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# Maternal choline supplementation during pregnancy to promote mental health in offspring

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## Abstract

**Aim:** There is increasing interest in the role of choline in brain development, including its possible role in promoting mental health and preventing mental illness. Choline is an essential micronutrient in fetal brain maturation. In more than 90% of pregnant women, choline intake has been found to be lower than the daily-recommended dose. The aim of this article is to review what is known about the effects of maternal choline supplementation on fetal brain development, early child development and mental health.

**Methods:** A narrative review of the literature.

**Results:** A limited number of studies suggest that maternal choline supplementation during pregnancy may enhance fetal brain development and improve early signs and symptoms that may predispose to mental illness.

**Conclusion:** The general low maternal choline intake during pregnancy, expected health benefits and low risks, make a plea for maternal choline supplementation to promote mental health. Choline supplementation may be especially important for pregnant women with a (family) history of severe mental illness and/or alcohol dependence.

## KEYWORDS

choline, maternal supplementation, mental health, phosphatidylcholine, prevention

## 1 | INTRODUCTION

The pathways to develop mental illness are multifactorial, including genetic vulnerabilities and environmental influences (e.g., diet, infections, pregnancy and birth complications, trauma and drugs abuse) (Stilo & Murray, 2019). The origin of vulnerability to mental illness can often be traced to the fetal period (Schlotz & Phillips, 2009).

Although primary prevention of severe mental illness is considered utopian, targeting potential prenatal causal factors may improve the mental health of offspring. Since fetal brain development is influenced by maternal nutrients, optimizing maternal prenatal micronutrition may be a possible target for primary prevention of mental health problems (Fusar-Poli et al., 2021; Sarris et al., 2015).

The Dutch Hunger Winter (1944–1945) is a well-known example of the effect of maternal malnutrition during pregnancy on the future

mental well-being of the child. For example, children in early gestation or conceived during the Hunger Winter were found to have approximately a 2-fold increased risk of developing schizophrenia, and prenatal exposure in the first-trimester to starvation during the Hunger Winter is associated with an increased risk to develop addiction later in life (Franzek et al., 2008; Susser & Lin, 1992).

To date, there is growing evidence that nutrition in the late foetal and early neonatal period has an important effect on neurodevelopment throughout the lifespan (Georgieff et al., 2018). Malnutrition may be an important first step in a cascade of, often subtle, changes in critical fetal brain development, childhood development, and consequently the development of severe mental health problems later in life (Georgieff et al., 2018).

Choline is closely related to the B-vitamin family (György & Goldblatt, 1940). It is present in foods such as meat, milk, and eggs

and available as a dietary supplement. There is also endogenous production of choline, however, this fails to meet bodily demands (Institute of Medicine, 1998). The Department of Health and Human services, Food and Drug Administration (FDA) recommended in 2016, largely in line with European recommendations, a daily intake of choline of 550 mg in adulthood and during pregnancy (Food and Drug Administration, HHS., 2016). However, in 2016, the FDA did not support the notion of a general inadequate choline intake in pregnant women nor linked this to health risks in children, leading to no statements for mandatory labeling (Food and Drug Administration, HHS., 2016). In this review evidence is presented, that may lead to reconsidering the idea of adequate choline intake during pregnancy.

Choline is an essential micronutrient that is, by analogy to folic acid and vitamin D, of utmost importance for normal fetal brain development (Freedman et al., 2021). This nutrient is a precursor of acetylcholine, a component of the two major phospholipids in membranes (phosphatidylcholine and sphingomyelin) in the central nervous system (Blusztajn et al., 1987). Choline is also a donor of methyl groups via its metabolite betaine that is required to synthesize the universal methyl donor S-adenosylmethionine (SAM) (Zeisel, 2017). Its metabolites enable choline to participate in pathways that affect the methylation of genes related to memory and cognitive functions at several developmental stages, and choline can alter neural activity by modifying gene methylation and expression (Bekdash, 2018). In addition, choline may protect against neural and metabolic insults, which is particularly evident when the fetus is exposed to alcohol (Derbyshire & Obeid, 2020).

