Modulation of prenatal stress via docosahexaenoic acid supplementation: implications for child mental health

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Pregnant women living in poverty experience chronic and acute stressors that may lead to alterations in circulating glucocorticoids. Experimental evidence from animal models and correlational studies in humans support the hypothesis that prenatal exposure to high levels of glucocorticoids can negatively affect the developing fetus and later emotional and behavioral regulation in the offspring. In this integrative review, recent findings from research in psychiatry, obstetrics, and animal and human experimental studies on the role of docosahexaenoic acid in modulation of the stress response and brain development are discussed. The potential for an emerging field of nutritionally based perinatal preventive interventions for improving offspring mental health is described. Prenatal nutritional interventions may prove to be effective approaches to reducing common childhood mental disorders.

INTRODUCTION

There is convincing evidence from multiple studies that used a variety of methodologies and were performed in different species that the mother's level of psychosocial stress during pregnancy is significantly associated with suboptimal developmental outcomes in her offspring. Evidence from controlled animal studies demonstrates that maternal stress during pregnancy can permanently compromise neurodevelopment in the offspring.^{1,2} Prenatal stress has been linked to a range of adverse outcomes in the offspring, including disturbances in attention,^{3,4} impaired learning and disruption in neurogenesis,^{1,5} and increased anxiety-like behaviors.³ The strength of the causal claim that maternal stress affects the development of offspring is based on rigorous controlled experiments in which the prenatal effect is distinguished from postnatal effects by using methods such as cross-fostering or nursery rearing. Furthermore, there is now good evidence that at least some aspects of the underlying mechanisms

have been identified. The strongest candidate is the maternal hypothalamic–pituitary–adrenal (HPA) axis, although other systems are likely to be involved. Prenatal stress causes long-term alterations in the functioning of the offspring's HPA axis,^{6,7} and each of the phenotypic outcomes identified above can be linked to disruptions in the HPA axis. A pathway by which prenatal stress impairs fetal stress architecture may be via downregulation of placental 11 β -hydroxysteroid dehydrogenase type 2, which is the enzyme that metabolizes cortisol into its inactive form, cortisone.^{8–10}

Several nonexperimental, prospective, studies of humans have shown that maternal stress during pregnancy is associated with outcomes and psychological processes relevant to mental health including obstetric complications,¹¹ shorter gestational length,¹² smaller infant size at birth,¹³ individual differences in the diurnal rhythm and reactivity of the offspring's HPA axis,^{14,15} and temperamental problems.¹⁶ This pattern of findings in humans closely mirrors the findings from controlled animal studies.¹⁷

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Given this strong evidence for the negative impact of maternal stress during pregnancy on the offspring and the viable hypothesis that prenatal stress disrupts the programming of the systems involved in stress response, including the HPA axis, it is important to initiate studies of the prevention of the negative effects of prenatal stress in humans. This is especially relevant for sociodemographically vulnerable populations of women who are at higher risk for adverse birth outcomes¹⁸ and whose offspring show evidence of less optimal neurodevelopmental outcomes,¹⁹ including mental health problems.²⁰ For example, women living in poverty have higher rates of preterm birth, and their infants have lower birth weights.²¹ African American women living in dense, urban areas with high levels of poverty appear to have the highest risk for adverse birth outcomes.²²

Adequate prenatal nutrition is a critical component of subsequent healthy growth and development, and brain development is particularly sensitive to adequate proteins and lipids.^{23,24} There are several reviews on the importance of n-3 fatty acids for offspring cognition and vision^{25–27} and on the role of fatty acid status and supplementation in the etiology and treatment of physical and mental disorders across the lifespan.^{27,28} In contrast, the present review was conducted from the perspective of a prenatal programming hypothesis²⁹; the focus is, thus, on the recent findings from psychiatry, obstetrics, and animal and human research available through PubMed with particular emphasis on the role of docosahexaenoic acid (DHA) in the modulation of prenatal stress as it relates to offspring neurodevelopment. The aim was to determine whether the existing literature on the role of fatty acids in regulation of prenatal stress supports fatty acid supplementation during pregnancy among vulnerable populations as a targeted preventive intervention for common childhood mental disorders by buffering the developing fetus from the deleterious effects of maternal stress during pregnancy.

SECULAR CHANGES IN CONSUMPTION OF POLYUNSATURATED FATTY ACIDS

Polyunsaturated fatty acids (PUFAs) are comprised of two families: 1) linoleic acid and its n-6-derivative, arachadonic acid, and 2) α -linoleic acid and its n-3 derivatives, eicosapentaenoic acid and DHA. Omega-6 fatty acids are mostly found in plant oils, whereas n-3 fatty acids are found mostly in marine oils. The most important and abundant PUFA in the brain is DHA, which serves a critical role in neural functioning.^{23,24} PUFAs are not synthesized endogenously. Consequently, diet determines the level of fatty acid

available to the central nervous system. Because n-6 and n-3 fatty acids compete for the same enzymes required for desaturation and elongation, a higher ratio of n-6 to n-3 PUFAs in the diet reduces the availability of DHA. Over the past several decades, dietary intake of n-3 PUFAs has decreased in the United States, whereas dietary intake of n-6 PUFAs has held relatively steady.^{30,31} In a recent review, average intake of n-3 fatty acids from seafood in the United States was <150 mg/day, which is far less than the optimal consumption of 250 mg/day.³² Among pregnant women living in low-income environments, n-3 fatty acid intake and blood levels of DHA are approximately a quarter of the recommended levels for pregnant women.³³ Importantly, changing the level of fish consumption is not the only mechanism by which to increase n-3 PUFAs, as fish oil supplementation during pregnancy has been shown to increase DHA levels in maternal and cord plasma and erythrocyte phospholipids.³⁴

