Choline

Disclaimer

This chapter describes the background for setting dietary reference values for Choline in the 6th edition of the Nordic Nutrition Recommendations (NNR2022). Rima Obeid and Therese Karlsson has been assigned as authors. The present version of the chapter has been peer reviewed by Anthea Van Parys and Sari Hantunen and considered by the NNR2022 Committee. The chapter is now open for public consultation. The hearing responses will be publicly available and carefully considered by the NNR2022 Committee. All input considered by NNR2022 Committee as scientifically valid and relevant will be forwarded to the authors for consideration. Please note that sustainability aspects and other issues such as obesity, physical activity, and burden of diseases will be integrated at a later stage, if relevant. The NNR Committee is responsible for setting the dietary reference values. The suggestion for setting of dietary reference values will be open for public consultation at a later stage, before the NNR2022 Committee reach the final conclusion, and are not included in the document now available for public consultation.

Abstract

Choline is an essential nutrient with metabolic roles as a methyl donor in one carbon metabolism and as a precursor for membrane phospholipids and the neurotransmitter, acetylcholine. Choline content is particularly high in liver, eggs, and wheat germ although it is present in a variety of foods. The main dietary sources of choline in the Nordic and Baltic countries are meat, dairy, eggs and grain. A diet that is devoid of choline causes liver and muscle dysfunction within three weeks. Choline requirements are higher during pregnancy and lactation than in non-pregnant women. Although no randomized controlled trials are available, observational studies in human, supported by coherence from interventional studies with neurodevelopmental outcomes and experimental studies in animals strongly suggest that sufficient intake of choline during pregnancy is necessary for normal brain development and function in the child. Observational studies suggested that adequate intake of choline could have positive effects on cognitive function in older people. However, prospective data are lacking, and no intervention studies are available in the elderly.

Introduction

Choline is a water-soluble quaternary amine with a molecular weight of 104.2 g/mol. Foods contain water-soluble (free choline, phosphocholine, glycerophosphocholine) and lipid soluble choline compounds (phosphatidylcholine and sphingomyelin). Phosphatidylcholine accounts for approximately 95% of total choline in animal tissues. The remaining 5% of tissue choline consists of free choline, phosphocholine, glycerophosphocholine, Cytidine 5'-diphosphocholine

(CDP-choline) and acetylcholine (1). Choline is oxidized to betaine. Betaine supports folate as an alternative methyl donor in one carbon metabolism that plays a central role in cell metabolism and DNA-methylation. In addition, choline is needed to produce phospholipids that are major constitute constituent of cell membranes and play a role in hepatic lipid metabolism. Choline is also used to produce the neurotransmitter acetylcholine. Therefore, choline is related to major metabolic pathways (one-carbon and lipid) that have been associated with chronic diseases. Choline has been recognized an essential nutrient in human by the Food and Nutrition Board of the US National Academy of Sciences of the US Institute of Medicine (IOM, 1998) (2) and later on confirmed by European Food Safety Authority Panel on Dietetic Products, Nutrition and Allergies (EFSA, 2016) (3). A small amount of choline can be synthesized de-novo from phosphatidylethanolamine via phosphatidylethanolamine methyl transferase (PEMT) in the liver. However, depletion-repletion studies have provided evidence that dietary restriction of choline in human causes liver and muscle damage, while feeding choline can avert these symptoms (4). Therefore, the endogenous synthesis of choline is not sufficient and dietary sources of choline are necessary to maintain health, making choline an essential nutrient for humans.

The Adequate Intake (AI) levels for choline for different age groups and life stages have been defined by the IOM in 1998 (Table 1). In 2016, the EFSA Panel considered that Average Requirements and Population Reference Intakes for choline cannot be derived for adults, infants and children, and instead AIs (3) were defined (Table 1). The aim of this chapter is to describe the present evidence on a potential role for choline in health-related outcomes upon which Dietary Reference Values (DRVs) could be based.