Choline acts as an  $\alpha$ -7 nicotinic acetylcholine receptor ( $\alpha$ 7nAChR) agonist, is acetylated to acetylcholine and can directly replace acetylcholine to activate nicotinic receptors (Alkondon et al., 1997). Activation of the nicotinic receptors by choline facilitates the transition of excitatory and inhibitory neurotransmission to their maturational status (Liu et al., 2006; Lozada et al., 2012). These nicotinic receptors are located in brain regions related to memory and cognition, and particularly decreased numbers of  $\alpha$ -7nAChR and polymorphisms are associated with cognitive impairments in schizophrenia (Levin, 2012).

The significance of adequate choline intake during the critical period of pregnancy is increasingly acknowledged (Korsmo et al., 2019). Although more maternal choline may be synthesized during pregnancy to meet the increased fetal demand of the fetus, 90%–95% of pregnant women consume less than the daily-recommended amount of choline (550 mg/day) during pregnancy and lactation (Brunst et al., 2014). Inadequate intake of choline can potentially disrupt progenitor cell migration, proliferation, apoptosis and differentiation; thus, adversely affect brain development (Zeisel, 2011).

The maximum doses of choline were derived from the lowest observed side-effect (hypotension) in humans is 3.5 g/day for an adult (Zeisel & Corbin, 2012). Very high intakes of choline (more than 3500 mg a day in adults) are associated with a fishy body odour, vomiting, excessive sweating and salivation, and liver toxicity (Zeisel & Corbin, 2012). In view of these potential health risks, the upper limit of daily intake in humans aged 14–18 years is set at 3000 mg per day, and for 19 years or older 3500 mg per day, both for men and women.

During pregnancy and lactation, the same maximum daily doses are advised (Institute of Medicine, 1998).

This narrative review aims to summarize the current evidence on the potential role of maternal choline and maternal choline supplementation to improve fetal brain maturation, child development and specifically early symptoms of schizophrenia spectrum disorder, autism spectrum disorder, and fetal alcohol spectrum disorder (FASD).

## 2 | METHODS

A narrative review of the literature was conducted in PubMed, Embase, and PsycINFO, from inception to 22 January 2022. The search was based on search terms ‘Choline’ AND ‘phosphatidylcholine’ AND ‘pregnancy’ AND ‘schizophrenia spectrum disorder’ AND ‘autism spectrum disorder’ AND ‘alcohol use disorder’ AND ‘fetal alcohol spectrum disorder’. Preclinical and human studies were independently identified by the first and last author (SKS and HK) and discussed in case of inconsistencies. Cross-references were used to identify additional relevant articles. In this review, various relevant preclinical and clinical studies are highlighted.

## 3 | RESULTS

### 3.1 | Schizophrenia spectrum disorders

Neurocognitive distress, verbal and motor retardation in early childhood are well established in elderly adolescents and young adults who are believed to be at risk for a diagnosis on the psychosis spectrum (Barnes et al., 2022). Schizophrenia in humans is recognized on a median age of 25 years, there are no very specific biological markers, nor specific markers in early child behaviour, that can be used as specific predictors for the vulnerability to develop schizophrenia (Kim et al., 2020; Solmi et al., 2022).

