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Prenatal Primary Prevention of Mental Illness by Micronutrient Supplements in Pregnancy

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Genes, infection, malnutrition, and other factors affecting fetal brain development are a major component of risk for a child's emotional development and later mental illnesses, including schizophrenia, bipolar disorder, and autism. Prenatal interventions to ameliorate that risk have yet to be established for clinical use. A systematic review of prenatal nutrients and childhood emotional development and later mental illness was performed. Randomized trials of folic acid, phosphatidylcholine, and omega-3 fatty acid supplements assess effects of doses beyond those adequate to remedy deficiencies to promote normal fetal development despite genetic and environmental risks. Folic acid to prevent neural tube defects is an example. Vitamins A and D are currently recommended at maximum levels, but women's incomplete compliance permits observational studies of their effects. Folic acid and phosphatidylcholine supplements have shown evidence for improving childhood emotional development associated with later mental illnesses. Vitamins A and D decreased the risk for schizophrenia and autism in retrospective observations. Omega-3 fatty acid supplementation during early pregnancy increased the risk for schizophrenia and increased symptoms of attention deficit hyperactivity disorder, but in later pregnancy it decreased childhood wheezing and premature birth. Studies are complicated by the length of time between birth and the emergence of mental illnesses like schizophrenia, compared with anomalies like facial clefts identified at birth. As part of comprehensive maternal and fetal care, prenatal nutrient interventions should be further considered as uniquely effective first steps in decreasing risk for future psychiatric and other illnesses in newborn children.

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AJP AT 175
Remembering Our Past As We Envision Our Future

July 1959: Longitudinal Observations of Biological Deviations in a Schizophrenic Infant

Barbara Fish described the course of an infant born with fluctuating motor problems who developed schizophrenia.

(Am J Psychiatry 1959; 116:25–31)

Fetal brain development, the combined effect of the genotype and the environment in the womb, influenced by the mother's nutrition, infection, psychiatric status, and substance abuse, is the earliest developmental step in risk for mental illness. The odds ratio for the offspring developing schizophrenia after severe maternal malnutrition is 2.7 (1). The odds ratio for the offspring developing schizophrenia after maternal infection ranges from 2.1 for common respiratory infections to 5.0 for genital-reproductive infections (2). There is a substantial genetic component as well. Children with family histories of schizophrenia have increased risk for later mental illnesses (odds ratio=4.2) (3). Many genes associated with mental illnesses are expressed in the fetus before birth, some at considerably higher levels than in adult life, consistent with their role in fetal brain development (4, 5). Maternal depression, anxiety and stress, smoking, and alcohol abuse are other risk factors for subsequent mental illness in the child (6–9). No single determinant inevitably causes mental illness, and frequently several factors each with small effect size combine, such as infection and genetic risk (10). The resulting abnormalities in fetal brain development have been demonstrated as the first sign of risk for future illness by retrospective studies of abnormalities in newborns who later develop mental illness in adulthood (11).

The unique period of fetal brain development has not received much attention in clinical practice as a time for specific interventions, beyond good prenatal care, to ameliorate future risk for mental illness. Maternal psychiatric treatments are directed to the pregnant woman's psychopathology, and the possibility that they might also affect the fetus positively is less frequently considered, despite evidence that maternal depression increases the risk for the child's development of mental illness. The initial concern has been that antidepressants' toxic effects might include increased risk for mental illness. For example, maternal antidepressants were identified as a risk factor for autism, a finding later challenged by studies controlling for the maternal psychopathology that prompted antidepressant prescription (12, 13). Good nutrition is an obvious recommendation, but the possibility that specific micronutrients might be increased to prevent future mental illness is just

emerging. This approach has had dramatic effects with folic acid supplementation on a wide range of fetal developmental disorders, including spina bifida, microcephaly, and cleft palate (14, 15).

THE DEVELOPMENTAL CONTEXT OF PRENATAL PREVENTION

Prospective studies of the development of mental disorders have largely focused on newborns who are deemed to be at high risk either because one of their parents has a mental disorder or because the infant is showing early signs of abnormal development, first characterized in a 1959 *American Journal of Psychiatry* article by Barbara Fish as fluctuating delays in motor development (16, 17). Fish reported that one such child whom she identified in infancy as high risk later developed schizophrenia. Elaine Walker was among the first to observe early developmental signs in retrospective studies of home movies of infants who developed schizophrenia as adults. She proposed that defects in early motor movement, such as asymmetrical limb movements during crawling, and in the early expression of social features like smiling, were manifestations of problems in fetal brain development that later led to mental illness (11, 18).