Methods

Based on initial scoping reviews (ScRs) (5) and public consultations conducted end of 2020, the NNR2022 Committee decided to incorporate a chapter on choline for the first time. Choline was not selected for a *de novo* systematic review. In the scoping review of the NNR2022 Committee, the EFSA Panel Publication in 2016 (3) was identified as a reliable source of evidence, since it was based on systematic literature review. The present chapter on choline is based on the evidence as judged by the EFSA Panel. In addition, we reviewed the literature cited there and the original report of the IOM, 1998 where choline was first considered an essential nutrient. We searched in PubMed to identify articles published after the EFSA report (in 2016) addressing the association between choline intake and health outcomes relevant to Nordic countries. During preparation of this chapter (March to September 2021), we searched PubMed using terms containing "choline"[MeSH Terms] OR "choline"[All Fields]) in combination with several MeSH terms that cover the outcomes of interest such as; "cardiovascular diseases", "stroke", "pregnancy", "cognitive function", "memory", "dementia", "pregnancy", "lactation", "birth defects", "brain development", "liver function". The authors conducted the search in different health areas with a time limit between 2016 and 2021. The most relevant articles identified by this non-systematic review were included in this chapter. The EFSA report was assessed using AMSTAR 2 tool and based on information from the EFSA report 2016 (3) and an external scientific report describing literature search and review process (6). Based on AMSTAR 2 the EFSA is judged of moderate quality due to flaws in relation to lack of information of predetermined methods, selection/data extraction in duplicate and sources of founding. However, the report is based on a comprehensive literature search, appropriate risk of bias assessment and justification of excluded studies. Therefore, we consider it to be a reliable source of evidence.

Physiology and metabolism

Choline absorption and tissue distribution

Choline in the diet is actively taken up by the enterocytes via the saturable organic cation transporters choline transporter-like protein 1 (CTL1) also called solute carrier family 44 member 1 (SLC44A1). After ingesting phosphatidylcholine (main choline storage form in animal tissues), plasma free choline raises to show a peak level after 3-4 hours and it is cleared within approximately 8 hour (7). Both bile secretion and liver portal circulation participate in choline homeostasis and incorporate hydrophobic choline forms such as phosphatidylcholine into chylomicrons. Phospholipases convert dietary and bile phosphatidylcholine to choline.

Water-soluble choline forms may enter the portal circulation unchanged. The unabsorbed choline is converted by gut bacteria to trimethylamine (TMA) that enters the blood stream and metabolized in the liver to trimethylamine-N-oxide (TMAO). The proportion of choline absorbed from the diet is not well defined but may depend on the form of choline in the diet, bile secretion, and gut microbiota.

At least three types of cellular transporters are responsible for universal or specific tissue distribution of free choline. CTL1 or SLC44A1 is a low affinity universal choline transporter present in all tissues such as kidney and placental tissues, enterocytes, hepatocytes, mitochondria and synaptosomes. This transporter provides the cell with choline needed for the synthesis of phospholipids and betaine.

Presynaptic cholinergic nerve terminals are rich in a high-affinity choline transporter (CHT; solute carrier family 5 member 7 encoded by SLC5A7), which is a carrier-mediated sodium-, chloride- and ATP-dependent saturable uptake system. The third choline transporter (OCT1-3: a member of the solute carrier 22 family SLC22A1-3), is present in the blood–brain barrier and erythrocyte membranes and it has a high affinity for choline (8).

Saturable and non-saturable choline uptake mechanisms are operating in the mammary epithelium, with the non-saturable system operating at higher maternal choline supply. The mammary epithelium is capable of converting free choline to other choline-containing compounds. Choline is transported from the mother to the foetus across the placenta (9) via a specific transport system on both the maternal and fetal side of the syncytiotrophoblast (10).