However, abnormalities in the development of cerebral inhibition, expressed for example in impaired sensory gating functioning, are an important pathophysiological abnormality in many patients with schizophrenia (Ross et al., 2013a). Cerebral inhibition develops during the critical period of fetal and early postnatal life and can be studied in animals as well as human (Ross et al., 2010). Activation of fetal  $\alpha$ 7nAChR's by choline facilitates the development of cerebral inhibition (Ross et al., 2013b). Sensory gating disturbances are often described as an inability to filter redundant sensory stimuli, which typically manifests as an inability to ‘gate’ (filter) redundant or unnecessary stimuli into the brain (Freedman et al., 2003). Sensory gating impairments are defined as problems associated with cognitive difficulties in signal detection and attention, and can be evaluated by studying the effects of paired clicks on an EEG, 50 milliseconds after the click, the so-called P50 wave (Adler et al., 1982). Schizophrenia has been related to a reduced number of hippocampal  $\alpha$ -7nAChR's and polymorphisms in the alfa7-gene (Levin, 2012; Martin & Freedman, 2007).

### 3.1.1 | Preclinical studies

In 2008, Stevens et al. studied the effects of prenatal choline supplementation in mice (5 g/kg choline chloride) on sensory inhibition in their offspring using EEG (Stevens et al., 2008). The authors found that offspring from choline-supplemented mice showed substantially improved sensory/cerebral inhibition during gestation compared to control mice.

Nickerson et al. studied in 6 rats whether prenatal choline supplementation protects against cognitive impairments, motor deficits, and neuronal degeneration precipitated by the neurotoxin dizocilpine (MK-801) (Nickerson et al., 2017). MK-801 is a NMDA antagonist, which is often used in rodent models of schizophrenia. At low doses, it can cause cognitive impairments, and at higher doses, it can cause motor impairment, anhedonia, and neuronal degeneration. Nickerson et al. found that prenatal choline supplementation (in a range of 5 g/kg choline chloride) is neuroprotective against cognitive impairments; it consolidates memory and protects against a reduction of hippocampal cell proliferation after MK-801 induced cognitive impairments, and it reduces MK-801 induced abnormal motor response (e.g., locomotion and ataxia) (Nickerson et al., 2017).

### 3.1.2 | Clinical studies

In 2012, Wu et al. evaluated possible associations between maternal plasma-free choline and its metabolites during pregnancy and the neurodevelopment of the child at 1–18 months of age in a prospective study (Wu et al., 2012). Maternal blood was collected at 16 and 36 weeks of pregnancy, and the child's neurological development was assessed at 18 months of age for 154 mother–child pairs. The median maternal plasma free choline at 16 and 36 weeks gestation were (interquartile range) 6.70 (5.78–8.03) and 9.40 (8.10–11.3)  $\mu\text{mol/L}$ , respectively. Estimated choline intakes were (mean  $\pm$  SD)  $383 \pm 98.6$  mg/day, so lower than the recommended 450 mg/day. Their study showed that higher choline levels in the first half of pregnancy are associated with better cognitive development in infants, as measured by the Bayley Scales of Infant Development-III.

Boeke et al. estimated the association between choline level during the first and second trimester in pregnant women and the visual memory of the offspring in 895 mother–child pairs (Boeke et al., 2013). Median choline intakes were as follows: quartile 1: 260 mg/day, quartile 2: 30 mg/day, quartile 3: 344 mg/day, quartile 4: 392 mg/day. Visual memory was measured by the Wide Range Assessment of Memory and Learning (second edition, WRAML2). Their study showed that higher maternal intake of choline during pregnancy was associated with modestly better visual memory of the child at 7 years of age.

Hunter et al. evaluated the possible role of choline levels in Afro-American women during pregnancy in the development of their offspring (Hunter, Hoffman, McCarthy, et al., 2021). Afro-American pregnant women had lower 16-weeks' pregnancy plasma choline levels (mean 5.48  $\mu\text{M}$ , SD 1.40) compared to Caucasian/other ethnic groups

( $N = 183$ , 25 Afro-American women) with a mean plasma choline of 6.58, SD 1.90. Lower choline was associated with a lower gestational age of offspring at birth and with reduced auditory P50 inhibition. Hunter et al. concluded that inhibitory and behavioural problems are associated with lower prenatal choline in offspring of Afro-American women, suggesting a possible predisposition to later mental disorders such as schizophrenia that could be improved by prenatal choline or phosphatidylcholine supplementation (Hunter, Hoffman, McCarthy, et al., 2021).

