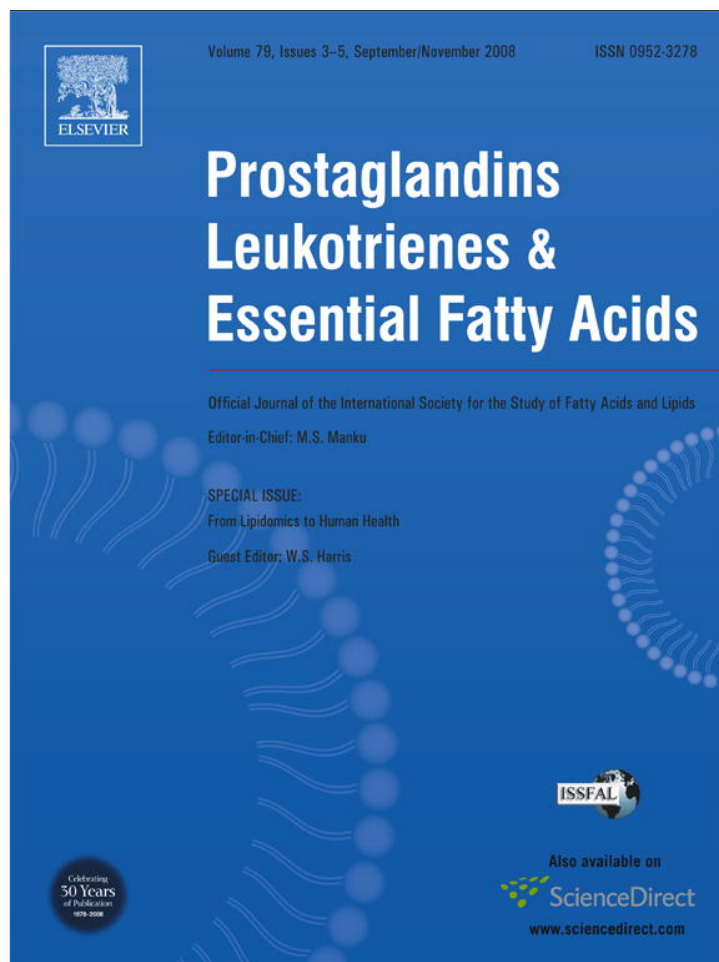


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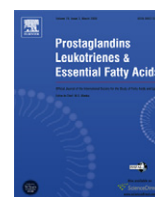
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Docosahexaenoic acid and cognitive function: Is the link mediated by the autonomic nervous system?

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A B S T R A C T

Docosahexaenoic acid is a long-chain polyunsaturated fatty acid that is found in large quantity in the brain and which has repeatedly been observed to be related in positive ways to both cognitive function and cardiovascular health. The mechanisms through which docosahexaenoic acid affects cognition are not well understood, but in this article, we propose a hypothesis that integrates the positive effects of docosahexaenoic acid in the cognitive and cardiovascular realms through the autonomic nervous system. The autonomic nervous system is known to regulate vital functions such as heart rate and respiration, and has also been linked to basic cognitive components related to arousal and attention. We review the literature from this perspective, and delineate the predictions generated by the hypothesis. In addition, we provide new data showing a link between docosahexaenoic acid and fetal heart rate that is consistent with the hypothesis.

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1. The effects of DHA

Docosahexaenoic acid (DHA, 22:6n-3) is a long-chain polyunsaturated fatty acid (LC-PUFA) member of the *n*-3 fatty acid family found in all cell membranes. Because the accumulation of fatty acids in cell membranes is influenced by the kind and amount of *n*-3 fatty acids in the diet, there exists the potential for dietary fatty acids to influence many physiological functions.

1.1. Cardiovascular function

The best documented effects of DHA are in the realm of cardiovascular function. Studies in adults have shown that fish consumption and marine LC-PUFA supplementation lowers the risk of arrhythmias and reduces both blood pressure and heart rate (HR) [1,2]. Increased heart rate variability (HRV) with greater vagal predominance has also been reported with consumption of these fatty acids. Reduced HR and increased HRV results in higher stroke volume (a secondary effect of lower vascular resistance) and improved filling [3]. A meta-analysis of 30 randomized controlled trials provided evidence that fish oil consumption effectively lowers HR in humans, either directly or indirectly, by influencing cardiac electrophysiology and thereby improves

autonomic tone, vascular resistance and ventricular efficiency that ultimately has a favorable effect on cardiovascular health [4].

1.2. Behavioral and cognitive development

It has also been established that DHA is important in early development. Over the past several decades, evidence has been accumulating on positive effects on sensory, cognitive, and behavioral function. The initial outcome measured was visual acuity and that showed positive effects of DHA status and supplementation, though not in all studies [5]. Less frequently, clinical trials of DHA supplementation during gestation and infancy have studied and found benefits on behavioral development, including improved performance on global developmental tests [6], higher order cognitive tasks and intelligence [7,8].