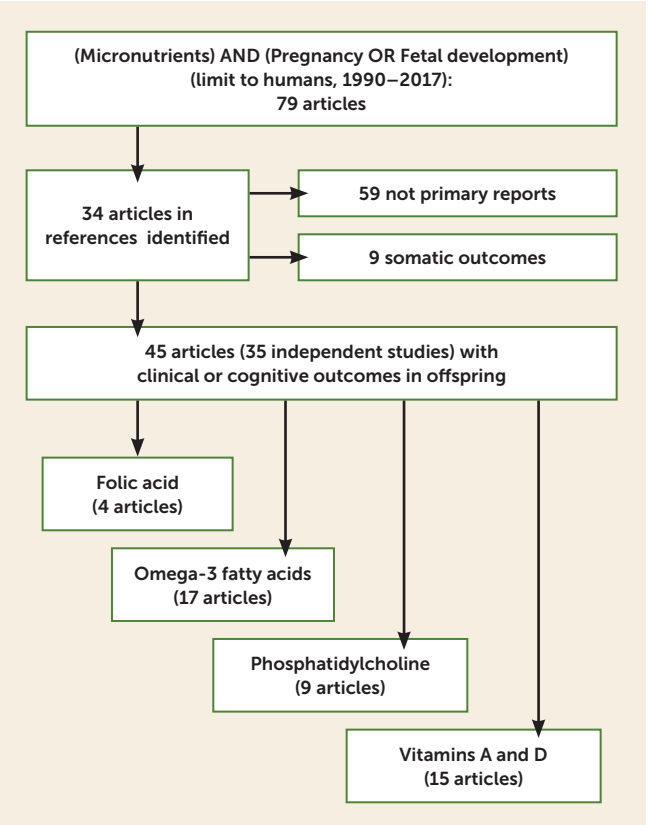
Regardless of risk, no baby is born with schizophrenia or bipolar disorder or autism spectrum disorder (ASD). The developmental expression of risks whose neurobiology occurred earlier (e.g., in fetal brain development) interacts with additional risk factors throughout childhood and adolescence, both genetic and environmental, that contribute to the final expression of illness in adulthood (4, 19). Poor attachment to the mother is a cause as well as an early sign of later psychopathology (20). Other signs of future psychopathology emerge during subsequent development. For schizophrenia, early attentional and social deficits have been observed retrospectively in children as young as 3–4 years of age (21, 22). These early childhood symptoms, while not inevitably predictive of later illness, nonetheless indicate the developmental track of an individual toward possible illness.

POSSIBLE STRATEGIES FOR PRENATAL PREVENTION AND THEIR INVESTIGATION

The strategies that led to the adoption of folic acid supplementation as a universal primary prevention for midline developmental defects are instructive. Observational studies of children born with these defects identified possible folic acid deficiency in mothers. Small randomized controlled trials provided proof of efficacy. The British Medical Research Council then funded large multisite trials (14, 16). Results showed that the folic acid supplement plus multivitamins robustly reduced the incidence of cleft palate, spina bifida, and some forms of microcephaly, with little difference for whether the woman's diet provided adequate amounts. Study of micronutrient interventions for mental illness follows similar lines. Most reports are observational, based on maternal choice of which nutrients to take and when to take them and on prenatal serum levels. The only prenatal nutrient other than folic acid to reach the stage of large multisite randomized trials with longer-term follow-up is omega-3 fatty acids, with trials for prevention of childhood wheezing and the development of cognition (23, 24). Prospective trials assess the development of emotional and behavioral problems and cognitive deficits associated with future mental illness as their outcome. Effects on incidence of mental illness itself, notably schizophrenia, have only been ascertained retrospectively with banked sera from several decades earlier because of the long interval between birth and appearance of illness in early adulthood.

The experience with folic acid is that an effective intervention ameliorates several different developmental abnormalities. The overlapping genetic and environmental risk factors for major mental illnesses suggest that a similar broad range of outcomes may occur with the nutrients discussed here, including illnesses with common features such as the affective and schizophrenia spectrum psychoses and autism, as well as behavioral and cognitive abnormalities that do not reach criterion for an illness.

FIGURE 1. Selection of Articles for a Review of Prenatal Micronutrient Supplementation for the Prevention of Mental Illness



METHOD

A MEDLINE search for the keyword "micronutrients" combined with "pregnancy" or "fetal development" from 1990 through 2017 was conducted for human studies. Seventy-nine articles

TABLE 1. Major Studies of Prenatal Dietary Supplements to Enhance Fetal Development[a]