The research group of Hunter et al. also evaluated the effects of higher maternal plasma choline concentrations on attention and social problems in children (Hunter, Hoffman, D'Alessandro, et al., 2021). Of 183 healthy mothers who participated in their study, 162 complied with pregnancy assessments (at 16 weeks) and brought their newborns for study at 1 month of age. Of these women, 83 continued with the assessments until the fourth year. The attention problems and withdrawn syndrome scales on the Child Behaviour Checklist 1½–5 were the primary outcome measures. Higher maternal plasma choline ( $\geq 7.7$   $\mu\text{M}$ ) was associated with fewer attention problems in children, and in male children with less social withdrawal (Hunter, Hoffman, D'Alessandro, et al., 2021).

In a double-blind, placebo-controlled study by Ross et al. choline supplementation, with phosphatidylcholine (PC) 3600 mg per day, was given to 100 healthy pregnant women starting in the second trimester (week 17) and continued until delivery (Ross et al., 2013a). The main finding was that at 33 days after birth, 76% of the infants whose mothers had received choline showed cerebral inhibition as measured by EEG parameters (P50), while 43% of the placebo-treated group a significant difference. In a follow-up study, 40 months after birth, parental assessments, of children in the choline group ( $N = 23$ ) indicated fewer attention problems and less social withdrawal compared to the placebo group ( $N = 26$ ) (Ross et al., 2016).

Caudill et al. conducted a randomized, double-blind, control study (Caudill et al., 2018). Pregnant women entering their third trimester were randomized to consume 480 mg choline/day ( $n = 13$ ) or 930 mg choline/day ( $n = 13$ ) as a maternal supplement until delivery. The results indicated that maternal consumption of approximately twice the recommended amount of choline during the last trimester improves infant information processing speed.

In 2012, Cheatham et al. investigated in a double-blind randomized controlled trial whether phosphatidylcholine (PC) supplementation in pregnant women improves the cognitive abilities of their offspring (Cheatham et al., 2012). One hundred and forty pregnant women were randomly assigned to a group receiving 750 mg per day PC or a placebo from 18 weeks of pregnancy to 90 days postpartum. They did not find that choline improved the cognitive functioning of the infants' ( $n = 99$ ) at 10 and 12 months of age. The PC supplements were well tolerated.

### 3.1.3 | Critical appraisal

To study the effects of maternal choline on the development of severe mental disorders such as schizophrenia spectrum disorders is a

major challenge. The major problem is the large time lag between supplementation of maternal choline and the average age at which schizophrenia spectrum disorder is diagnosed, about 20 years later. Moreover, the multifactorial origin of schizophrenia spectrum disorders complicates the identification of any definite causal factors. The limited number of animal and clinical studies consistently show that higher maternal choline levels and human maternal choline supplementation are associated with improved early neurocognition and social development in children, including some measures (e.g., P50) that are also found in (high-risk) populations of patients with schizophrenia spectrum disorders (Caudill et al., 2018). Maternal choline and phosphatidylcholine supplementation are well tolerated. The number of studies and populations studied are small, especially only a very limited number of children could be studied for a longer period of time (years), while selection bias in the follow-up period cannot be ruled out (Boeke et al., 2013; Caudill et al., 2018; Hunter, Hoffman, D'Alessandro, et al., 2021; Hunter, Hoffman, McCarthy, et al., 2021; Ross et al., 2016). Also, the markers studied, including the P50, are although associated with the risk to develop schizophrenia, not specific to predict increased rates of change in the development of psychotic disorders such as schizophrenia. In conclusion, fundamental and animal studies suggest that human studies on maternal choline supplementation to prevent severe mental illnesses are warranted. Although the outcomes of clinical studies are in line with fundamental and animal studies, from the clinical studies it is not possible to conclude that maternal choline supplementation may contribute in the prevention of schizophrenia.