Choline metabolism

Choline is transported into the mitochondria where it is oxidized to betaine in a two-step enzymatic reaction mediated by the mitochondrial choline dehydrogenase (CHDH) and betaine aldehyde dehydrogenase (BADH) (mitochondrial or cytoplasmic) (**Figure 1**). This reaction occurs mainly in the liver and kidney. Betaine is a methyl donor in one-carbon metabolism and thus it interacts with other nutrients such as folate, vitamin B12, riboflavin, and the amino acid methionine. Metabolisms of choline and folate show interdependency (11-13). Both folate and choline (via betaine) are methyl donors and cooperative negative determinants of plasma total homocysteine (tHcy) (14-17).

Beside its role in one carbon metabolism, choline is required for synthesizing phospholipids such as phosphatidylcholine, which is the main storage form of choline and an essential component of cell membranes. Phosphatidylcholine is needed for lipoprotein assembly and secretion that are required for normal hepatic secretion of very low-density lipoprotein (VLDL)

from the liver, thus explaining that choline deficiency is associated with fatty liver. Moreover, choline is used to produce the neurotransmitter acetylcholine (mainly in the brain, heart, kidney and placenta).

The gene encoding PEMT enzyme is upregulated by estrogen that binds and activates estrogen-responsive elements in the gene (18). In women, the endogenous production of choline is subject to hormonal upregulation which was the argument used by IOM to define higher AIs for men compared to women. Moreover, in addition to polymorphisms in genes involved in one-carbon metabolism, several polymorphisms in PEMT gene have been described to have a potential effect on individual's predisposition to choline deficiency (19). However, the so far available studies on eventually higher requirement of subjects with certain genotypes did not provide sufficient evidence to justify the need to set higher intake recommendations of choline for the whole population.

Assessment of nutrient status

There are currently no optimal blood biomarkers that can accurately mirror choline deficiency or sufficiency. A biomarker should optimally show a dose-dependent association with the intake of choline. Several biomarkers have been measured in plasma/serum or breast milk in clinical studies. Examples of these markers are; free choline (20), total choline (include choline esters) (21), and other choline containing compounds such as phosphatidylcholine, glycerophosphocholine, sphingomyelin and phosphocholine (22, 23). The last four derivatives are highly available in breast milk and have been used in previous studies to compute total choline by summing up the single components (23, 24).

Higher choline intake from foods and/or supplements increases plasma free choline and betaine in adults (25, 26) and in pregnant women (i.e., 16 week of gestation) (27)**,** suggesting that the concentrations of these biomarkers could be a surrogate measure of maternal choline supply. Plasma concentrations of free choline decline in people fed a diet that is deprived of choline (4). The levels raise after feeding a meal that is rich in choline (i.e., 3 eggs) (25) or after providing choline in supplemental forms (i.e., phosphatidylcholine or choline bitartrate) (25, 28, 29). When choline is absorbed in the intestine, it is distributed to tissues, stored, engaged in lipid transport, or eliminated via the kidney within approximately 8 hours. Although fasting plasma concentrations of free choline and betaine show response to choline depletion (within 1-3 weeks) and repletion (acute and chronic), they may not accurately reflect small variations in dietary intakes and are thus not suited as markers of choline intake in clinical studies (30). The use of fasting plasma choline as an exposure variable in clinical studies may underestimate

between-individual variations in choline intake. Summing up several forms of concentrations of choline derivatives (i.e., free choline, phosphatidylcholine, phosphocholine, etc) is more likely to increase the accuracy of estimating choline content in breastmilk for example. There is certainly a need to search for surrogate markers or a combination of markers that reflect choline status.

Dietary intake in Nordic and Baltic countries

Choline content is particularly high in liver, eggs, and wheat germ although it is present in a variety of other foods. Also, the food additive lecithin which is rich in phosphatidylcholine can contribute to dietary choline. The main dietary sources of choline in the Nordic and Baltic countries are meat, dairy, eggs and grain (31). In food, choline is present either as free choline or in the esterified forms phosphatidylcholine, phosphocholine, glycerophosphocholine and sphingomyelin (32). Generally, a plant-based diet contains less choline than an animal-based diet (33). The global trend to reduce animal-source foods in order to attain sustainability goals implies that it may be difficult to achieve AIs of choline, especially in vulnerable population groups such as young women and infants. A "vegetarian tendency" dietary pattern was associated with lower intake coefficients for choline in women of childbearing age (34). Source of foods need to be considered in achieving AIs for choline moving toward a more plant-based diet.