Type of Trial	Subjects	Region or Country	Dose or Level and First Timing During Gestation	Effect	Limitations
Folic acid					
Prospective, randomized (25)	311 women	Europe	400 μg of 5-methyltetrahydrofolate compared with placebo at 20 weeks	Decreased reaction time with distractor at 8.5 years (d′=0.32)	130 of 311 children studied; no clinical ratings
Prospective, observational (26, 27)	3,210 women	Netherlands	≥400 μg of folic acid within first 10 weeks' gestation compared with no or later use	CBCL problems at 18 and 36 months; top 17th percentile (odds ratio=1.45, 95% CI=1.14–1.84)	Groups differ in sociodemographics; folic acid neonates 200 g heavier
Prospective, observational (14)	573 infants with facial clefts, 763 controls	Norway	≥400 μg of folic acid within 9 weeks	Decreased facial clefts (odds ratio=0.61, 95% CI=0.39–0.96)	Not effective in cleft palate without cleft lip
Prospective, randomized (15)	1,817 women, prior neural tube defect	U.K., Europe, Israel, Australia, Canada, U.S.S.R.	4 mg of folic acid at preconception until 12 weeks	Decreased neural tube defects (odds ratio=0.28, 95% CI=0.12–0.71)	No follow-up of other developmental traits
Retrospective, observational (28)	104,428 women	United States	400 μg of folic acid at first trimester	Increased asthma at 4.5–6 years (odds ratio=1.2, 95% CI=1.1–1.3)	Data only from Medicaid claims
Phosphatidylcholine					
Prospective, randomized (29, 30)	100 women	United States	6,300 mg of phosphatidylcholine at 15 weeks	Increased 1-month EEG sensory gating; decreased 3.5-year CBCL attention (d′=0.59) and social (d′=0.79) problems	50% attrition; parental CBCL reports only
Prospective, observational (31)	154 women	Canada	Plasma choline at 16 weeks' gestation	Increased Bayley cognition score at 18 months (β=6.054, SE=2.283)	Healthy women in uncontrolled study
Prospective, randomized (32)	24 women	Canada	550 mg compared with 100 mg of choline supplements in third trimester	Lower placental sFLT1, angiogenic factor in preeclampsia (d′=0.2)	Small study with no clinical outcome
Prospective, observational (33)	817 adults 33–55 years old	United States	Plasma trimethyl amine oxide, a choline bacterial metabolite	No increase in cardiac disease (odds ratio=1.03, 95% CI=0.71–1.52)	Patients were not supplemented
Omega-3 fatty acids					
Retrospective, observational (34)	57 adult cases and 95 controls	United States	DHA acid >1.45% of fatty acids in second or third trimester	Increased schizophrenia spectrum (odds ratio=2.38, 95% CI=1.19–4.76)	Mercury from high fish diet not tested
Prospective, randomized (24)	543 women	Australia	800 mg of fish oil at 20 weeks	Increased 7-year Conners ADHD score (d′=0.1)	Small effect in large sample
Prospective, randomized (23)	736 women and children	Denmark	2.4 g of fish oil at 24–26 weeks	Decreased wheezing at 3–5 years (odds ratio=0.69, 95% CI=0.49–0.97)	Trend suggests vitamin D equally effective
Prospective, randomized (35)	2,399 women	Australia	800 mg of fish oil at 20 weeks	Fewer gestations at <34 weeks (odds ratio=0.49, 95% CI=0.25–0.94)	More DHA induction (odds ratio=1.28, 95% CI=1.06–1.54)

continued

TABLE 1, *continued*

Type of Trial	Subjects	Region or Country	Dose or Level and First Timing During Gestation	Effect	Limitations
Vitamins A and D					
Retrospective, observational (36)	430 adult cases, 430 controls	Denmark	25(OH)D_3 <19.7 nM compared with >51 nM, low versus high quintiles	Increased schizophrenia (odds ratio=2.1, 95% CI=1.3–3.5)	Confounded with summer birth in high quintile
Retrospective, observational (37)	51 male adult cases, 4,616 in cohort	Finland	2,000 IU of vitamin D in first year of life	Decreased schizophrenia (odds ratio=0.23, 95% CI=0.06–0.95)	Effects only in males
Prospective, observational (38)	68 cases in birth cohort of 4,334	Netherlands	<25 nmol/L of vitamin D at 20 weeks	Increased autism spectrum at 6–9 years (odds ratio=2.42, 95% CI=1.09–5.07)	Small number of cases
Retrospective, observational (39)	186 cases in cohort of 1,194	New Zealand	Vitamin D intake >724 IU (highest quartile)	Decreased recurrent wheeze at 3 years (odds ratio=0.39, 95% CI=0.25–0.62)	Infection-related wheeze, not new incident asthma
Retrospective, observational (40)	55 cases, 106 controls	United States	<30 μg/dL of vitamin A at second trimester	Increased schizophrenia (odds ratio=3.05, 95% CI=1.06–8.79)	Higher levels in more educated women

[a] ADHD=attention deficit hyperactivity disorder; CBCL=Child Behavior Checklist; DHA=docosahexaenoic acid.

were identified, and their references were used to identify 34 additional articles. Thirty-five human studies and trials of individual nutrients were identified with reports of their results on subsequent child behavior, emotion, or cognition in one or more articles. We reviewed the resultant total of 45 articles, and an additional nine were selected as representative of somatic outcomes. Four supplements were identified: folic acid, fish oil omega-3 fatty acids, phosphatidylcholine, and vitamins D and A (Figure 1, Table 1). Preferred studies for discussion were retrospective epidemiological studies of disease prevalence, randomized prospective clinical trials, and large prospective observational studies. The metric used in each study, odds ratio, effect size (d′), or regression coefficient (β), is cited if it was statistically significant. Although animal model studies were not the focus of this review, a summary of translational and mechanistic studies is included to describe possible mechanisms responsible for the nutrients' effects (Table 2; see also the data supplement that accompanies the online edition of this review).

RESULTS

Folic Acid and the Baby's Risk for Mental Illness

Prospective assessment of the behavioral development of infants whose mothers took folic acid supplements in the Rotterdam Generation R study relied on the incomplete compliance of women with folic acid supplementation for cleft palate and spina bifida (23). Mothers were grouped into those who began folic acid within 10 weeks of conception, those who began after 10 weeks, and those who did not use supplements at all. The Child Behavior Checklist (CBCL) for ages 1.5–5 years, a standard instrument for parental report of infant behavior, was administered at 18 months and 3 years after birth (23, 24). The CBCL contains 99 items from which various axes are derived. This study reported two axes: emotional problems (emotionally reactive, anxious or depressed, somatic complaints, and social withdrawal) and behavioral problems (attention and aggression). The highest 17% of scores were considered to be significantly elevated because previous studies showed that children referred to treatment by parents and teachers are more likely to have scores at or beyond this level (49). At 18 months, children whose mothers did not take folic acid before 10 weeks' gestation more commonly had elevated problems as measured by the CBCL, specifically in social withdrawal, attention, and aggression (odds ratio=1.4, 95% CI=1.1–1.9). At 3 years of age, the children of mothers who did not take folic acid before 10 weeks' gestation continued to have emotional problems (odds ratio=1.45, 95% CI=1.14–1.84). Maternal folic acid plasma levels <7 nM at 13 weeks' gestation similarly predicted emotional problems (odds ratio=1.57, 95% CI=1.03–2.38). At 6 years of age, the children were assessed for autistic traits, defined as the highest 3% on the Pervasive Development Problems subscale of the CBCL and the highest 5% on the Social Responsive Scale. Folic acid supplementation at any time during pregnancy was associated with these higher scores on the two scales in a logistic regression analysis (β=−0.042, 95% CI=−0.068 to −0.017) (50).