## 3.2 | Autism spectrum disorder

A significant group of children who show signs of poor fetal development at birth are later diagnosed with autism spectrum disorder (ASD), a neurodevelopment disorder with multiple genetic and environmental risk factors (Raikkonen et al., 2012; Sucksdorff et al., 2015). Nutritional interventions are gaining attention as a complementary management strategy for ASD (Gogou & Kolios, 2020).

### 3.2.1 | Preclinical studies

In animal models, maternal iron deficiency increases the risk of ASD and schizophrenia-like behaviour in offspring (Tran et al., 2016). Tran et al. investigated the effects of maternal choline supplementation in male rat pups on (the transcriptome of) the hippocampus of the offspring to identify pathways through which choline reduces the development of long-term cognitive impairment (Tran et al., 2016). Their study showed a significant interaction between iron status and prenatal choline supplementation in effects on gene expression. Tran and colleagues concluded that choline supplementation in rat models reduces the adverse effect of iron deficiency, including those on gene networks thought to be related to both ASD and schizophrenia.

Langley et al. examined the effects of perinatal choline supplementation on social behaviour, anxiety, and repetitive behaviours in a mouse model of ASD (Langley et al., 2015). The offspring of pregnant mice were evaluated at two postnatal periods. Choline supplementation significantly reduced digging behaviour, did not affect locomotion, and improved social interaction disorders at 33–36 and 89–91 days, respectively. The authors concluded that choline intake during pregnancy and lactation may prevent or reduce deficits in social behaviour and anxiety, and reduce the display of some repetitive behaviours in an ASD mouse model.

The methylenetetrahydrofolate-reductase (MTHFR) gene, which codes for a key enzyme in one-carbon (C1) metabolism, is associated with an increased risk for ASD. MTHFR activity affects the C1 metabolic pathway, a biochemical pathway, which supplies methyl group donors, and is influenced by micronutrients such as folate, choline, and betaine (Pu et al., 2013). Orenbuch et al. studied the effects of prenatal or early postnatal diets enriched with one-carbon (C1) metabolism nutrients on ASD-like behaviour in MTHFR-deficient mice (Orenbuch et al., 2019). Prenatal or early postnatal supplementation of methyl-donors (folate acid, betaine, and choline) reduced the risk that these mice exhibit ASD-like behaviour. These results indicate that MTHFR deficiency may increase the risk of ASD-like behaviour in mice and that prenatal dietary intervention with C1 nutrients (e.g., choline) targeting MTHFR genotypes may reduce the risk of ASD-like behaviour (Orenbuch et al., 2019).

### 3.2.2 | Clinical studies

Inadequate intake of choline and betaine may adversely affect folate metabolism. Dysregulation of folate-dependent one-carbon metabolism is associated with ASD in children (Hamlin et al., 2013). Hamlin et al. evaluated the adequacy of dietary intake of choline and its derivative betaine in children with ASD (Hamlin et al., 2013). In 288 children with ASD, three-day food records were analysed. Choline and betaine plasma concentrations were measured exclusively in a subgroup of 35 children with ASD and 32-age matched control children. The results show that the subgroup of children classified with ASD has inadequate (low) plasma levels of choline and betaine.

Bahnfleth et al. conducted a randomized controlled trial in pregnant women who consumed 480 mg or 930 choline per day during the third trimester (Bahnfleth et al., 2022). In the offspring at age 7 years ( $n = 20$ ), sustained attention was evaluated using a signal detection task. Children in the 930 mg/day group showed superior levels of performance (vs. 480 mg/day group) on the primary endpoint the Sustained Attention Task and to maintain correct signal detecting, suggesting improved sustained attention.