Data on choline intake in the Nordic and Baltic countries is scarce and results from National population surveys are available only from one publication (31). In Swedish and Finnish adults aged 18 to ≥75 years, average reported choline intake ranged from 317 to 468 mg/day in men and 317 to 404 mg/day in women (31). In children, average choline intake ranged from 171 to 180 mg/day in Finnish children aged 1 to <3 years, 256–285 mg/day in children aged 3 to < 10 years, and 292–373 mg/day in children between 10 and <18 years (31).

Compared to other populations in Europe, the average reported intake of choline seems to be slightly higher in Nordic countries (31). However, reported mean choline intakes in Nordic countries were lower than the AIs especially in vulnerable groups such as young women and pregnant and lactating women. This implies that a large proportion of women in pregnancy age are not achieving optimal daily choline intake. For example, a national survey in Latvia has shown that estimated median intake of total choline was 356 [5^{th}, 95^{th} percentiles = 200, 592] mg/day in pregnant women and 288 mg/day in pregnant adolescents (31). These average intake values are similar to those among women from Sweden (n=807) [median (5^{th}, 95^{th} percentile) = 356 (186, 631) mg/d] and women from Finland (n= 710) [327 (177, 587) mg/d] implying that

choline may be under consumed on a population level. However, the only existing database as of today is the U.S. Department of Agriculture (USDA) database (32). There are no food composition data available in any of the Nordic or Baltic countries and national databases of choline content in foods are warranted. Thus, there is some uncertainty in the estimated choline intake from Nordic (and European) populations. There is also uncertainty about the health consequences of not achieving the adequate intake level of choline such as during pregnancy.

Health outcomes relevant for Nordic and Baltic countries

Pregnancy and lactation and infant's health

To calculate the additional need for dietary choline during pregnancy, the IOM estimated choline transfer from the mother to the fetus and of choline accretion in the fetus and placenta during pregnancy and this estimate was added to the requirements for non-pregnant women to get an AI of 450 mg/d for pregnant women. The EFSA panel considered that the approach followed by IOM is not feasible to set DRVs for pregnant women due to a lack of data. The EFSA panel recognized that choline requirement in pregnancy is higher than in non-pregnant women and that increased loss of choline in urine occurs during pregnancy. The AI for pregnant women (480 mg/d) was judged based on isometric scaling from the AI of non-pregnant women (400 mg/day) adjusted for a mean weight increase of 12 kg during pregnancy. During lactation, approximately 120 mg choline is secreted per day in human milk during the first 6 months of exclusive breastfeeding. Thus, the AI for choline lactating women was set to 520 mg/d (3). The AIs were not further linked to health outcomes in pregnant women or their children.

Choline administered to the mother reaches the mother's circulation as free choline, betaine, or other derivatives and appears to pass to the foetus or the child via active transport. This is evident from studies showing higher levels of choline and related derivatives in amniotic fluid, cord blood (29, 35, 36) and breast milk compared to mother plasma (37). Using [^{3}H]-choline in the dually-perfused human placenta have shown that choline perfusion was associated with 4% preferential transport towards the fetal circulation (9).

Maternal plasma concentrations of choline and betaine are subject to dynamic changes during pregnancy (38-40). Concentrations of choline increase in plasma of the women throughout gestation (+50% between first and third trimesters of pregnancy), while betaine levels decline within the same period (by approximately 36%) (38, 40).

Adequate choline intake during early life has been related to growth and brain development of the foetus and child.