All studies of infant outcomes from pregnancy have many confounding effects, especially in observational studies like the Generation R study, as opposed to trials with randomized treatment. Infants with folic acid deficiency weighed 200 g less. Mothers were younger, less educated, less likely to have

TABLE 2. Mechanistic Studies of Prenatal Interventions

Supplement	Effect	Model Mechanism
Folic acid	Increased neuronal development	Deficiency lowers Stat3, allowing increased neurite outgrowth (41)
	Imprinting of maternal genes	Biochemical role in one-carbon metabolism and methylation of DNA (42)
Phosphatidylcholine	Development of inhibitory neurotransmission	Activation of α7-nicotinic receptors induces the chloride transporter NKCC1, establishing a chloride gradient for GABA inhibition (43); effects blocked in *CHRNA7* null mice (43, 44)
Omega-3 fatty acids	Antiseizure effect in ketogenic diet but could also affect synapse formation in development	Accelerates inactivation and retards recovery of sodium and calcium channels in vitro, which decreases neuronal excitation (45)
	Reduces preterm birth	Reduces prostaglandin E2 and F2α in uterine decidual cells (46)
Vitamin D	Neuronal development	Interacts with Nurr1 to support development of dopamine neurons (47); activates low voltage (L-type) calcium channels to increase neurofilament phosphorylation (48)

planned their pregnancy, and less likely to be married, all of which may explain their failure to begin folic acid supplements before 10 weeks' gestation. The women were also more likely to be non-Western immigrants. They were more likely to smoke but less likely to have more than one alcoholic drink per week. Only 4% of the women who did not take folic acid and 28% of the women who took folic acid also took multivitamins. The mother's initiative to take folic acid meant that the timing of supplementation was confounded by these sociodemographic differences, but it also provided for groups of women who began the supplementation at different times in gestation. Differences between the women might also confound the assessment of outcome, which is based on maternal reports of children's behavior.

A trial involving 311 women randomized the women at 20 weeks' gestation to four groups: one group received 400 μg of methyltetrahydrofolate, the biologically active derivative of folic acid; one group received the folate with fish oil containing 650 mg of omega-3 fatty acids; one group received fish oil alone; and one group received placebos (25). The children of women who received only methyltetrahydrofolate had decreased time in the presence of a distractor at 8.5 years of age, compared with children in the other groups (d′=0.32). This trait is associated with schizophrenia and other mental illnesses, but only 130 children were studied, and no other laboratory or clinical ratings were performed.

Folic acid supplementation is generally recommended at 400–800 μg preconception, or at any point in early gestation that the pregnant woman can start, as a standard part of prenatal regimens worldwide because of its striking effect of decreasing facial clefts (odds ratio=0.61, 95% CI=0.12–0.71) (14). Supplements of up to 4 mg before 12 weeks' gestation have been found to be safe and effective in preventing open neural tube defects in women at high risk because of a previous child with a defect (odds ratio=0.28, 95% CI=0.12–0.71) (15). No follow-up of emotional or behavioral outcomes in childhood was performed on these children. The only adverse effect reported from standard folic acid supplementation is increased childhood asthma at 4.5–6 years (odds ratio=1.2, 95% CI=1.1–1.3) (28).

There are no retrospective studies showing that higher maternal folate levels are associated with a decreased incidence of schizophrenia. The large margin of safety of folic acid would support randomized testing of doses of up to at least 4 mg compared with the standard 400–800 μg.

Omega-3 Fatty Acids (Fish Oil)

The omega-3 fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid were studied in pregnancy following initial reports of higher levels of cognitive function in children whose mothers followed the Mediterranean diet during pregnancy (51). The Mediterranean diet differs from Western diets in many aspects, but fish oil and, specifically, omega-3 fatty acids are important differences. However, mixed effects of higher maternal omega-3 fatty acids have been found. For example, an observational study found that a lower ratio of omega-3 to omega-6 in the mother during pregnancy was associated with more autistic traits in the offspring, but the effect was primarily driven by higher levels of omega-6 as opposed to deficient levels of omega-3 (52).

Omega-3 fatty acid supplementation has had the longest double-blind clinical trial follow-up of any of the prospective interventions. The results have been disappointing. At 20 weeks' gestation, 543 women were randomized to 800 mg of fish oil or to placebo. The 7-year follow-up, through parental reports, showed a small but significant increase with fish oil in behavioral problems in attention deficit hyperactivity disorder (ADHD) (d′=0.1), consistent with results that had been observed at 4 years of age (25, 28, 50). A retrospective observational study in a Kaiser Permanente group found that mothers in the highest tertile of levels of the omega-3 fatty acid DHA had children with a twofold elevation of adult schizophrenia spectrum disorders (odds ratio=2.38, 95% CI=1.19–4.76) (52). Mothers in the lowest tertile did not have elevated risk.