### 3.2.3 | Critical appraisal

In line with studies designed to potentially prevent the development of schizophrenia spectrum disorders, one study found that lower

choline levels in children may be associated with autism. One clinical study found that choline supplementation, especially higher dosages, during pregnancy may improve neurocognition in offspring (Bahnfleth et al., 2022). However, we do not know if this improved neurocognition may predict a reduced risk to develop autism spectrum disorders. Although fundamental research suggests to study the role of maternal choline on the risk to develop autism, there is paucity of clinical studies to reach to a conclusion.

### 3.3 | Alcohol use disorder and the risk of developing fetal alcohol spectrum disorder

Prenatal alcohol exposure can disrupt brain development, leading to a variety of behavioural alterations including learning deficits, hyperactivity, and motor dysfunction also known as fetal alcohol spectrum disorder (FASD) (Hoyme et al., 2016; Thomas et al., 2000).

#### 3.3.1 | Preclinical studies

Animal studies show that perinatal choline supplementation can improve alcohol-induced learning disabilities and hyperactivity in rats exposed to alcohol during development (Thomas et al., 2000). Thomas et al. reported that the beneficial effects of perinatal choline supplementation in alcohol-treated rats are task-specific and suggest that choline is more effective in reducing cognitive deficits than motor deficits associated with alcohol exposure (Thomas et al., 2004).

In addition, in a randomized placebo-controlled study by Thomas et al., prenatal administration of choline to pregnant rats significantly reduced the severity of alcohol-related adverse effects on birth and brain weight, incisor emergence, and behavioural measures (i.e., motor coordination and balance, open field activity, spatial learning and working memory), particularly on changes in tasks that require behavioural flexibility (Thomas et al., 2009).

Idrus et al. conducted a randomized placebo-control trial to examine the influence of dietary choline deficiency in pregnant rats on the severity of various fetal alcohol effects (Idrus et al., 2017). Mice exposed to alcohol and a 40% of daily-recommended amount of containing choline diet showed exhibited eye opening, significantly less successes in hindlimb coordination, and were significantly overactive compared to the other groups whose intake was 70% and 100% of the recommended amount of choline. These data support the hypothesis that prenatal normalization of choline intake may prevent or reduce the effects of maternal alcohol consumption during pregnant in offspring (Idrus et al., 2017).

Bottom et al. found in their randomized control trial that choline supplementation in pregnant mice prevented severe developmental abnormalities in offspring resulting from prenatal alcohol exposure, including decreased body weight, brain weight, and cortical length (Bottom et al., 2020). They also found that choline could improve alcohol-induced abnormalities in intra-neocortical circuitry and gene expression by DNA hypomethylation in the developing neocortex.

#### 3.3.2 | Clinical studies

In 2015, the potential of micronutrients supplementation to ameliorate the effect of prenatal alcohol exposure was investigated in a prospective clinical study in pregnant women in Ukraine (Kable et al., 2015). A moderate/heavy alcohol-consuming pregnant group was compared to a low/unexposed pregnant group. The 374 women were assigned to three groups; (1) no supplements, (2) multivitamin-mineral supplements, and (3) multivitamin-mineral plus choline supplements (750 mg choline per day). Cardiac orienting responses during a habituation/dishabituation learning paradigm were obtained in offspring 6–12 months of age to assess neurophysiological encoding and memory of environmental events. Maternal nutritional status was also evaluated. The authors concluded that choline supplementation when administered along with routinely recommended prenatal multivitamin-mineral supplements (group 3), may be beneficial to offspring in terms of fundamental learning mechanisms related to encoding and remembering environmental events. These effects were found both in alcohol-exposed pregnancies as well as in pregnancies without or with low alcohol levels (Kable et al., 2015).