DOCOSAHEXAENOIC ACID AND PERINATAL DEPRESSION

In animal models, adverse changes in central nervous system functioning in offspring have been found after administration of selective serotonin reuptake inhibitors during pregnancy.^{35,36} As a result, alternative therapies for perinatal depression, including randomized controlled trials (RCTs) of essential fatty acids, have been explored. In general, the results provide little evidence for the efficacy of fatty acid supplements in reducing depressive symptoms or preventing postpartum depression. For example, Marangell et al.³⁷ conducted a randomized placebo-controlled clinical trial of 2 g/day of DHA or placebo for 6 weeks; the severity of postpartum depression ratings was not different between the two groups at the end of the trial. In a few studies, trends or inconsistent results were reported regarding the association between fatty acid supplementation and perinatal depression. Results from a large RCT conducted in Australia revealed nonsignificant trends of lower depression scores among women receiving DHA during pregnancy.³⁸ In a recently completed trial, DHA plasma levels were inversely associated with depression scores at 34–36 weeks gestation but not at other times during pregnancy or in the postpartum period.³⁹ As an adjunct treatment to standard psychopharmacologic interventions for depression, however, the addition of fatty acid supplementation was associated with greater overall improvement in depression during pregnancy compared with psychopharmacologic treatment alone.⁴⁰

DOCOSAHEXAENOIC ACID AS A MODULATOR OF STRESS HORMONES

Although PUFA supplementation does not appear to be effective in reducing clinically significant depressive symptoms in women during the perinatal period, it is possible that supplementation affects systems related to depression, such as those involved in regulating stress. This may explain the efficacy of PUFA supplementation as an adjunct treatment for depression. In animal studies, DHA supplementation was associated with a decreased stress response to controlled stimuli. For example, Takeuchi et al.⁴¹ reported that DHA supplementation reduced stress behaviors (e.g., rearing, smelling, freezing) that were manifest in response to a corticotropin-releasing hormone infusion and to a conditioned fear response. In a study designed to test the effects of DHA supplementation on cardiac responses to psychosocial stress, stressed Wistar rats receiving DHA supplements demonstrated lower heart and blood pressure compared with stressed rats whose diets were not supplemented.⁴²

In humans, fatty acid supplementation was also associated with reductions in stress reactivity in controlled studies. Maes et al.⁴³ found an association between university students' inflammatory cytokine responses to oral exams and serum n-3 PUFA levels. Students were above the mean in their serum n-3 PUFA levels prior to the stressor, demonstrating significantly lower levels and changes in several proinflammatory cytokines including interleukin-6. Results of a 12-week RCT of n-3 supplementation in healthy men who were exposed repeatedly to a social stressor revealed that n-3 supplementation modulated the cortisol stress response, especially among individuals who reported high levels of chronic stress.⁴⁴ Yehuda et al.⁴⁵ reported on the efficacy of a daily dose of 225 mg n-3 fatty acid (taken for 1 month) for reducing test anxiety among students. Morning cortisol levels were assessed at the beginning of the study and then 1 month later among 126 participants divided into 3 groups: students without test anxiety receiving no supplement, students with test anxiety receiving placebo, and students with test anxiety receiving a supplement containing 225 mg/day of n-3 fatty acid. Morning cortisol levels decreased significantly from the pre- to the post study periods in the supplement group, and the morning cortisol levels of these individuals were similar to those of the students without test anxiety. In contrast, pre- to post-study morning cortisol levels did not change in the placebo group. Delarue et al.⁴⁶ reported a blunting of the cortisol response to stress in the context of an open trial in seven participants. All participants received 7.2 g/day of fish oil and completed a mental arithmetic challenge

and the Stroop test at two time points, i.e., prior to and 3 weeks after supplementation. The magnitude of change in cortisol levels measured in response to the stressors significantly decreased from the pre- to the post-n-3 supplementation period.

Thus, there is growing evidence that supplementation with n-3 fatty acids can modify psychological responses to stressors. In the controlled experiments described above, the magnitude of the response of systems involved in the regulation of stress, including the HPA axis, was decreased by DHA supplementation.

EVIDENCE FOR AN ASSOCIATION BETWEEN DOCOSAHEXAENOIC ACID LEVELS DURING PREGNANCY AND OFFSPRING OUTCOMES

Fetal demand for DHA appears to increase during the third trimester when there is rapid development of the brain and retina.⁴⁷ Data from studies using rodent models firmly support the importance of DHA in neuronal arborization and synaptogenesis during fetal life⁴⁸ as well as myelination and synaptogenesis in the postnatal brain.⁴⁹

Tests of the association between DHA levels during pregnancy and offspring outcomes provide further evidence for the hypothesis that DHA modulates the effects of prenatal stress. These studies are summarized in Table 1 for experimental rodent models and in Table 2 for experimental and observational studies in humans. In experimental rodent models, deficient levels of DHA during pregnancy resulted in deficits in learning, such as habituation to novelty and latency to reach learning criteria⁵⁰; prolonged corticosterone response to restraint stress and longer periods of immobility during the Porsolt forced swim test⁵¹; and less exploration of environmental stimuli in the offspring,⁵² as determined via tests designed to assess constructs similar to distress disorders in humans. Takeuchi et al.⁴¹ demonstrated that pups of DHA-deficient dams spent less time in the open arms of a plus maze (indicative of higher stress levels) than the offspring of normally fed animals. A 1-week period of DHA supplementation to the diet of the pups, however, resulted in significant increases in time spent in the open arms of the maze. In one of the most compelling experimental studies to date, Feng et al.⁵³ demonstrated in a rodent model that DHA administration during pregnancy attenuated the effects of prenatal stress on offspring hippocampal functioning including observed learning and memory, apoptosis, and mitochondrial metabolism. In another rodent model, the offspring of dams that were supplemented with DHA and eicosapentaenoic acid beginning in pre-conception and continuing through lactation showed an attenuation of the behavioral and cognitive deficits