The biological effects of variable DHA in neuronal membranes include alterations in membrane biophysics and in the regulation of cell signaling and cell proliferation [9]. However, the causal path through which DHA affects behavioral and cognitive development is not at all clearly conceptualized. DHA is found in many brain structures [10], so its effects may be specifically linked to the timing and location of neuronal deposition during development. Effects on attention have been found with variable DHA exposure or status in early development [11,12].

Attention is among the most basic cognitive functions. The most fundamental conceptualization of the construct of attention is as a behavioral state that is closely associated with concepts of

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alertness and arousal [13,14] that enhances or facilitates learning [15]. The brain regions centrally responsible for initiating, sustaining, and modulating attention are among the same regions that mediate vital functions such as respiration, sleep–wake cycles, and cardiac activity and control [16].

In this article we will explore and develop the hypothesis that the effects of DHA on cardiac and cognitive function may be achieved through effects on the autonomic nervous system (ANS). To accomplish this, we will briefly review the nature of the ANS, the linkages between cardiac and cognitive function as mediated by the ANS and the relevant literature on the relation of DHA to ANS function. New data on the association between DHA supplementation in pregnancy and fetal HR that is in accord with the hypothesis will be presented. We will end with a delineation of the directions for future study that the hypothesis suggests.

2. The autonomic nervous system

The ANS maintains internal homeostasis of the organism by regulating functions of heart muscle, smooth muscle and hormone secretion [17]. The peripheral ANS is separated into two anatomically and functionally different divisions, the sympathetic nervous system and the parasympathetic (vagal) nervous system. The peripheral ANS is controlled by the central nervous system (CNS) through complex neuronal interconnections that form a functional entity known as the central autonomic network (CAN) [18]. The output of the CAN is mediated through preganglionic sympathetic and parasympathetic neurons that innervate the heart via the stellate ganglia and vagus nerve. The interaction of these inputs to the sino-atrial node of the heart is the source of variability and control of HR; thus HRV is an index of central-peripheral neural feedback and CNS–ANS integration. Through the CAN, the brain controls visceromotor, neuroendocrine, pain and behavioral responses essential for behavior, adaptability and survival [18].

Respiratory sinus arrhythmia (RSA) is the high-frequency HRV linked to the respiratory cycle and is a reflection of the phasic vagal control of the heart, (i.e., “vagal tone”). Respiration alters HR via the myelinated vagus, originating in the nucleus ambiguus and terminating at the sino-atrial node. HR increases during inspiration and decreases during expiration. On an electrocardiogram, this is seen as a shortening and lengthening of the R-R interval (heart period) that results in an oscillatory pattern in the HR trace at the same frequency as the respiratory cycle.

Recently, the broader health significance of autonomic balance and vagal function has been recognized. Autonomic imbalance occurs when one branch of the ANS dominates over the other, more often sympathetic hyperactivity or parasympathetic hypoactivity [19]. When the inhibitory influences of the parasympathetic nervous system are deficient, an autonomic imbalance occurs and this has been associated with increased morbidity and all-cause mortality [20]. The model of neurovisceral integration emphasizes the importance of higher order brain systems, such as the medial prefrontal cortex, that are involved in cognitive and affective processes, and proposes that inhibitory control over sympatho-excitatory circuits in the brainstem is vital to preservation of the organism and key to good health [21].

2.1. The ANS and modulation of HR in development

Early in gestation, fetal HR is primarily under control of the sympathetic nervous system [22]. As the parasympathetic nervous system matures, fetal HR decreases from an average 175 bpm in the first trimester to 140 bpm at term [23]. With increasing gestational age and increased influence from the

parasympathetic nervous system, HR becomes more variable. Around 30 weeks gestational age (GA), distinct HR patterns associated with fetal activity states begin to emerge [24].

Developmental increases in cardiac vagal activity serve as an index of the developmental changes in the ability of the ANS to mediate physiological and behavioral activity [25]. This is the precursor for emotional, cognitive and behavioral regulation [26]. There is evidence that inter-individual differences in HR and HRV persist from prenatal to postnatal life [27,28]. Measures of heart period (R-R interval) and RSA are frequently used as an index of the physiological foundation of infant behaviors and to predict later developmental outcomes [29,30]. There are significant developmental increases in heart period and RSA from 4 months to 4 years of age [31] which continue until at least 7 years of age [32], paralleling the development of behavioral self regulation [33]. Assessing vagal function, as indexed by RSA, has become a useful and important index of autonomic control and reactivity in studies of disease, development, and psychological research.