Coles et al. evaluated the impact of several nutrients, including choline, on reducing adverse effects of alcohol exposure, examining timing and dose of alcohol and effects of dietary supplementation (Coles et al., 2015). Alcohol consuming and nondrinking pregnant women were randomized to one of three groups; (1) no supplements, (2) multivitamin-mineral supplements, and (3) multivitamin-mineral plus choline supplements (750 mg daily). Their children ( $n = 367$ ) were tested at 6 months using the Bayles scales of infant development, which proceeds standard scores for behaviour, mental development index (MDI), and psychomotor development index (PDI). Mental development was significantly affected by peri-conceptual alcohol dosages. More alcohol was related to lower scores, and men were more adversely affected by it than women. In general, those who received micronutrient supplementation scored better, however PDI scores did not differ between groups, but were influenced by peri-conceptual alcohol dose. After 6 months, the protective effects of choline appeared to be specific to the improvement in problem-solving and prelinguistic abilities (Coles et al., 2015).

In 2018, Jacobson et al. conducted a randomized, double-blind, placebo-controlled clinical trial to examine the feasibility and acceptability of a choline supplementation intervention during pregnancy (Jacobson, Carter, Moltano, Meintjes, et al., 2018). Seventy heavy drinkers, recruited in mid-pregnancy, were randomly assigned to receive a daily oral dose of 2 g of choline or a placebo from the time of enrollment until delivery. Adherence and side effects were assessed in monthly (unused) choline counts and interviews. Blood samples obtained at enrollment and at 4 and 12 weeks after randomization were examined for plasma choline concentration. Results showed that adherence was good-to-excellent (median of doses taken 74%). Compared with a placebo arm, plasma choline levels at 4 weeks (continued to week 12) were significantly higher in the choline supplementation group. Adherence was not related to social economic status factors, intellectual function, or alcohol consumption. The only reported side

effect was a small increase in nausea/dyspepsia (Jacobson, Carter, Molteno, Meintjes, et al., 2018).

Subsequently, in a second publication of the same study, was reported on the growth and cognitive function in the offspring, following maternal choline supplementation (Jacobson, Carter, Molteno, Stanton, et al., 2018). Each participant was instructed to take 2 daily doses (1 in the morning, 1 in the evening) from the time of enrollment until delivery. Each dose of choline supplement consisted of 1.25 g choline bitartrate, which contained 1 g of bioavailable choline cation. Data from 69 heavy drinking pregnant women were analysed. The primary outcome was eyeblink conditioning (EBC), a form of classical conditioning to study neural structures and mechanisms underlying memory and learning. Somatic growth was measured at birth, 6.5 and 12 months, and recognition memory and processing speed at 6.5 and 12 months using the Fagan Test of Infant intelligence. Within the choline arm, maternal adherence to the protocol strongly predicted EBC performance. Infants of mothers who have been choline-treated ( $n = 31$ ) were more likely to meet the criterion for conditioning on EBC compared to the placebo group. Although newborns in both study groups were small at birth, choline-treated infants exhibited significantly catch-up growth in both weight and head circumference at 6.5 and 12 months. At 12 months, the infants in the choline arm had higher scores for novelty preferences, suggesting better visual recognition memory (Jacobson, Carter, Molteno, Stanton, et al., 2018).

### 3.3.3 | Critical appraisal

The risk of developing alcohol dependence in women who continue to abuse alcohol during pregnancy is multifactorial. Poor maternal nutritional status is often associated with alcohol dependence. The limited number of animal studies identified, consistently suggest that choline supplementation in pregnant animals may reduce the harmful effects of alcohol on brain-development in offspring. The findings in the limited number of human studies are consistent with the animal studies. In contrast, the limited number of human studies do not allow firm conclusions, as choline supplementation was sometimes combined with supplementation of other micronutrients, and the outcome measures were diverse and the follow-up period of the studies was short-term (Coles et al., 2015; Jacobson, Carter, Molteno, Stanton, et al., 2018; Kable et al., 2015).