Table 1 Evidence for an association between docosahexaenoic acid levels during pregnancy and offspring outcomes in experimental rodent models

Reference	Model/design	Dependent measure	Results
Moriguchi et al. (2000) ⁵⁰	Compared two generations (F2 = 20; F3 = 20) of male offspring of dams whose diets were n-3-deficient (including DHA) (<i>n</i> = 20) versus adequate (<i>n</i> = 20) beginning prenatally and continuing through lactation and in the postnatal diet of the offspring	Motor activity, behavior in elevated plus maze and learning acquisition in water maze	Motor activity in terms of time (<i>P</i> < 0.01) and distance (<i>P</i> < 0.005) was increased over time in the F3 generation of n-3-deficient dams; for both generations, offspring of the n-3-deficient group showed a longer escape latency (F2, <i>P</i> < 0.05; F3, <i>P</i> < 0.005) and delayed learning in the water maze (F2 <i>P</i> < 0.005; F3 <i>P</i> < 0.005) compared with the n-3-adequate group; no group differences in behavior in the plus maze
Takeuchi et al. (2003) ⁴¹	Compared offspring of dams with n-3-deficient versus adequate diets from preconception through pregnancy and lactation; offspring of n-3-deficient dams were given either a normal diet (<i>n</i> = 8) or a DHA-enriched diet (<i>n</i> = 8); these two groups of animals were compared with offspring of n-3-adequate dams who were fed a commercial diet on response to stress	Behavioral and anxiety-like response to environmental and biological stressors	Offspring of n-3-deficient dams spent less time in open arms of plus maze than offspring of n-3 adequate dams (<i>P</i> < 0.05); this effect was significantly attenuated by 1 week of supplementation with DHA (<i>P</i> < 0.05); DHA supplementation also attenuated CRH-induced anxiety-like behaviors including CRH-induced changes in rearing (<i>P</i> < 0.05), smelling, (<i>P</i> < 0.01), and feeding (<i>P</i> < 0.01)
Feng et al. (2012) ⁵³	Compared 10 male and female offspring from each of four groups: control, PRS, PRS + 100 mg/kg DHA/day, and PRS + 300 mg/kg DHA/day	Offspring learning; biomarkers of oxidative damage; apoptosis	Maternal DHA administration ameliorated the PRS effects on spatial learning in the Morris water maze in both the low (<i>P</i> < 0.05) and high (<i>P</i> < 0.01) doses of DHA; PRS significantly increased oxidative damage to proteins, and both the low (<i>P</i> < 0.05) and high (<i>P</i> < 0.01) doses of DHA inhibited increases in oxidative damage; PRS caused increased apoptosis signaling, and both low and high doses of DHA inhibited the PRS-induced increase, although these effects varied by sex
Palsdottir et al. (2012) ⁵²	Compared 10 randomly selected female pups from dams who received n-3-deficient diets to 10 randomly selected female pups from dams who received n-3-enriched diets beginning at embryonic day 16 through weaning	Anxiety-related behavioral responses to environmental and social stimuli	Offspring of fatty acid-deficient dams evidenced significantly less object recognition (<i>P</i> < 0.05), spent less time in dark environments (<i>P</i> < 0.05), and spent less time in closed arms of the plus maze (<i>P</i> < 0.05); no differences in social interaction or behavior in open field environment were observed
Chen and Su (2012) ⁵¹	Compared male offspring of dams with n-3-deficient (<i>n</i> = 18) versus adequate (<i>n</i> = 18) diets during pregnancy and lactation to males who received n-3-deficient (<i>n</i> = 20) versus adequate (<i>n</i> = 20) diets during postweaning	Biological and behavioral response to stressors	Prewaning manipulation of DHA resulted in prolonged corticosterone response to restraint stress (<i>P</i> < 0.005), less time in open arms of plus maze (<i>P</i> < 0.05), and longer periods of immobility (<i>P</i> < 0.01) in the forced swim test at 10 weeks; these effects were not observed as a result of postweaning DHA levels
Pudell et al. (2014) ⁵⁴	Two pups each from dams with (<i>n</i> = 20) and without (<i>n</i> = 20) DHA and eicosapentaenoic acid supplementation from preconception through pregnancy lactation were distributed into those undergoing sham or OBx at postnatal day 80: resulting in four groups: sham control (<i>n</i> = 20), OBx control (<i>n</i> = 15), sham + supplementation (<i>n</i> = 20), and OBx + supplementation (<i>n</i> = 15)	Anxious behavior during elevated plus maze, depressive behavior during forced swim test, and learning task	Significant interaction effect between supplementation and OBx, with OBx animals spending less time in open arms of plus maze (<i>P</i> = 0.001), showing decreased swimming (<i>P</i> = 0.001) and increased immobility (<i>P</i> = 0.01) during forced swim test, and showing lower performance on discrimination task than other groups including OBx + supplementation animals

Abbreviations: CRH, corticotropin-releasing hormone; DHA, docosahexaenoic acid; OBx, olfactory bulbectomy; PRS, prenatal restraint stress.