A number of trials of DHA supplementation in pregnancy have shown positive effect on attention and neurological signs in the first 5 years of life (53–57), but other trials have not shown differences (24, 35, 58, 59). The positive effects of fish oil in one observational trial disappeared when the socioeconomic differences between the mothers were considered (60). Another study found that the effect of fish was compromised by the mercury content (61). A meta-analysis of 11 studies concluded that the positive effects were biased by

two of the trials (62). DHA supplementation postpartum is particularly effective for preterm female infants with birth weight less than 1,250 g. The supplement, six 500 mg capsules of DHA containing tuna oil, or the equivalent in formula, was given to the lactating mother in a randomized controlled trial. At 18 months of age, corrected for gestational age at birth, there was a significant improvement in the cognitive development of the infants who received supplements. Full-term and higher birth weight preterm infants did not show a significant effect (63, 64).

Other benefits from fish oil supplementation have been more consistently observed. The same randomized trial that later found increased ADHD symptoms at 7 years of age had previously found a decreased incidence of premature gestation at <34 weeks with fish oil supplementation (odds ratio=0.49, 95% CI=0.25–0.94), fewer babies with birth weight less than 2,500 g, and less admission of babies for neonatal intensive care (35). A meta-analysis of 21 controlled studies found a 5.8-day increase in gestational age of the newborn, a 22% reduced risk for early preterm delivery, higher infantile birth weight (51.23 g), and a 23% lower risk of low birth weight (65). Although the cognitive and behavioral findings in trials of omega-3 fatty acid do not consistently support the benefit of these improvements in birth outcomes, they are associated with enhanced fetal development, including brain development. For example, infants who are born prematurely have an increased odds ratio (2.6) of developing ADHD (66).

A placebo-controlled trial found that 2.4 g of fish oil supplementation, beginning at 24–26 weeks' gestation, had a striking effect on the incidence of childhood wheezing at age 3–4 years (odds ratio=0.69, 95% CI=0.49–0.97) (21). The trial indicated a decreased effectiveness in women with higher maternal vitamin D levels, which the investigators interpreted as caused by the two interventions targeting the same mechanism. There was no assessment of behavioral symptoms in the children.

An assessment of how omega-3 fatty acids can be administered to protect against premature birth and infant wheezing, while minimizing the risk for mental illness, would seem to be a next step. Translational studies have identified a putative mechanism of the beneficial effect on premature birth, but the mechanisms of effects on brain function are far from established (see the online data supplement). Increased understanding of the mechanism of effects on childhood behavior and risk for mental illness could guide clinical strategies to retain the considerable clinical benefit of omega-3 fatty acids and diminish any risk for future mental illness.

Phosphatidylcholine

Choline supplementation is only now being recommended as a standard prenatal regimen (67). Phosphatidylcholine is the preferred dietary supplement because it is impervious to most colonic bacteria. It is converted in the blood to choline (68). Dietary choline itself is metabolized by colonic bacteria to trimethylurea, which imparts a fishy odor, or trimethylamineoxide, which is atherogenic (33). These metabolites are not increased by phosphatidylcholine supplements (68). A survey showed that fewer than half of pregnant women reach an adequate level through normal diet, the equivalent of 450 mg of choline daily (69). The dietary recommendation of 450 mg by the Institute of Medicine of the National Academy of Sciences was based on the level in adults that prevents increase in liver transaminase, an early indication of choline deficiency. For pregnant women, the amount was increased based on the observation that levels are elevated 10-fold in the placenta, amniotic fluid, and in the fetus itself (42). A case report noted very low levels of choline in a mother with bipolar disorder treated with lithium, but this finding has not been replicated (70). The Institute of Medicine recommends an upper limit of phosphatidylcholine of 24,000 mg/day for pregnant women older than 18 years, equivalent to 3,500 mg of choline, which indicates a large margin of safety for supplements (42). The upper limit is half the amount observed to cause hypotension and diarrhea.

An observational study measured plasma choline at 16 weeks' gestation and found significant correlation with infant cognitive scores at 18 months of age as measured on the Bayley Scales of Infant Development (β=6.054, SE=2.283), with no effect on folic acid or vitamin B_{12} levels (31).

The first double-blind controlled trial administered 5,000 mg of phosphatidylcholine containing 750 mg of choline, a 200% increase over the 360 mg estimated from diet (71). The maternal supplement was begun by 18 weeks of gestation and continued through the first month of lactation. Plasma choline levels were twice the mean for the placebo-treated women. The trial found no effect on cognition as measured at 1 year of age by the infant's ability to find an object concealed by the investigator after different delays, up to 24 hours later. The strength of the trial is the complete measurement of choline and its metabolites in the mother's plasma. A weakness is that the primary cognitive task undergoes linear improvement from 6 to 24 months, which means that infants' performance was still developing at a substantial rate at the time of testing (72). Forty-six percent of infants could not complete the testing protocol, in addition to 39% who dropped out of the study before assessment.