The EFSA Panel evaluated two case–control studies for the association between maternal choline intake and neural tube defects (NTDs) in the offspring (41, 42). The association between choline intake and risk of NTDs was inconsistent, and it was recognized that the association may be influenced by the intake of other nutrients and the PEMT genotype of the mother. The data on choline intake and risk of NTDs were not used to derive DRVs for choline. Since the EFSA systematic review of the literature, three additional case-control studies on maternal choline intake/or status and neural tube defects became available and were entered in a recent meta-analysis. A pending systematic review and meta-analysis of five case-control studies (21, 41-46) including 1131 mothers of children with NTD and 4439 control mothers showed that low maternal intake or status of choline are associated with higher odds ratio (OR) for NTD [pooled estimate (95% confidence intervals) = 1.36 (1.11, 1.67)]. The 95% prediction intervals were (0.78, 2.36) (Obeid et al., formally accepted for publication). Some of the studies originated from the US and Canada were conducted after the fortification with folic acid that could show interaction with choline on the development of the neural tube. Randomized controlled trials (RCTs) using choline (without folic acid) to prevent NTDs are not ethical. The results of the meta-analysis combined with the experimental evidence in animals strongly suggest that the relationship between insufficient maternal choline and the risk of NTD is likely to reflect a causal relationship. Future studies are warranted.

The amount of total choline in breast milk is higher than in maternal blood (47) and it raises by 114% from the stage of colostrum (2-6 days) to 6-7 days postpartum (24). Ilcol et al., found that free choline in breast milk was positively correlated to free choline and choline-containing phospholipids in maternal serum (23). In addition, higher choline and choline-containing derivatives in breast milk were associated with higher levels of serum free choline in the infant (23). Experimental studies on mice suggest that the main part of maternal choline intake is extracted into breast milk (48).This evidence is supported by human studies showing that higher maternal choline intake from the diet [750 mg choline/d on top of the diet versus placebo] was associated with higher breast milk phosphatidylcholine (37). Therefore, increasing choline intake of lactating women can influence not only maternal serum/plasma choline, but also breast milk choline derivatives (37) and thereby choline intake available for the infants and choline status of the infants.

RCTs support positive effects of maternal choline supply on some domains of child neurodevelopment (self-regulation) and neurocognition (learning and memory) (49-51). However, available RCTs have provided higher daily intake of choline than the present

adequate intake and have measured very heterogeneous outcomes. Studies with larger sample size and well-planned outcomes are still warranted.

Non-interventional studies investigated the association between child serum total and free choline or choline intake and neurodevelopment/neurocognition at different ages (between 6 months and 7 years) and showed mixed results (27, 52-58) which could be due to measuring non-fasting choline and the fact that choline levels in blood are not a good estimate of choline status or intake.

Cognitive function in elderly people

The systematic review conducted by the EFSA panel identified one prospective cohort study that investigated the association between habitual intake of choline and cognitive function in 1,391 men and women (aged 36–83 years) free of dementia at baseline (3). Performances of verbal and visual memory were significantly better with higher choline intake but there were no significant effects for verbal learning and executive function (59). A recent prospective cohort study with participants from the Kuopio Ischaemic Heart Disease Risk Factor Study including 2497 Finnish men aged (42-60 y) examined the relationship between total choline and phosphatidylcholine intake on incidence of dementia (60). After 21.9 years follow-up, higher phosphatidylcholine intake, but not total choline intake, was associated with a decreased risk of dementia (60). Thus, a few observations in healthy adults imply a positive role of dietary choline in cognitive functions but the prospective data on relationships between choline intake and cognitive function are limited and no results from intervention studies are available.

Fatty liver

The effects of choline on the liver have been shown in depletion and repletion studies and in studies among patients receiving parenteral nutrition. Moreover, feeding healthy adult's men a choline deficient diet (13 mg/d) for 3 weeks caused 30% lowering of plasma choline and phosphatidylcholine, depletion of choline stores in the liver and elevated serum alanine aminotransferase activity (ALT), suggesting incipient liver damage (4). This effect was averted when the participants received 500 mg/d choline (i.e., plasma choline increased and serum ALT declined) (4). Moreover, patients receiving parenteral nutrition that was depleted of choline had low plasma choline and developed liver steatosis as shown by elevated plasma liver enzyme activities (ALT) (61). Plasma free choline was increased and steatosis of the liver declined within 1to 6 weeks after starting choline supplementation versus the placebo (62, 63). The liver-damaging effect of choline deficiency is likely to be unique and not fully prevented by other