Table 2 Evidence for an association between docosahexaenoic acid levels during pregnancy and offspring outcomes in humans

Reference	Model	Sample	Design	Dependent	Results
Helland et al. (2003, 2008) ^{58,59}	RCT	Follow-up of offspring of 341 healthy Norwegian women aged between 19 and 35 years: 84 offspring at age 4 years and 143 at age 7 years	Mothers of 48 offspring randomized to DHA supplementation (10 mL cod liver oil containing 1,183 mg DHA) and 36 to corn oil beginning at 18 weeks of gestation through 3 months postpartum	IQ and achievement testing at ages 4 and 7 years	At age 4 years, offspring whose mothers received cod liver oil during pregnancy had IQ scores that were significantly higher than those whose mothers received corn oil during pregnancy (106.4 versus 102.3; $P < 0.05$); effects were not maintained at age 7 years
Hibbeln et al. (2007) ⁵⁶	Observational	Pregnant women living in Bristol, United Kingdom, from 1991 to 1992; total sample = 14,451	Test association between maternal report of sea fish consumption at 32 weeks of gestation (none versus 1–340 g/week versus >340 g/week) and child social development functioning from age 6 months to 81 months ($n = 8,801$) and IQ at 8 years ($n = 5,449$)	Parent report on the strengths and difficulties questionnaire, a developmental screener, and an abbreviated IQ test	Compared with offspring of mothers who reported >340 g of sea fish per week, offspring whose mothers reported no sea fish intake during pregnancy were significantly more likely to evidence suboptimal prosocial, fine motor, communication, and social development in toddlerhood and preschool and lower verbal IQ at age 8 years with odds ratios ranging from 1.18 ($P < 0.001$) for fine motor skills at 18 months to 1.45 ($P < 0.0001$) for IQ at 8 years
Makrides et al. (2010) ³⁸	RCT	Follow-up of offspring from 2,399 healthy Australian women average age of 28.9 years: 726 offspring at age 18 months	Mothers of 351 offspring randomized to DHA supplementation (800 mg/day) and 375 to placebo beginning at 20 weeks of gestation	Bayley scales of infant development at age 18 months	Mean cognitive and language scores did not differ between the two groups; significantly fewer children from the DHA group had cognitive scores in the delayed range compared with controls (3.1% versus 6.4%)
Escalano-Margarit et al. (2011) ⁶⁰	RCT	Follow-up of offspring from 315 healthy European women: 167 offspring at age 4 years and 148 offspring at age 5.5 years	Mothers randomized to DHA supplementation (500 mg/day), 37 to DHA + 400 µg of folate, 40 to 400 µg of folate, and 47 to placebo beginning at 20 weeks of gestation	Fine motor, gross motor, posture and muscle tone, reflexes, balance, and perceptual-motor development at ages 4 and 5 years	No group differences at either age; however, cord blood and maternal DHA levels at delivery were higher among children with optimal neurodevelopmental scores compared with suboptimal scores at age 5 years (5.0 versus 2.9; $P < 0.001$)
Kohlboeck et al. (2011) ⁵⁷	Observational	416 children from 3,097 births for whom cord blood and follow-up data at age 10 years were available	Test association between DHA levels in cord blood and later emotional and behavioral functioning	Parent report on the strengths and difficulties questionnaire at age 10 years	Significant negative association between DHA levels in cord blood and overall behavior problem scores at age 10 years: (exp)β = 0.94; $P < 0.001$
Judge et al. (2012) ⁶²	RCT	48 healthy women aged 18–35 years; 69% Hispanic, 12.5% African American, 6.3% white	27 participants randomized to 3, 5, or 7 cereal bars/week each containing DHA (300 mg/bar) and 21 participants to placebo bars beginning at 24 weeks of gestation	Neonatal sleep–wake states on postnatal days 1 and 2	Offspring of mothers receiving DHA evidenced fewer arousals during quiet (2.70 versus 3.55) and active (17.41 versus 24.04) sleep on postnatal day 1 and fewer arousals during quiet sleep (3.55 versus 5.44) on postnatal day 2
Carlson et al. (2013) ⁵⁵	RCT	350 healthy women aged 16–35.9 years; 9.2% Hispanic, 41% African American, 49.8% white	178 participants randomized to DHA supplementation (600 mg/day) and 172 to placebo beginning at 8–20 weeks of gestation	Gestation, birth weight and length, head circumference	Offspring of mothers receiving DHA were less likely to be born prior to 34 weeks of gestation (0.6% versus 4.8%) and were less likely to have a birth weight of <1,500 g (0% versus 3.4%)
Gustafson et al. (2013) ⁶¹	RCT	67 healthy women aged 16–35.9 years; 37.3% African American, 46.3% white, 13.4% Hispanic, 3% Asian	35 participants randomized to DHA supplementation (600 mg/day) and 32 to placebo beginning at 12–20 weeks of gestation	Fetal heart rate and variability at 24, 32, and 36 weeks; neonatal behavioral assessment scale scores at 1–14 days	Offspring of mothers receiving DHA showed significantly higher heart rate variability (e.g., root mean square of successive differences = 6.5 for DHA group versus 4.8 for placebo at 36 weeks of gestation) and received higher scores on autonomic (18.13 versus 14.83) and motor (26.07 versus 23.08) scores on the neonatal behavioral assessment scale

Abbreviations: DHA, docosahexaenoic acid; RCT, random controlled trial.

typically elicited by olfactory bulbectomy, a manipulation that results in a phenotype consistent with depression in humans.⁵⁴

To date, studies of DHA levels in pregnant women and the impact on their offspring have been largely focused on immediate birth outcomes including birth weight, infant head circumference, and length of gestation. In a recently completed RCT of DHA supplementation during the second half of pregnancy in approximately 300 women, DHA supplementation resulted in significantly longer gestation, heavier and longer newborns, and offspring with larger head circumferences.⁵⁵

