  | 1 small apple  |
|           | 1 cup strawberries (about 8 large strawberries)  |  |
| Lunch     | 1 whole wheat tortilla   | 2 cups chopped romaine lettuce   |
|           | 2 oz roasted, skinless chicken breast  | <b>2 oz roasted, skinless chicken breast</b>   |
|           | 1/4 cup each: hummus + chopped cucumber + chopped spinach + fat-free feta cheese                     | 1/2 cup each: chopped red onion + chopped tomato + chopped cucumber + fat-free feta cheese |
|           | 4 large Kalamata olives  | 1/2 cup cooked orzo pasta  |
|           | 1/2 cup cooked whole grain pasta   | 1 tablespoon each: olive oil + balsamic vinegar 2 slices whole-wheat pita bread            |
|           | 2 tablespoons each: chopped zucchini + chopped tomato + sliced black olives + Italian salad dressing | 1/4 cup hummus   |
| Snack     | 1/2 cup grapes   | 1/2 cup plain, nonfat Greek yogurt   |
|           | 1/2 oz roasted, unsalted almonds (about 11 almonds)  | 1/2 cup blueberries  |
|           |  | 1 tablespoon wheat germ  |
| Dinner    | 3 oz turkey burger   | <b>3 oz salmon</b>   |
|           | 1 whole-wheat hamburger bun  | <b>1 cup cooked Brussels sprouts</b>   |
|           | 2 leaves romaine lettuce   | 3/4 cup cooked couscous  |
|           | 2 slices tomato + 1 thick slice red onion  | 1/4 cup each: chickpeas + chopped bell pepper + chopped red onion + fat-free feta cheese   |
|           | 2 teaspoons yellow mustard   |  |
|           | 25 sweet potato fries  |  |
|           | Total calories: 2167   | Total calories: 2184   |
|           | <b>Total choline: 238 mg</b>   | <b>Total choline: 466 mg</b>   |

<sup>a</sup>Bold type foods are those that contain 46 mg or greater choline per standard serving. Based on a 2000-kcal/d diet per the 2015–2020 Dietary Guidelines for Americans and intended to meet nutritional needs for children 9 years or older and adults.

into adulthood are still largely absent from the scientific literature. The majority of the US population is not consuming sufficient choline to meet the AI. The AI (unlike an EAR) cannot be used to estimate the prevalence of inadequacy,<sup>8,13–16</sup> and more research is needed. Additional dose response data by genotype in adults is

greatly needed to fully elucidate dietary requirements for choline before EARs and RDAs can be developed. Lack of an EAR severely limits the interpretation of the population intake data because it is not possible to assess whether an intake below the AI results in suboptimal health status. Observational data will likely play a critical role in the