2.2. The ANS and cognition

The ANS has been linked with many cognitive functions, particularly with functions that facilitate learning. At the turn of the 20th century, the Yerkes–Dodson law [34] articulated the nature of the relationship between arousal and performance, thus implicitly integrating ANS output with cognitive ability. ANS functions were subsequently linked to many aspects of psychological function [35]. Perhaps the clearest link between ANS function and the fundamental steps of information processing involves the physiological changes to the occurrence of an event [36]. The orienting reflex (OR); which is a cluster of behavioral and physiological responses that occur in response to a novel or unexpected stimuli, has been historically linked to exploration and learning [37,38]. When a stimulus occurs, there is a clear behavioral response that indicates the initiation of attention (i.e., the direction of the sensory receptors toward the source or location of the stimulus). This behavioral response is also accompanied by autonomic indicators, such as changes in HR, respiration, skin conductance, pupil size and motor activity. Subsequent formulations attempted to refine and dissociate different response components from the autonomically driven OR; for example, Graham and Clifton [39] concluded that more intense or threatening stimuli tend to activate the sympathetic nervous system (e.g., cardiac acceleration) while stimuli eliciting interest or curiosity would activate parasympathetic responses (e.g., cardiac deceleration). The Lacey's [40,41] proposed a similar, but more wide-ranging model termed “directional fractionation,” in which parasympathetic activation represented stimulus intake, and sympathetic activation represented stimulus avoidance [42]. In considering the link between ANS function and cognition, it is critical to note that parasympathetic driven responses (cardiac deceleration, slowed respiration, pupil dilation, reduced skin conductance) to stimuli or events have the presumed effect of reducing random or unwanted “noise” in the CNS, a fundamental characteristic of attention and a facilitator of learning [13]. Sympathetic activation more closely characterizes increased arousal which, as noted above, is a more phasic moderator of cognitive performance.

A discussion of the mechanisms through which ANS and cognitive functions are mediated are beyond the scope and page limitations of the current paper. It has been suggested that ANS changes in attention are a result of the behavioral events that occur in response to a stimulus or event [43]. However, the more widely accepted notion at this time [33,44] posits that the ANS changes seen at the initiation of cognitive functions such as

attention and arousal are attributable to a common, neurally regulated mechanism. Evidence supports the existence of such a mechanism at the level of mammalian brain stem organization; this is mediated by a dual vagal complex and that links autonomic processes in particular with attention, action, and other psychological constructs such as emotion. Indeed, four ascending brainstem systems have been integrally implicated in attention and arousal, and in the modulation of various forms of cognitive behavior [45–48]. This suggests that measures of cardiovascular response to stimuli (in particular, measures of variability such as vagal tone derived from RSA) will be associated with various developmental and adult cognitive and affective outcomes. At this point, there is considerable evidence in its favor of this model [49]. The links between ANS function and cognition are bidirectional; that is, initiation of physiological changes will produce changes in attention and arousal, and initiation of attention and arousal will produce changes in ANS indicators.

Infant autonomic control is linked to the degree of maturation and integrity of the ANS. Small for gestational age and preterm infants with decreased vagal function are more vulnerable, less able to adjust quickly to stressful stimuli and are shown to have suboptimal neurodevelopmental outcomes [29,50,51]. Conversely, higher vagal activity and self regulation in infants has been positively correlated with higher Bayley scores [52], better social skills [29], shorter visual fixation duration [53], and increased attention [54].

2.3. DHA and ANS function

DHA is the second most abundant LC-PUFA in the CNS and with arachidonic acid (AA) constitutes approximately 50% of the total fatty acids in neuronal membrane phospholipids [9]. The developing fetus receives maternal DHA by transfer across the placenta and DHA accumulates in the CNS during the third trimester. After birth, the infant receives DHA from mother's milk or DHA-supplemented infant formula.

Between 30 and 34 weeks gestational age there is a period of rapid brain growth, myelination and synaptogenesis. Two important physiologic oscillators emerge during the third trimester: (1) the sleep–wake cycle where distinct quiet and active states are observed and (2) increased parasympathetic control over heart rhythms. While studies have investigated the importance of DHA intake for preterm and term infant visual and cognitive development, few studies have considered the influence of DHA on ANS maturation and regulation.

Observational studies of human milk-fed vs. formula-fed infants prior to 2002 when DHA was added to US infant formulas showed that human milk-fed infants had lower HR and higher HRV than their bottle formula-fed cohorts [55–57]. Recent experimental studies of LC-PUFA supplementation in human infants and non-human infant primates suggest that supplementation during infancy could have positive cardiovascular effects. Healthy Danish infants were supplemented with fish oil (or no oil) in cow's milk or infant formula from 9 to 12 months of age. Fish oil supplementation effectively increased red blood cell DHA levels and lowered HR with a trend towards higher HRV. These findings suggest that adding fish oil to the diet had a beneficial effect on HR in healthy infants similar to the effect seen in adults [58].