A few investigators have observed an association between DHA consumption during pregnancy and later child developmental functioning. Using a population-based sample of close to 12,000 women, Hibbeln et al.⁵⁶ tested the association between maternal report of seafood consumption during pregnancy and offspring development. Women who reported greater psychosocial adversity, including lower education and overcrowding in the home, were less likely to consume three or more servings of fish per week. After controlling for these psychosocial factors, however, low or no fish consumption during pregnancy was significantly associated with suboptimal communication skills, verbal IQ, fine motor skills, and social communication in the child, with findings extending out to age 8 years. In another observational study, a test of the association between levels of fatty acids in cord blood and maternal report of behavioral and emotional problems in children at 10 years of age revealed significant negative associations; higher levels of fatty acids were associated with lower levels of behavior problems.⁵⁷

The results of studies evaluating offspring neurodevelopment have been mixed among the few double-blind, randomized, controlled studies of DHA supplementation during pregnancy in humans. Helland et al.⁵⁸ assigned 341 women to receive either 10 mL/day of cod liver oil (1,183 mg DHA) or corn oil beginning at gestational week 18 and continuing through postpartum month 3. All of the mothers breastfed their infants during this period. At the age of 4 years, the children's cognitive development was assessed. Children whose mothers received cod liver oil during pregnancy had IQ scores that were significantly higher than children whose mothers received corn oil during pregnancy (IQ, 106.4 versus 102.3; $P < 0.05$). Even after controlling for birth outcomes, cod liver oil intake during infancy, and other potential confounding variables, maternal intake of cod liver oil during pregnancy was the only significant predictor of IQ at age 4 years. These effects were not maintained at age 7 years.⁵⁹ Positive associations between DHA supplementation

and offspring neurodevelopment in another RCT were observed only when the odds of scoring in the highest range as a function of DHA levels in cord blood were tested.⁶⁰ Other RCTs of DHA supplementation during pregnancy have resulted in higher heart rate variability and higher scores on the neonatal behavioral assessment scale⁶¹ and in more protected sleep during the neonatal period.⁶²

In the DHA to Optimize Mother Infant Outcome Study, a large RCT of DHA supplementation in a community sample of pregnant Australian women, supplementation resulted in fewer preterm births. However, there were no effects on later cognitive functioning assessed in a subsample of children at age 18 months.³⁸ One possible reason for the mixed findings in humans is that DHA effects may be observed primarily in vulnerable populations with respect to maternal health or under conditions of stress with respect to offspring functioning. In the majority of experimental animal studies, effects of DHA on offspring functioning were observed under conditions of manipulated prenatal stress and/or manipulated stress exposure in the offspring as opposed to typical functioning. Even in the DHA to Optimize Mother Infant Outcome Study there was evidence of efficacy among subpopulations. Although mean cognitive scores did not differ between the two groups, toddlers in the control groups were more likely than toddlers in the DHA group to have scores in the delayed range.³⁸

POTENTIAL FOR IMPROVING MENTAL HEALTH OUTCOMES IN VULNERABLE POPULATIONS VIA FATTY ACID SUPPLEMENTATION DURING PREGNANCY

The extant data support the following hypotheses: that prenatal stress confers neurodevelopmental risks in offspring; that DHA supports a more modulated response to stress; that DHA levels during pregnancy are associated with neurodevelopment in offspring; and that supplementing the diet of mothers with DHA during pregnancy can lead to more optimal outcomes in the child. Importantly, research using animal models shows that DHA administration during pregnancy attenuates the effects of prenatal stress on offspring neurodevelopment. Although the literature on both animals and humans supports the hypothesis that fatty acid supplementation may be most beneficial for pregnant women exposed to high levels of stress, to date no investigator has tested whether supplementing the diets of women who are experiencing acute and/or chronic stress will improve maternal health and reduce the suboptimal development outcomes in humans.

In the United States, higher levels of acute and chronic stress are found among families living in

low-income environments than among families living in other income environments; neighborhood disorder, lack of safety, and exposure to violence are all significantly higher in areas with lower per capita income.^{63,64} African Americans live in poverty at a disproportionately high rate of more than a quarter.⁶⁵ Pregnant women living in poverty are at higher risk for poor nutrition during pregnancy⁶⁶ and are more likely to experience pregnancy complications.¹⁸ This is especially true for African American women living in urban low-income environments.²²

Greater exposure to psychosocial stress during the prenatal period has been hypothesized to be a primary mechanism by which poverty confers risk for physical and mental health disorders to the offspring.^{67,68} This is a viable hypothesis given the data on the impact of race and poverty on the functioning of the HPA axis and stress reactivity. Higher levels of cortisol in the afternoon and evening were found among individuals living in a low socioeconomic environment compared to individuals living in a high socioeconomic environment.⁶⁹ Within a sample of postmenopausal women caring for a disabled family member, African American women were more likely to demonstrate a significant increase in cortisol in response to a psychosocial stressor than were European American women.⁷⁰ Race differences in HPA-axis functioning and stress reactivity were also observed during pregnancy. High levels of cumulative stress were associated with elevations in corticotropin-releasing hormone, a key factor in HPA-axis regulation, among pregnant African American women but not among pregnant Hispanic women.⁷¹ Data from studies that used exposure to a controlled stressor provide evidence for racial differences in inflammatory response (i.e., interleukin-6) to stress, with African American pregnant and nonpregnant women showing higher responses than European American pregnant and nonpregnant women.⁷² In a study in which both cortisol and proinflammatory cytokines were measured during pregnancy, minority race and low-income status were characterized by high levels of cortisol without a compensatory decrease in cytokines, suggesting impaired feedback between the neuroendocrine and immune systems.⁷³

Thus, race and socioeconomic status appear to impact both the diurnal rhythm and feedback loop of the stress response system as well as the interface between the HPA axis and other systems critical for maintaining health, such as immune functioning. These data provide further support for the hypothesis that health disparities among racial minorities and families living in poverty may be due, in part, to differential exposure to prenatal stress. Research aimed at reducing prenatal stress among vulnerable populations could

have a significant impact on the mental health of children.