**TABLE 3 Menu Model for a Choline-Focused Vegetarian Diet<sup>a</sup>**

|           | Vegetarian Diet  | Choline-Focused Vegetarian Diet                                 |
|-----------|--|---|
| Breakfast | 1 cup cooked oats  | ½ cup nonfat Greek yogurt                                       |
|           | 1/3 cup raspberries                                      | ½ cup soy milk  |
|           | 1 tablespoon each: honey + flaxseeds                     | 1 cup spinach   |
|           | 2 tablespoons low-fat granola                            | ½ cup each: frozen peaches + frozen raspberries                 |
|           | ½ oz chopped walnuts                                     | 1 tablespoon wheat germ   |
|           | 1 cup soy milk   | 1 trail mix bar   |
| Snack     | 1½ oz low-fat cheddar cheese                             | ½ oz roasted, unsalted almonds (about 11 almonds)               |
|           | 1 small apple  | 1 small apple   |
| Lunch     | 1 medium baked sweet potato with skin                    | 1½ cups cooked whole grain pasta                                |
|           | ½ cup cooked brown rice                                  | ½ cup cherry tomatoes   |
|           | ¼ cup low-sodium black beans                             | 2 oz part skim mozzarella cheese                                |
|           | 1 tablespoon reduced-fat sour cream                      | 2 tablespoons each: chopped basil + olive oil                   |
|           | 2 tablespoons each: guacamole + cotija cheese            | 1 teaspoon balsamic vinegar                                     |
|           | Season with cumin + chili powder + cilantro              |   |
| Snack     | 1 large banana   | <b>1 hard-boiled egg</b>  |
|           | 1 granola bar  | 1½ oz low-fat cheddar cheese + 5 whole grain crackers           |
| Dinner    | ½ cup firm tofu  | 2½ oz veggie burger   |
|           | 1 cup cooked quinoa                                      | 1 whole wheat hamburger bun                                     |
|           | ½ cup each: boiled bok choy + broccoli                   | 2 leaves romaine lettuce  |
|           | ½ cup cabbage  | 2 slices tomato   |
|           | ½ oz roasted, unsalted cashews                           | 1 thick slice red onion   |
|           | 1 cup soy milk   | 2 teaspoons yellow mustard                                      |
|           | 1 tablespoon each: rice vinegar + sesame oil + olive oil | <b>1 cup roasted Brussels sprouts</b> , with olive oil + garlic |
|           | 1 teaspoon low-sodium soy sauce                          | 1 cup soy milk  |
|           | Total calories: 2094                                     | Total calories: 2110  |
|           | <b>Total choline: 331 mg</b>                             | <b>Total choline: 431 mg</b>                                    |

<sup>a</sup>Bold type foods are those that contain 46 mg or greater choline per standard serving. Based on a 2000-kcal/d diet per the 2015–2020 Dietary Guidelines for Americans and intended to meet nutritional needs for children 9 years or older and adults.

revision of the DRIs, particularly for calculating an EAR, since ethical barriers prohibit clinical deprivation of any essential nutrient in humans. Cognition data may facilitate calculation of an EAR during gestation and lactation; however, markers of liver (serum ALT and AST) and muscle function (serum creatine kinase) are also needed and likely the strongest indicators of the choline requirement in

healthy nonpregnant, nonlactating adults. Participants attending the roundtable agreed that these dose-response data are needed before identifying choline as a “nutrient of public health concern” in US nutrition policy.

There was general consensus from the more than 40 experts present at the roundtable meeting that the USDA

**TABLE 4 Menu Model for a Choline-Focused Healthy US-Style Eating Pattern<sup>a</sup>**

|           | Healthy US-Style Eating Pattern        | Choline-Focused Healthy US-Style Eating Pattern                  |
|-----------|--|--|
| Breakfast | 1 slice whole grain bread              | <b>1 egg</b>   |
|           | 1 tablespoon peanut butter             | 1 slice whole grain bread  |
|           | 1 cup nonfat milk                      | 1 cup strawberries (about 8 large strawberries)                  |
|           | 1 large banana                         |  |
| Snack     | ¾ oz pretzels (about 15 mini pretzels) | 1 large banana   |
|           | ¼ cup carrot sticks                    | 1 trail mix bar  |
|           | ¼ cup hummus                           |  |
| Lunch     | 2 slices whole grain bread             | 2 cups romaine lettuce   |
|           | 1.5 oz low-sodium turkey deli meat     | ½ medium avocado   |
|           | 1 tablespoon fat-free mayonnaise       | ⅓ cup each: chopped tomato + chopped cucumber + shredded carrots |
|           | 1 lettuce leaf                         | 1.5 oz low-fat cheddar cheese                                    |
|           | 1 large tomato slice                   | 2 oz canned salmon, drained                                      |
|           | 1 cup nonfat milk                      | 2 tablespoons balsamic vinaigrette                               |
|           | 1 cup carrot sticks                    | 2 oz sourdough baguette  |
|           | ¼ cup red pepper yogurt dip            |  |
|           | 1 oz low-sodium whole grain crackers   |  |
| Snack     | ½ cup plain, nonfat yogurt             | ½ oz roasted, unsalted almonds (about 11 almonds)                |
|           | 1 large orange                         | ½ cup sugar snap peas  |
|           | ¾ cup mixed, unsalted nuts             |  |
| Dinner    | 2 cups pasta                           | 1 cup brown rice   |
|           | 1 cup low-sodium marinara sauce        | 1 cup steamed broccoli, carrots and peppers                      |
|           | 2.5 oz lean ground beef                | <b>3 oz lean beef</b>  |
|           | 1 cup nonfat milk                      | 1 cup nonfat milk  |
|           | Total calories: 2138                   | Total calories: 1898   |
|           | <b>Total choline: 276 mg</b>           | <b>Total choline: 443 mg</b>                                     |