methyl donors such as methionine (64). Fatty liver is prevalent in the general population, especially in individuals with overweight or obesity and in patients with type 2 diabetes mellitus. The contribution of insufficient choline intake and status to fatty liver on a population level is not well studied. More studies are warranted because foods rich in choline are also rich in fats thus making it more challenging to detangle the effect of choline from that of fats and excess nutrition.

Cardiovascular disease incidence and mortality

A SR (EFSA scientific opinion) identified two prospective cohort studies on dietary choline and cardiovascular disease (CVD) incidence (3). These two large prospective cohort studies in men and women without prior CVD, did not show a significant relationship between choline intake and risk of CVD (65, 66). EFSA concluded that data on choline intake and risk of CVD cannot be used to derive DRVs for choline (3). This is supported by results from recent prospective cohort studies showing no associations between choline intake and risk of total CVD, coronary heart disease, stroke or atrial fibrillation (67-69).

Observations from a few recent cohort studies show conflicting results on dietary choline intake and CVD mortality. In a Japanese cohort of 29,279 men and women, higher intake of total choline and sphingomyelin was associated with no or higher risk of CVD mortality, respectively (70). In two large U.S cohorts, a higher intake of choline and phosphatidylcholine was associated with increased risk of CVD mortality (71, 72). In a study by Yang et al. (73) including three cohorts from U.S and China, no association between dietary choline and risk of stroke mortality was reported. An increased risk of ischemic heart disease mortality in the highest quintile of choline intake compared with the lowest was reported for two of the three cohorts with no association in one cohort (73). Thus, a few observations in healthy adults imply a possible positive association of dietary choline with CVD mortality but results are conflicting. Prospective data on relationships between choline intake and CVD mortality in European populations are lacking and no results from intervention studies are available.

Type 2 diabetes mellitus

In a finish cohort of 2332 men aged 42-60 years from the Kuopio Ischaemic Heart Disease Risk Factor Study, baseline total choline and phosphatidylcholine intakes were associated with a lower risk of type 2 diabetes after a mean of 19.3-year follow-up (74). The associations with total choline intake were generally weakened after multiple adjustments, while for phosphatidylcholine there seems to be a dose-response associations, suggesting that the source

or the form of choline in the diet could have differential effect on the risk of diabetes. On the other hand, higher intake of phosphatidylcholine was associated with higher risk of type 2 diabetes mellitus in a large U.S cohort (75). Future RCTs and prospective observational studies may provide better evidence on the association between choline (or phosphatidylcholine) intake and the risk of type 2 diabetes.

Safety

Side effects reported after using high doses of oral choline [between 7.5-20 g/day] were hypotension, gastrointestinal symptoms and fishy body odour. The lowest choline intake where side effects were observed was 7.5 g/d. Thus upper tolerable level of choline was set to 3.5 g/day for adults after after the application of an uncertainty factor 2 (2, 3). Choline is metabolized by gut bacteria into trimethylamine (TMA) that is converted by the liver to TMAO. Elevated TMAO has been shown to be associated with renal dysfunction and prevalent cardiovascular diseases (76, 77). Studies on choline consumptions (i.e., from eggs (25, 78-80) as determinant of plasma or urinary TMAO show considerable between-individual heterogeneity and generally low (79) or even no effect on TMAO (25, 78, 80) and a dependency on gut microbiota (81, 82), choline source (supplements versus diet) (83) and choline form (81). Whereas choline intake from eggs for instance failed to show an effect on gut microbiota (80) and also no firm evidence on cardiovascular risk. It remains unclear whether TMAO is a result or a culprit of cardiovascular disease or related clinical conditions such as renal dysfunction.