CONCLUSION

In summary, several areas of research converge to support future investigations of the efficacy of prenatal fatty acid supplementation as a preventive intervention for child mental health problems. First, a primary means by which prenatal stress affects offspring development is via exposure of the fetus to high levels of glucocorticoids released by the mother. Second, experimental data in animals demonstrate that DHA supplementation can buffer such effects and protect the integrity of systems involved in cognition as well as behavior and emotion regulation. Third, RCTs of fatty acid supplementation in humans support positive effects on gestational length and provide some evidence for more optimal neurodevelopment in the offspring. This research focus on prenatal DHA supplementation in humans has not yet been applied to vulnerable populations, nor have dimensions of psychological functioning been assessed as outcome measures. Future research is needed to determine whether DHA supplementation is associated with a more modulated response to stress and more optimal behavioral and emotional regulation in the human infant, even within the context of exposure to significant prenatal stress. If such an association can be established, then a comprehensive program of research on the mechanisms by which these associations evolve can be launched, with the aim of informing the prevention of suboptimal mental health outcomes among vulnerable children.

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REFERENCES

1. Chapillon P, Patin V, Roy V, et al. Effects of pre-and postnatal stimulation on developmental, emotional, and cognitive aspects in rodents: a review. *Devel Psychobiol.* 2002;41:373–387.
2. Weinstock M. The potential influence of maternal stress hormones on development and mental health of the offspring. *Brain Behav Immun.* 2005;19:296–308.
3. Schneider ML, Moore CF, Kraemer GW, et al. The impact of prenatal stress, fetal alcohol exposure, or both on development: perspectives from a primate model. *Psychoneuroendocrinology.* 2002;27:285–298.
4. Keenan K, Bartlett TQ, Nijland M, et al. Poor nutrition during pregnancy and lactation negatively impacts neurodevelopment of the offspring: evidence from a translational primate model. *Am J Clin Nutr.* 2013;98:396–402.
5. Coe CL, Lulbach GR, Schneider ML. Prenatal disturbance alters the size of the corpus callosum in young monkeys. *Devel Psychol.* 2002;41:178–185.
6. Henry C, Kabbaj M, Simon H, et al. Prenatal stress increases the hypothalamic-pituitary-adrenal axis response to stress in young and adult rats. *J Endocrinol.* 1994;6:341–345.