<sup>a</sup>Bold type foods are those that contain 46 mg or greater choline per standard serving. Based on a 2000-kcal/d diet per the 2015–2020 Dietary Guidelines for Americans and intended to meet nutritional needs for children 9 years or older and adults.

Birth to 24-Months and Pregnant Women Program and the 2020–2025 Dietary Guidelines Advisory Committee should consider the recommendations from the American

Medical Association and AAP,<sup>9,10</sup> as well as the recent scientific literature presented at the roundtable meeting and summarized in this article. Roundtable attendees offered the

**TABLE 5 Menu Model for a Choline-Focused Pregnancy Eating Pattern<sup>a</sup>**

|   | Healthy Pregnancy Eating Pattern                  | Choline-Focused Healthy Pregnancy Eating Pattern   |
|---|---|--|
| Breakfast                                   | 1½ cups toasted whole grain oat cereal            | <b>1 hard-cooked egg</b>   |
|   | 1 cup nonfat milk                                 | 1 large peach  |
|   | ½ cup blueberries                                 | 1 slice whole grain bread  |
|   | ½ cup sliced banana                               | 1 tablespoon jelly<br>1 cup nonfat milk  |
| Snack                                       | ½ whole grain bagel                               | 1 whole wheat tortilla   |
|   | 1 cup nonfat milk                                 | 2 tablespoons peanut butter  |
|   | ½ cup each: blueberries + sliced banana           | ½ large banana   |
| Lunch                                       | 2 slices whole grain bread                        | 2 cups chopped romaine lettuce   |
|   | 3 oz roasted turkey breast                        | <b>3 oz canned salmon, drained</b>   |
|   | ½ avocado   | ½ cup sliced strawberries  |
|   | 2 leaves romaine lettuce                          | ¼ cup chopped red onion  |
|   | 2 slices tomato                                   | 1½ oz mozzarella cheese  |
|   | 1 thick slice red onion                           | ½ cup quinoa   |
|   | 1 tablespoon mayonnaise                           | 1 tablespoon each: slivered almonds + unsalted pumpkin seeds                                 |
|   | 1 cup chopped romaine lettuce                     | 2 tablespoons light balsamic vinaigrette   |
|   | ¼ cup each: corn kernels + low-sodium black beans | 2 oz whole grain roll  |
|   | 2 tablespoons shredded cheddar cheese             |  |
|   | 1 tablespoon ranch dressing                       |  |
| Season with cumin + chili powder + cilantro |   |  |
| Snack                                       | 1 oz bag vegetable chips                          | ½ cup each: baby carrots (about 6 baby carrots) + cherry tomatoes                            |
|   | ½ oz roasted, unsalted almonds (about 11 almonds) | 5 low-sodium whole grain crackers  |
| Dinner                                      | 1½ cups whole grain penne pasta                   | <b>3 oz lean beef</b>  |
|   | ¼ cup each: peas + sliced zucchini                | 1 cup cooked brown rice  |
|   | 2 cups spinach                                    | ½ cup each: edamame + <b>chopped Brussels sprouts</b> + sliced carrots + chopped bell pepper |
|   | ½ cup light alfredo sauce                         | ½ cup mandarin oranges   |
|   | 1 cup nonfat milk                                 | 1 cup nonfat milk  |
|   | Total calories: 2365                              | Total calories: 2493   |
|   | <b>Total choline: 317 mg</b>                      | <b>Total choline: 506 mg</b>   |