In a second double-blind clinical trial, which is from our group, 50 women took 6,300 mg of phosphatidylcholine daily from week 17 of gestation though delivery, a 250% increase in choline levels over their normal diet. After birth, the newborns received 100 mg of liquid phosphatidylcholine from 2 weeks postbirth until 3 months of age. Fifty women and their newborns were given placebos. Because of the newborns' limited behavioral repertoire, the principal outcome measure was P50 auditory evoked potential inhibitory sensory gating at 1 month of age. This measure was previously shown to be abnormal in infants whose parents had psychosis or whose mothers smoked or were depressed, all risk factors associated with later schizophrenia in the offspring (73). Abnormality was defined as inhibition below the 95th percentile for subjects who had no known mental illness (74). At

1 month of age, the group who received phosphatidylcholine supplementation had significantly fewer infants with abnormal P50 inhibitory sensory gating (d′=0.7) (29).

The same cohort was reexamined at 3.5 years of age with the CBCL. Children from phosphatidylcholine-supplemented pregnancies, now on regular diets, had significantly fewer problems noted in attention and social interaction (30). This effect was related to their P50 sensory gating at 1 month of age. The magnitude of improvement in CBCL ratings at 3.5 years for the phosphatidylcholine-supplemented children, compared with a control group of children who received placebo (for attention problems, d′=0.59; for social problems, d′=0.79), was similar to the magnitude of decline found in a retrospective study of adults with schizophrenia compared with a control group, whose parents had rated them on the CBCL based on their recall of their child at 3–4 years of age (21). The intervention was found to be equally effective for infants who have a mother with schizophrenia, as well as for mothers who experienced an infection during pregnancy (30, 75). The findings were unchanged when some infants were reassessed at age 4, but none of the subjects have been seen later in childhood or adolescence to determine if they eventually became clinically ill. However, 23% of males and 15% of females in the placebo group had CBCL ratings of attention or social problems in the range of children who are referred by parents or schools for clinical intervention, compared with 7% of males and 11% of females in the phosphatidylcholine-treated group (49). Strengths of this study are the assessment of emotional behavior and its relation to an early neurobiological marker and a *CHRNA7* genotypic effect in the infants. Effects of phosphatidylcholine supplementation on both electrophysiology and behavior, compared with placebo, were more marked in children who have a *CHRNA7* promoter variant associated with schizophrenia. Weaknesses are the study's small size and the 50% attrition of the groups by 4 years of age as mothers were lost to contact.

A randomized clinical trial of third-trimester choline supplementation (550 mg compared with 100 mg of choline chloride added to a controlled diet containing 480 mg) found increased placental methylation of the genes for corticotropin-releasing hormone and the glucocorticoid receptor (*NR3C1*), which moderate the cortisol reaction that can damage the placenta and fetus (7, 76). Cord blood cortisol was reduced by 30% in the newborns of mothers who received the higher dose of choline. A smaller randomized trial of the same levels of supplementation found lower placental sFLT1, an angiogenic factor associated with preeclampsia (d′=0.2) (32). None of the studies of phosphatidylcholine in the literature found significant adverse effects for mother or infant.

Most trials find that phosphatidylcholine supplements protect against maternal risk factors associated with schizophrenia and other mental conditions in the offspring and decrease the development of traits associated with later mental illness in adulthood, but as for folic acid, there are no retrospective studies showing that maternal choline lowers the incidence of schizophrenia itself.

Vitamins D and A

Vitamins D_3 and A_1 were initially assessed in retrospective observation of banked serum (40, 77). Part of the motivation for investigating these vitamins was the well-known effect of season of birth on risk for schizophrenia. In the largest study of vitamin D levels and schizophrenia, neonatal blood samples from 430 Danish case-control pairs were studied (36). The levels of $25(OH)D_3$, the circulating form of vitamin D that is produced by liver metabolism, were divided into quintiles based on levels in the control subjects. Neonates in the fourth quintile (40.5–50.9 nmol/L) were the least likely to develop schizophrenia. Those above and below this level were more likely to do so (odds ratio=2.1, 95% CI=1.3–3.5). Forty-four percent of the sample was in the fourth quintile, mostly individuals born from June through September, because of the effect of sunlight on vitamin D levels. For infants to be born in other seasons, the dose of vitamin D supplementation that might be recommended is unknown, beyond standard prenatal multivitamin preparations. In a separate observational postnatal cohort from Finland, male infants who were given 2,000 IU daily of vitamin D in the first year of life had less than 25% of the risk for schizophrenia compared with the rate found for those who did not receive such supplementation (odds ratio=0.23, 95% CI=0.06–0.95). There was no difference for females (37).

Vitamin D has subsequently been studied prospectively in observational studies. In the Dutch Generation R study, lower levels of midgestation maternal and cord blood $25(OH)D_3$ were associated with higher scores on the Social Responsiveness Scale used to measure autism-related traits (78). In this cohort, ASD itself was more likely to occur in individuals whose mothers had midgestational vitamin D deficiency (odds ratio=2.42, 95% CI=1.09–5.07) (38).

As in all observational studies, whether prospective or retrospective, the fundamental causative factor cannot be easily isolated from possible confounding effects. For the Danish study, the infants with lower vitamin D levels were more likely to be children of immigrants. The effect from season of birth could be ascribed to higher rates of maternal infection, with gestation occurring in the winter cold and flu season. However, the investigators point out that higher maternal vitamin D levels are associated with lower risk for maternal infection. The vitamin D effect on mental illness has been replicated in observational studies worldwide (39, 79–85). Vitamin D has also been found to reduce infant wheezing related to infection (odds ratio=0.39, 95% CI=0.25–0.62) and to reduce the risk of preterm birth <37 weeks (86, 87).