7. Weinstock M. Does prenatal stress impair coping and regulation of hypothalamic-pituitary-adrenal axis? *Neurosci Biobehav Rev.* 1997;21:1–10.
8. Glover V, Bergman K, Sarkar P, et al. Association between maternal and amniotic fluid cortisol is moderated by maternal anxiety. *Psychoneuroendocrinology.* 2009; 34:430–435.
9. O'Donnell KJ, Bugge Jensen A, Freeman L, et al. Maternal prenatal anxiety and downregulation of placental 11 β -HSD2. *Psychoneuroendocrinology.* 2012;37:818–826.
10. Seckl JR. Glucocorticoids, feto-placental 11 beta-hydroxysteroid dehydrogenase type 2, and the early life origins of adult disease. *Steroids.* 1997;62:89–94.
11. Lou HC, Hansen D, Nordentoft M, et al. Prenatal stressors of human life affect fetal brain development. *Devel Med Child Neurol.* 1994;36:826–832.
12. Dayan J, Creveuil C, Marks MN, et al. Prenatal depression, prenatal anxiety, and spontaneous preterm birth: a prospective cohort study among women with early and regular care. *Psychosomatic Med.* 2006;68:938–946.
13. Wadhwa PD, Sandman CA, Porto M, et al. The association between prenatal stress and infant birth-weight and gestational-age at birth: a prospective investigation. *Am J Obstetrics Gynecol.* 1993;169:858–865.
14. Keenan K, Gunthorpe D, Grace D. Parsing the relations between SES and stress reactivity: examining individual differences in neonatal stress response. *Infant Behav Devel.* 2007;30:134–145.
15. O'Connor TG, Ben-Shlomo Y, Heron J, et al. Prenatal anxiety predicts individual differences in cortisol in pre-adolescent children. *Biol Psychiatry.* 2005;58: 211–217.
16. Huizink AC, Robles de Medina PG, Mulder EIJ, et al. Psychological measures of prenatal stress as predictors of infant temperament. *J Am Acad Child Adolesc Psychiatry.* 2002;41:1078–1085.
17. Talge NM, Neal C, Glover V. The Early Stress, Translational Research and Prevention Science Network: Fetal and Neonatal Experience on Child and Adolescent Mental Health. Antenatal maternal stress and long-term effects on child neurodevelopment: how and why? *J Child Psychol Psychiatry.* 2007;48: 245–261.
18. Giscombé CL, Lobel M. Explaining disproportionately high rates of adverse birth outcomes among African Americans: the impact of stress, racism, and related factors in pregnancy. *Psychol Bull.* 2005;131:662–683.
19. Noble KG, McCandless BD, Farah MJ. Socioeconomic gradients predict individual differences in neurocognitive abilities. *Dev Sci.* 2007;10:464–480.
20. Reiss F. Socioeconomic inequalities and mental health problems in children and adolescents: a systematic review. *Soc Sci Med.* 2013;90:24–31.
21. Ruth CA, Roos N, Hildes-Ripstein E, et al. The influence of gestational age and socioeconomic status on neonatal outcomes in late preterm and early term gestation: a population based study. *BMC Pregnancy Childbirth.* 2012;12:62.
22. Kent ST, McClure LA, Zaitchik BF, et al. Area-level risk factors for adverse birth outcomes: trends in urban and rural settings. *BMC Pregnancy Childbirth.* 2013;13:129.
23. Walker CD. Nutritional aspects modulating brain development and the responses to stress in early neonatal life. *Prog Neuro-psychopharmacol Biol Psychiatry.* 2005; 29:1249–1263.
24. English JA, Harauma A, Föcking M, et al. Omega-3 fatty acid deficiency disrupts endocytosis, neurogenesis, and mitochondrial protein pathways in the mouse hippocampus. *Front Genet.* 2013;4:208.
25. Decsi T, Koletzko B. N-3 fatty acids and pregnancy outcomes. *Curr Opin Clin Nutr Metab Care.* 2005;8:161–166.
26. Uauy R, Dangour AD. Nutrition in brain development and aging: role of essential fatty acids. *Nutr Rev.* 2006;64(Suppl):S24–S33.
27. Riediger ND, Othman RA, Suh M, et al. A systemic review of the roles of n-3 fatty acids in health and disease. *J Am Diet Assoc.* 2009;109:668–679.
28. Assisi A, Banzi R, Buonocore C, et al. Fish oil and mental health: the role of n-3 long-chain polyunsaturated fatty acids in cognitive development and neurological disorders. *Int Clin Psychopharmacol.* 2006;21:319–336.
29. Barker D. The fetal origins of adult disease. *Proc R Soc Lond B Biol Sci.* 1995;262: 37–43.
30. Ailhaud G, Massiera F, Weill P, et al. Temporal changes in dietary fats: role of n-6 polyunsaturated fatty acids in excessive adipose tissue development and relationship to obesity. *Progress in Lipid Res.* 2006;45:203–236.
31. Blasbalg TL, Hibbeln JR, Ramsden CE, et al. Changes in consumption of omega-3 and omega-6 fatty acids in the United States during the 20th century. *Am J Clin Nutr.* 2011;93:950–962.
32. Micha R, Khatibzadeh S, Shi P, et al; Global Burden of Diseases Nutrition and Chronic Diseases Expert Group NutriCoDE. Global, regional, and national consumption levels of dietary fats and oils in 1990 and 2010: a systematic analysis including 266 country-specific nutrition surveys. *BMJ.* 2014;348: g2272.
33. Stark KD, Beblo S, Murthy, M, et al. Comparison of bloodstream fatty acid composition from African-American women at gestation, delivery, and postpartum. *J Lipid Res.* 2005;45:516–525.
34. Escolano-Margarit MV, Campoy C, Ramirez-Tortosa MC, et al. Effects of fish oil supplementation on the fatty acid profile in erythrocyte membrane and plasma phospholipids of pregnant women and their offspring: a randomised controlled trial. *Br J Nutr.* 2013;109:1647–1656.
35. Cabrera-Vera TM, Garcia F, Pinto W, et al. Effect of prenatal fluoxetine (Prozac) exposure on brain serotonin neurons in prepubescent and adult male rat offspring. *J Pharmacol Exp Ther.* 1997;280:138–145.
36. Coleman FH, Christensen HD, Gonzalez CL, et al. Behavioral changes in developing mice after prenatal exposure to paroxetine (Paxil). *Am J Obstet Gynecol.* 1999;181: 1166–1171.
37. Marangell LB, Martinez JM, Zboyan HA, et al. A double-blind, placebo-controlled study of the omega-3 fatty acid docosahexaenoic acid in the treatment of major depression. *Am J Psychiatry.* 2003;160:996–998.
38. Makrides M, Gibson RA, McPhee AJ, et al; DOMInO Investigative Team. Effect of DHA supplementation during pregnancy on maternal depression and neurodevelopment of young children: a randomized controlled trial. *JAMA.* 2010;304: 1675–1683.
39. Mozurkewich EL, Clinton CM, Chilimigras JL, et al. The Mothers, Omega-3, and Mental Health Study: a double-blind, randomized controlled trial. *Am J Obstet Gynecol.* 2013;208:313. e1–e9.
40. Deligiannidis KM, Freeman MP. Complementary and alternative medicine for the treatment of depressive disorders in women. *Psychiatr Clin North Am.* 2010;33:441–463.
41. Takeuchi T, Iwanaga M, Harada E. Possible regulatory mechanism of DHA-induced anti-stress reaction in rats. *Brain Res.* 2003;964:136–143.
42. Rousseau D, Moreau D, Raederstorff D, et al. Is a dietary n-3 fatty acid supplement able to influence the cardiac effect of the psychological stress? *Mol Cell Biochemistry.* 1998;178:353–366.
43. Maes M, Christophe A, Bosmans E, et al. In humans, serum polyunsaturated fatty acid levels predict the response of proinflammatory cytokines to psychologic stress. *Biol Psychiatry.* 2000;47:910–920.
44. Hellhammer J, Hero T, Franz N, et al. Omega-3 fatty acids administered in phosphatidylserine improved certain aspects of high chronic stress in men. *Nutr Res.* 2012;32:241–250.
45. Yehuda S, Rabinovitz S, Mostofsky DI. Mixture of essential fatty acids lowers test anxiety. *Nutr Neurosci.* 2005;8:265–267.
46. Delarue J, Matzinger O, Binnert C, et al. Fish oil prevents the adrenal activation elicited by mental stress in healthy men. *Diabetes Metab.* 2003;29: 289–295.
47. Rioux FM, Lindmark G, Hernell O. Does inadequate maternal iron or DHA status have a negative impact on an infant's functional outcomes? *Acta Paediatrica.* 2006;95:137–144.
48. McNamara RK, Carlson SE. Role of omega-3 fatty acids in brain development and function: potential implications for the pathogenesis and prevention of psychopathology. *Prostaglandins, Leukot Essent Fatty Acids.* 2006;75: 329–349.
49. Fernstrom JD. Effects of dietary polyunsaturated fatty acids on neuronal function. *Lipids.* 1999;32:161–169.
50. Moriguchi T, Griener RS, Salem, N. Behavioral deficits associated with dietary induction of decreased brain docosahexaenoic acid concentration. *J Neurochem.* 2000;75:2563–2573.
51. Chen HF, Su HM. Fish oil supplementation of maternal rats on an n-3 fatty acid-deficient diet prevents depletion of maternal brain regional docosahexaenoic acid levels and has a postpartum anxiolytic effect. *J Nutr Biochem.* 2012;23:299–305.
52. Palsdottir V, Månsson JE, Blomqvist M, et al. Long-term effects of perinatal essential fatty acid deficiency on anxiety-related behavior in mice. *Behav Neurosci.* 2012;126:361–369.
53. Feng Z, Zou X, Jia H, et al. Maternal docosahexaenoic acid feeding protects against impairment of learning and memory and oxidative stress in prenatally stressed rats: possible role of neuronal mitochondria metabolism. *Antioxid Redox Signal.* 2012;16:275–289.
54. Pudell C, Vicente BA, Delattre AM, et al. Fish oil improves anxiety-like, depressive-like and cognitive behaviors in olfactory bulbectomized rats. *Eur J Neurosci.* 2014; 39:266–274.
55. Carlson SE, Colombo J, Gajewski BJ, et al. DHA supplementation and pregnancy outcomes. *Am J Clin Nutr.* 2013;97:808–815.
56. Hibbeln JR, Davis JM, Steer C, et al. Maternal seafood consumption in pregnancy and neurodevelopmental outcomes in childhood (ALSPAC study): an observational cohort study. *Lancet.* 2007;369:578–585.
57. Kohlboeck G, Glaser C, Tiesler C, et al; LISAPlus Study Group. Effect of fatty acid status in cord blood serum on children's behavioral difficulties at 10 y of age: results from the LISAPlus Study. *Am J Clin Nutr.* 2011;94:1592–1599.
58. Helland IB, Smith L, Saarem K, et al. Maternal supplementation with very-long-chain n-3 fatty acids during pregnancy and lactation augments children's IQ at 4 years of age. *Pediatrics.* 2003;111:39–44.
59. Helland IB, Smith L, Blomén B, et al. Effect of supplementing pregnant and lactating mothers with n-3 very-long-chain fatty acids on children's IQ and body mass index at 7 years of age. *Pediatrics.* 2008;122:e472–e479.
60. Escolano-Margarit MV, Ramos R, Beyer J, et al. Prenatal DHA status and neurological outcome in children at age 5.5 years are positively associated. *J Nutr.* 2011; 141:1216–1223.
61. Gustafson KM, Carlson SE, Colombo J, et al. Effects of docosahexaenoic acid supplementation during pregnancy on fetal heart rate and variability: a randomized clinical trial. *Prostaglandins Leukot Essent Fatty Acids.* 2013;88:331–338.