At present we consider TMAO as inappropriate outcome to set the UL for choline intake. We recommend considering the UL of choline of 3.5 g as defined by the EFSA and IOM. For instance, in order to exceed the 3.5 g/day intake of choline, a person must eat 2.94 kg Salmon per day. Exceeding this intake through a natural diet on long term is very unlikely and most available supplements provide between 100 mg and 1 g choline on top of the natural diet.

Requirement and recommended intakes

It is generally well recognized that the present AIs of choline are not achieved through the diet on a population level. It is also recognized that the AIs intakes were not related to clinical health outcomes. The lack of food composition databases, data on food dietary intakes and optimal biomarkers make the interpretation and generalizability of results from observational studies very difficult. Interventional studies with controlled choline intake or RCTs (e.g. with appropriate comparator) are the most reliable way to link choline to health outcomes. Also studies showing a dose-response relationship are needed to strengthen the present evidence on the role of choline in some outcomes such as maternal-child health or cognitive function in elderly people. Most of the available RCTs on maternal supplementation and child neurocognition or neurodevelopment have limitations. However, most RCTs achieved total choline intakes (diet plus supplements) of 1 g/d or higher, suggesting that a possible positive effect of choline on brain function may be expected at levels that are almost twice as high as the present AI for pregnant and lactating women.

There are several gaps in knowledge in the field of choline nutrient. For instance, there are polymorphisms in enzymes involved in choline and folate metabolisms that could interfere with choline requirements. In addition, because animal foods are the main source of choline in the diet, some of the associations between choline intake and health outcomes could be abolished due to other components in the same food sources such as fats. Moreover, the health effects of choline need further investigations since they might differ depending on the choline forms that in turn could influence bioavailability and metabolic path. There could be interactions between choline, folate and vitamin B12, thus choline could in theory show stronger effects on health outcomes in people with low folate status, while its role becomes less important when folate status is high.

Reasoning behind the recommendation

Choline intake recommendations by the EFSA and IOM were based on depletion-repletion studies among adults who showed liver damage after cutting choline from the diet and this sign was corrected after administering 500 mg choline/d. Intervention studies in pregnant women using 480 mg/d (vs. 960 mg/d) showed no consistent effect on health outcomes, thus supporting the view that 480 mg/d was sufficient to maintain health. According to the EFSA and IOM, the AI of choline for pregnant women (480 mg/d and 450 mg/d) and lactating women (520 and 550 mg/d) are similar. The recommendations of sufficient choline intake for pregnant and lactating women as suggested by the EFSA appear to be justified. However, intakes above this

level maybe needed for brain development implying that pregnant and lactating women may need to achieve higher choline intake through supplements.

Table 1. Adequate Intake for choline as set by EFSA and IOM pannels.

	IOM – 1998			EFSA – 2016	
Life stage	**Age**	**AI (mg/d)**		**Age**	**AI (mg/d)**
		Males	**Females**		
Infants	0-6 months	125	125	0-6 months	120
	7-12 months	150	150	7-11 months	160
Children	1-3 years	200	200	1-3 years	140
	4-8 years	250	250	4-6 years	170
	9-13 years	375	375	7-10 years	250
	14-18 years	550	400	11-14 years	340
				15-17 years	400
Adults	≥19 years	550	425	≥18 years	400
Pregnancy	-	-	450	-	480
Lactation	-	-	550	-	520
LOAEL	-	7500	7500	7500	7500
UL	-	3500	3500	3500	3500

AI: adequate intake; EFSA: European Food Safety Authority; IOM: Institute of Medicine; LOAEL: Lowest Observed Adverse Effect Level; UL: Tolerable Upper Intake Level