## 4 | DISCUSSION

The articles reviewed suggest that maternal choline supplementation during pregnancy may enhance fetal brain development (i.e., increased cerebral inhibition), has neuroprotective effects (e.g., on prenatal stress or alcohol intake), improves cognitive performance (i.e., memory, information processing speed and attention), and decreases psychosocial withdrawal behaviour of children (Nickerson et al., 2017; Ross et al., 2016; Wu et al., 2012). In women with alcohol use disorder, maternal choline supplementation may reduce early

physical signs and symptoms indicative of fetal alcohol spectrum disorder in offspring (Coles et al., 2015; Jacobson, Carter, Molteno, Meintjes, et al., 2018). Maternal choline supplementation was well tolerated, and no meaningful adverse effects were described in animal or human studies. Our findings are in line with a systematic review and meta-analyses of Obeid et al. on the associations between prenatal and early postnatal choline intake, brain development, and neurocognitive function of children (Obeid et al., 2022). Obeid et al. concluded that interventional designs showed that higher maternal choline intakes during the second half of pregnancy (550 mg up to 1 g/d on top of the diet) were safe and likely to demonstrate favourable effects on several domains of child neurocognition, such as memory, attention, and visuospatial learning versus the comparators (Obeid et al., 2022). Our findings are also in accordance with a study of Derbyshire et al., suggesting that maternal or child choline supplementation during the first 3 years support normal brain development, improves neural and cognitive functioning and protects against neural and metabolic insults (Derbyshire & Obeid, 2020).

However, to confirm the hypothesis that prenatal choline supplementation may ultimately help to reduce the risk of developing mental disorders is challenging. Most mental disorders are multi-causal and multifactorial in nature. Genetic and environmental factors affecting fetal and early child development all contribute to mental health and influence the likelihood of developing mental illness. In addition, the first episodes of schizophrenia, for example, usually do not fully manifest until a median age of 25 years, and consequently clinical studies must have a very long-term follow-up period (Solmi et al., 2022). Cognitive and behaviour performance, as well P50 in EEG, tend to improve in children whose mothers received choline supplementation (Ross et al., 2016). Unfortunately, although these markers of brain maturation and inhibition are associated with severe psychiatric problems such as schizophrenia or autism, they cannot reliably identify individuals at risk for mental illness.

The limited number of clinical studies that were found all have methodological limitations, for example, small sample sizes, limited follow-up times or large attrition numbers at follow-up. All studies examined not directly, but indirectly a relation between maternal choline supplementation and signs (e.g., behaviour, cognitive and social functioning) that may predict the development of schizophrenia, autism or FASD. In addition, some pragmatic questions remain unanswered; in what trimester should choline be administered (timing), until when (duration), and in what doses (dose)? It is reasonable to assume that maternal choline supplementation should be associated with the development of brain structures or circuits dependent on that nutrient.

The current literature on prenatal choline supplementation seems promising, and may potentially help to improve early childhood development in a safe, relatively inexpensive and feasible way. Nevertheless, the number of studies is considered too limited to recommend maternal choline supplementation in general guidelines. RCTs with a large number of participants are needed. In comparison, the recommendation of folic acid and vitamin D supplementation in guidelines is based on a limited number of RCTs with several thousand women

(Kiely et al., 2020; Prevention of neural tube defects, 1991; Zeisel & Dudás, 1992).

In future research, more clinical, prospective, and methodologically high-quality studies with a large sample size and a long-term follow-up period are wanted to further investigate the effects of prenatal choline supplementation, particularly in populations at increased risk of developing severe mental illness, such as those with a (family) history of mental illness or alcohol dependence.

## 5 | CONCLUSION

In the majority of women, choline intake during pregnancy is below the recommended amount, with potential adverse effects on fetal brain development and early child development, including an increased risk of developing severe mental illness. The general low maternal prenatal choline levels, expected health gains, and low risks, argue that even in the absence of definitive clinical evidence, maternal choline supplementation may be considered, especially in pregnant women with a (family) history of severe mental illness and women consuming alcohol during pregnancy.

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### CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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