62. Judge MP, Cong X, Harel O, et al. Maternal consumption of a DHA-containing functional food benefits infant sleep patterning: an early neurodevelopmental measure. *Early Hum Dev.* 2012;88:531–537.
63. Evans GW. A multi-methodological analysis of cumulative risk and allostatic load among rural children. *Devel Psychol.* 2003;39:924–933.
64. Ewart CK, Suchday S. Discovering how urban poverty and violence affect health: development and validation of a neighborhood stress index. *Health Psychol.* 2002;21:254–262.
65. DeNavas-Walt C, Proctor BD. U.S. Census Bureau Current Population Reports, P60-249, Income and Poverty in the United States. Washington, DC: U.S. Government Printing Office; 2014.
66. Fowles ER, Gabrielson ML. First trimester predictors of diet and birth outcomes in low-income pregnant women. *J Commun Health Nurs.* 2005;22:117–130.
67. Reynolds RM, Labad J, Buss C, et al. Transmitting biological effects of stress in utero: implications for mother and offspring. *Psychoneuroendocrinology.* 2013;38:1843–1849.
68. Robinson M, Oddy WH, Li J, et al. Pre- and postnatal influences on preschool mental health: a large-scale cohort study. *J Child Psychol Psychiatry.* 2008;49:1118–1128.
69. Chen E, Paterson LQ. Neighborhood, family, and subjective socioeconomic status: how do they relate to adolescent health? *Health Psychol.* 2006;25:704–714.
70. Wilcox S, Bopp M, Wilson DK, et al. Race differences in cardiovascular and cortisol responses to an interpersonal challenge in women who are family caregivers. *Ethnic Dis.* 2005;15:17–24.
71. Tse AC, Rich-Edwards JW, Koenen K, et al. Cumulative stress and maternal prenatal corticotropin-releasing hormone in an urban U.S. cohort. *Psychoneuroendocrinology.* 2012;37:970–979.
72. Christian LM, Glaser R, Porter K, et al. Stress-induced inflammatory responses in women: effects of race and pregnancy. *Psychosom Med.* 2013;75:658–669.
73. Corwin EJ, Guo Y, Pajer K, et al. Immune dysregulation and glucocorticoid resistance in minority and low-income pregnant women. *Psychoneuroendocrinology.* 2013;38:1786–1796.