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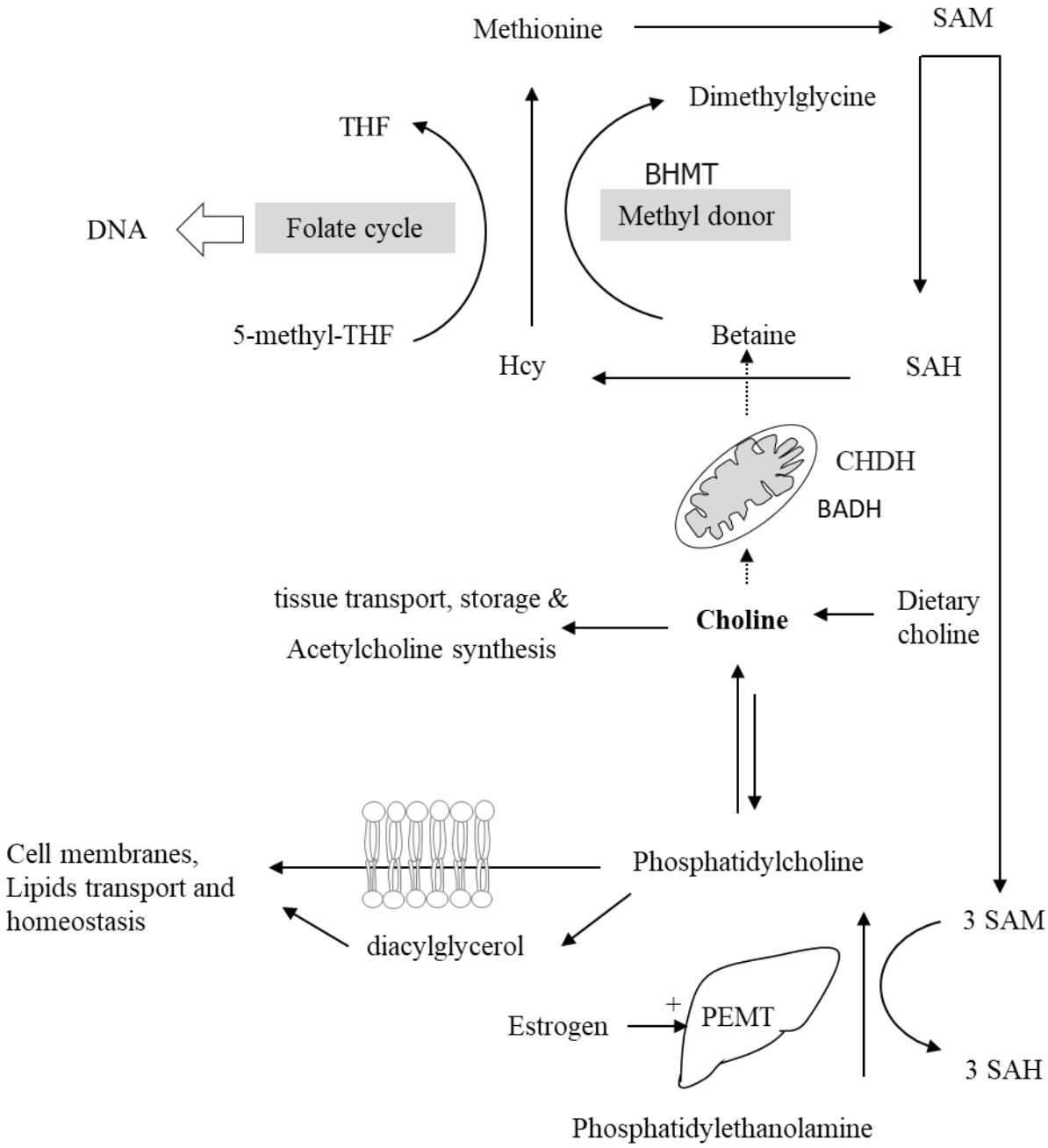

Figure 1. Choline metabolism. BADH, betaine aldehyde dehydrogenase, BHMT, betaine-homocysteine methyltransferase; CHDH, choline dehydrogenase; Hcy, homocysteine; PEMT, phosphatidylethanolamine N-methyltransferase; SAH, S-adenosylhomocysteine; SAM, S-adenosylmethionine; THF, tetrahydrofolate (Obeid R, unpublished figure).