<sup>a</sup>Bold type foods are those that contain 46 mg or greater choline per standard serving. Based on a 2400-calorie diet: Dietary patterns based on the MyPlate Daily Checklist and nutrient recommendations for pregnant women established by the Academy of Nutrition and Dietetics and the American Congress of Obstetricians and Gynecologists. The calorie level selected and food group amounts associated with this calorie level were based on the average age (26 years), height (5 ft 4 in), and weight (166 lb) of a US female.

following call to action for policy-makers and the nutrition science community:

1. There is compelling evidence from nationally representative surveys and cohort studies that demonstrate that most of the US population does not meet the current AIs and that excessive intakes above the ULs are absent; establishment of an EAR is critical for determining the point where low intakes result in adverse health outcomes. The choline requirement of an individual depends on one's genotype and more should be done to educate consumers and health professionals on the importance of choline-rich foods in the diet. Choline must be integrated into the prenatal supplement regimen.
2. Current research suggests that failing to achieve the AI is likely detrimental to health, particularly in regard to liver and muscle function in healthy adults, as well as cognitive function in the developing fetus and infant. Adverse neurological consequences due to suboptimal maternal choline intakes may be identified in future human clinical research. We must focus on providing resources to all health professionals on the potential consequences of choline inadequacy.
3. At present, advocating for dietary guidance that helps individuals meet the AI is needed. This is particularly needed for pregnant/lactating women and infants.
4. Research foundations, the industry, and government agencies such as the National Institutes of Health should consider future studies that have the potential to provide data that could inform revision of the DRIs for choline to include an EAR and RDA as well as support other nutrition policies and programs.

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## CRITICAL WINDOW FOR OBESITY PREVENTION IDENTIFIED

A large study found that most obese adolescents experienced the most pronounced weight gain during early childhood, between 2 and 6 years of age. Weight gain slowed after that but continued and led to a higher degree of obesity during adolescence than in childhood. In this secondary analysis, researchers analyzed the body mass index (BMI) trajectory over time in a population-based cohort of 51 505 children who had at least 1 clinical visit with a pediatrician during childhood (0-14.9 years of age) and another visit during adolescence (15.0-18.9 years of age). They stratified participants by age and weight groups. For weight groups, BMI and height were expressed as SD scores from standards. The groups were defined as underweight (BMI SD score of  $-5$  to less than  $-1.28$ ), normal weight (BMI SD score of  $-1.28$  to  $<1.28$ ), overweight (BMI SD score of  $1.28$  to  $<1.88$ ), and obese (BMI SD score of  $1.88$  to  $<5$ ). For each weight group in adolescence, the researchers examined the percentages of participants who had been in each weight group during childhood.

Most adolescents with normal weight had been of normal weight throughout childhood. Most obese adolescents had been of normal weight during infancy; however, 53% of obese adolescents had been overweight (22%) or obese (31%) from age 5 years onward, with a BMI SD score that continued to increase as they aged.

The investigators then flipped the approach and stratified participants by their childhood weight group and then looking forward calculated the proportion of each group who became underweight, normal weight, overweight, or obese during adolescence. The vast majority (90%) of those who were obese at age 3 years were overweight or obese as adolescents. Among the adolescents with obesity, the highest acceleration in yearly BMI increments was seen between ages 2 and 6 years, with BMI continuing to rise thereafter. Compared with children whose BMI was stable during childhood, the risk for overweight or obesity during adolescence was higher for children with high acceleration in yearly BMI increments during early childhood but not during the school years. Approximately half of those who were overweight at age 2 years or younger returned to a normal weight during adolescence, but for those who were obese at 3 years of age, 90% were likely to be overweight or obese during adolescence. Only a few young children with obesity went back to normal weight. Those who were lean usually remained lean as adolescents. Identification of what may be a critical window for predicting childhood weight gain provides an opportunity for intervention to prevent obesity in children at risk.

Source: Geserick M, Vogel M, Gausche R, et al. Acceleration of BMI in early childhood and risk of sustained obesity. *N Engl J Med* 2018; 379:1303-1312.

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