Vitamin A levels during the second trimester were assessed in 12,000 pregnant women enrolled in the Kaiser Permanente health plan. The 55 offspring who developed schizophrenia spectrum disorders were compared with control subjects. Maternal plasma levels below 30 μg/dL, the level generally considered as deficient, were associated with increased risk

TABLE 3. Summary of Findings for Nutrients With Possible Prenatal Preventive Effect[a]

Intervention	Current Recommended Daily Allowance	Study Dose, Timing	Major Developmental Finding	Other Conditions	Known Adverse Effects
Folic acid	400–800 μg[b] plus 200 μg from diet	400 μg at preconception to 10 weeks' gestation (27)	Decreased emotional problems (child)	Decrease in cleft lip, spina bifida	Infant wheezing increased
Phosphatidylcholine	3,150 mg (450 mg of choline) from diet	6,300 mg at preconception to 16 weeks' gestation (30)	Decreased social and attention problems (child)	Possible decrease in preeclampsia	Trimethylamine N-oxide cardiotoxicity (in men with cardiac disease)
Omega-3 fatty acids (fish oil)	Up to 300 g of low mercury–containing fish per week	2.4 g of fish oil daily at 24–26 weeks' gestation for wheeze (23)	Increased risk for schizophrenia spectrum (adult)	Premature birth and infant wheezing decreased	Increased ADHD symptoms at 7 years
Vitamins A and D	Supplement of 2,567 IU[b] of vitamin A and 600 IU[b] of vitamin D, plus amounts from diet and sunlight	1,000 IU of vitamin D_3 for infants up to 1 year of age, 2,000 IU in northern countries (37)	Decreased schizophrenia (adult) with both vitamins A and D	Infant wheezing decreased	Teratogenicity with vitamin A intake >8,000 IU (diet plus supplement)

[a] ADHD=attention deficit hyperactivity disorder.
[b] Amount in most standard prenatal vitamins.

of schizophrenia in the offspring (odds ratio=3.05, 95% CI=1.06–8.79) (77).

Unlike the other nutrients, vitamins A and D have upper limits defined by their potential toxicity. Therefore, supplementation should not be greater than the amount in standard multivitamins. The daily recommendation in the United States for vitamin D is 600 IU for pregnant women and 400 IU for infants. Upper tolerable limits are 4,000 IU for pregnant women and 1,000 IU for infants. However, these recommendations assume adequate calcium intake and exposure to sunlight and may differ, particularly in winter seasons in countries with limited sunlight (88). An association with teratogenicity has limited the recommendation in the United States for vitamin A in pregnancy to 8,000 units from diet and supplements combined (89). Most supplements contain 2,500 units.

DISCUSSION

This review identified studies of four types of prenatal maternal dietary interventions to promote fetal brain development and decrease subsequent risk for mental illness. The key findings are summarized in Table 3. Vitamins A and D and folic acid are already in common clinical use. Higher serum levels of vitamins A and D appear to promote brain development and to decrease risk for schizophrenia, but their potential toxicity limits their use to currently recommended amounts. Folic acid is also currently in prenatal vitamins but at levels far below those shown to be safe and effective for neural tube defects. Folic acid has benefits for the development of the fetal brain and subsequent child behavior and cognition, but it has not been shown specifically to prevent schizophrenia. Omega-3 fatty acids increase the risk for later schizophrenia and modestly increase childhood ADHD symptoms, but they also substantively decrease the risk of both premature birth and childhood wheezing. Phosphatidylcholine supplements have been more recently studied prospectively and have generally been found to promote the development of the fetal brain and subsequent childhood behavior, but no retrospective epidemiological studies have been performed.

Optimal dosages and timing should consider not only the fetal brain effect but the effect on other systems as well. For example, higher omega-3 fatty acid levels before 20 weeks' gestation were found to increase the risk of schizophrenia, but administration after 24 weeks' gestation decreased the risk of childhood wheezing (23, 34). Vitamin D effects on premature birth are related to administration in the third trimester, and effects on risk for schizophrenia have been observed with postnatal administration (37, 87). Phosphatidylcholine is probably best given preconception because levels in the first trimester are much lower than in the second trimester or at delivery (90). Dose can be affected by genotype. African people who live in countries with diets low in phosphatidylcholine nonetheless have normal choline levels in pregnancy, perhaps because they do not have variants in *PEMT*, the gene for the enzyme phosphatidyl-ethanolamine methyl transferase that regulates choline levels, whereas in Chinese people, who have *PEMT* variants, these variants are associated with risk for schizophrenia (91, 92). Environmental factors are also important, particularly for vitamins A and D. In Nordic individuals, deficiency is highly related to the low sunlight in winter (36). Nordic women with darker skin require higher levels, if their exposure to sunlight is poor

TABLE 4. Prenatal Nutrient Studies Registered as in Progress

Principal Investigator, Country	Title	Type of Trial, Dose, Timing	Principal Outcome	Registry and Date
C. Grant, Australia	Randomized placebo-controlled study of vitamin D during pregnancy and infancy	Randomized; mothers receive 2,000 IU of vitamin D and infants receive 800 IU, compared with 1,000 IU and 400 IU for each	Infant 25(OH) vitamin D >75 nM at 6 months	Australian New Zealand Clinical Trials Registry, ACTRN12610000483055; 2010
M.C. Hoffman, United States	Choline supplementation during pregnancy: impact on attention and social withdrawal	Randomized; 9 g of phosphatidylcholine at 15 weeks	Child Behavior Checklist rating at 3.5 years	ClinicalTrials.gov, NCT03028857; 2017
J. Zhu, China	Effects of genomic and metabolomic variations of choline on risk of preterm birth and clinical outcomes in preterms	Prospective, observational; effects of plasma choline level during gestation	Preterm birth incidence	ClinicalTrials.gov, NCT02841813; 2016

(93). Future clinical use of the nutrients can be designed to consider all these modulators of effectiveness to maximize benefits and minimize any adverse effects.

Interventions can be directed to pregnancies considered at risk or, like folic acid, to the general population. Children of mothers who have schizophrenia are more likely to have abnormal fetal brain development than children of other mothers, but only 10% of ill individuals have children with schizophrenia (94). Thus, the criterion of having an ill parent does not identify who will inevitably become ill. Many women may consider themselves to be at low risk for transmitting mental illness because it is not present in their family, but common, unpredictable maternal infections during pregnancy, including upper respiratory viruses and urinary tract infections, transform the pregnancy to higher risk for the development of the fetus (2).

Public health is an important component of the research agenda. Only 50% of pregnancies are planned, and for some interventions, such as folic acid, preconception use is more effective. Furthermore, fewer than 50% of women currently take folic acid and other vitamins at any time during pregnancy (95). Food and Drug Administration requirements for additives to common foods, like vitamin D to milk, may be helpful, but for folic acid they are not as effective as preconception use of supplements. Dietary sources for phosphatidylcholine are also insufficient (69). Innovation and assessment of better ways to ensure use of evidence-based recommendations for women of childbearing age are needed.

It is unlikely that any single prenatal intervention will prevent mental illnesses in all individuals. The effect size for some of the interventions approaches the effect size for common respiratory infection (odds ratio=2.1), but none approach the effect size that might fully overcome genetic risk (odds ratio=4.2) for a parent or sibling with schizophrenia. However, exposure to respiratory infection during pregnancy is more common than family history of schizophrenia in a close relative. The combinations of nutrients that would further increase effectiveness have not been assessed. Nutrients are only part of good maternal care to promote fetal brain development and to ameliorate risk for mental illness in the offspring. Treatment of maternal psychiatric illnesses during gestation, a significant risk factor for the infant's later mental illness, is an intervention that psychiatrists, obstetricians, and primary care physicians already provide (see the online data supplement). A model for the public health role of prenatal prevention of mental illness may be cardiac disease. The decline in heart attack deaths occurs not from a single fully effective intervention but from a combination of improved diet and exercise beginning early in childhood; antismoking campaigns in adolescence; statins, antihypertensives, and aspirin in older adults; and then advances in interventions for heart attacks themselves (96).

In the usual course of medical research, interventions are well substantiated before being released for general medical use. Surely no period of life should be better protected than gestation, which mandates even a higher standard of evidence. There are only 35 studies on which to base conclusions, only five of which are randomized controlled trials. Only three ongoing studies were found in registries, and their full results will not be known until the offspring grow to ages when effects can be measured (Table 4). There are no U.S. government–regulated standards for prenatal vitamins, but various bodies are now making specific recommendations that may be helpful in guiding families and their doctor. The American Medical Association (AMA) in June 2017, in response to an initiative from the National Medical Association, advocated for a change in the manufacture of prenatal vitamins to incorporate increased levels of choline (67). AMA delegates observed that many pregnant women do not achieve even the minimum dietary amount previously recommended by the National Academy of Medicine (450 mg). The AMA's deliberation also noted the positive effects observed in the clinical trial using the equivalent of 900 mg reviewed in the present work (97). The resulting resolution

advises that an "evidence-based" amount be included in the prenatal supplement.

To obtain such evidence for any nutrient will require new research agendas that emphasize prenatal clinical trials of interventions, early biomarkers of their effectiveness developed in translational models, and then longer-term follow-up through childhood developmental stages into adulthood. Deficiencies in some nutrients, folic acid and vitamin D, have been found to persist into the first psychotic episode (98). Trial designs based upon randomized clinical trials with relatively short-term follow-up for medication in adults are not applicable because of the unique features of prenatal trials. Randomization to placebo requires consideration that fetal development is a unique stage; later reassignment to an active treatment cannot fully remediate defects in brain development that occur before birth. Preconception initiation of a nutrient often is more effective than initiation during gestation, but informed women who plan their children before conception may not consent to be randomized. Instead, they can choose to initiate the nutrients themselves. Follow-up is lengthy, essentially spanning two generations of patients, mother and child, and thus two generations of the researchers themselves. Intermediate effects on childhood behavior will be valuable findings because waiting decades for final data on illness in adulthood means that the generations born in that interval will not receive any guidance on treatment. Finally, large numbers of subjects are necessary because of the many additional risk factors that impinge between conception and illness. These considerations suggest that such trials may need to be conducted over platforms like social media rather than in traditional biomedical settings.

In the absence of definitive evidence, parents currently planning pregnancy now have difficult decisions about nutrient supplements. The mother is unlikely to receive fully effective levels of the currently studied nutrients from diet alone. Adverse effects of supplements are few at the doses studied, but it would be premature to conclude that they are nonexistent. Conversely, there is only one opportunity in each child's life for intervention to enhance fetal brain development and protect the child against developmental risks that arise in this period (99).

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