Three-year-old Rhesus monkeys fed formulas containing DHA and AA as infants had significantly higher HRV when under stress than monkeys fed formulas without DHA and AA [59]. It is notable that the dietary intervention was only from birth until weaning after which both groups were fed ordinary monkey chow without DHA and AA. Early dietary supplementation of DHA and AA appears to have induced a cardiac programming

effect that persisted well beyond the period of DHA and AA exposure.

Intrauterine exposure of DHA has also been shown to modulate sleep. Cheruku et al. [60] studied the sleep patterns of 1–2 day old infants and found that the infants born to women with higher plasma phospholipid DHA had more mature sleep-state patterning.

Healthy, human milk-fed newborns had superior arousability when newborn neurobehavioral outcomes were tested using the Brazelton Neonatal Behavioral Assessment Scale (NBAS). A few investigators have posited that enhanced arousability [61,62] and higher scores for orientation/engagement, emotional regulation, motor quality and total behavior scores using the NBAS [63] may be due to components in breast milk, including DHA. However, maternal breast milk DHA level is a reflection of maternal DHA stores available to the fetus during intrauterine transfer therefore; the positive behavioral effects seen in these studies are likely due to increased availability to the fetus in the 3rd trimester as opposed to DHA intake from breast milk after birth.

There have been several calls to examine the constructs of *arousal and attention* in studies of LC-PUFA status and supplementation in infancy and childhood [6,59]. Measures of attention appear to be particularly sensitive to DHA status, as evidenced by a number of studies showing positive results in infancy [11,12,64–66]. One study showed supplementation as specifically improving sustained attention performance in late childhood [67] although another showed improvements in most cognitive measures except attention [68].

There have been reports of abnormal LC-PUFA (DHA and/or AA) profiles in children with attention-deficit disorder [69–72]. These have motivated studies of remediation with supplementation of DHA, AA and/or gamma linolenic acid. Such supplementation universally increased LC-PUFAs in a positive direction; however, remediation was associated with improvement in symptoms in some [73,74] but not other trials [75,76].

3. New data: fetal HR and DHA supplementation

Fetal biomagnetometry has emerged as a reliable and sensitive tool for monitoring fetal ANS development [77–79]. Biomagnetic cardiac signals (magnetocardiogram or MCG) are measured by a detector that is inductively coupled to a superconducting quantum interference device (SQUID) that acts as a low-noise, high-gain, current-to-voltage converter. Fetal MCG offers the precision required for measures of HRV based on accurate detection of R-R intervals from 24 weeks GA to term. We have used MCG to obtain measures of fetal HR, HRV and fetal movements as part of a fetal neurobehavioral assessment [80].

The study was approved by the University of Kansas Medical Center Human Subjects Committee (protocol #9297). A total of 40 subjects were studied between 24 and 38 weeks gestation. The MCG was recorded using an investigational 83 channel dedicated fetal biomagnetometer (CTF systems, subsidiary of VSM MedTech Ltd.) housed in a magnetically shielded room to reduce the interference from external environmental magnetic fields. The data were acquired with a 300 Hz sampling rate over an 18 min recording session and digitally filtered offline. Multivariate data were presented to an Infomax ICA algorithm implemented in EEGLAB toolbox [81] in order to separate contributions from spatially distinct electrophysiologic sources. The fiducial points (R peaks) were automatically estimated by a template matching algorithm applied on the root-mean-square signal across channels. False negative and false positive detections were manually corrected. Fetal activity state was determined from the HR pattern [82]. Indices of HRV were determined from Poincaré plots [83]

where SD1 is a measure of short-term HRV, SD2 is a measure of overall HRV and the SD1:SD2 ratio is a measure of sympatho-vagal balance.

We recorded maternal prenatal vitamin and supplement use. All women reported taking prenatal vitamins. Out of these women, 10 reported consuming DHA or DHA/EPA supplements based on the recommendation of their health care provider or by their own choice. The average daily dose of DHA was 200 mg. All 10 women took the supplements during the 2nd and 3rd trimester. Fetal sex, activity state and GA were matched to an unsupplemented fetus and mean HR and HRV indices were compared. When possible, subjects were followed longitudinally but it was not possible to obtain data at every time point in all subjects. The total number of subjects (supplemented plus

unsupplemented control) for each GA tested are: 24 wks $n = 6$, 28 wks $n = 16$, 32 wks $n = 18$, 36 wks $n = 16$, 38 wks $n = 12$.

Fetal HR from 24 to 38 weeks GA is shown in Fig. 1. There was no group difference in fetal HR at 24 and 28 weeks. However, from 32 to 38 weeks, fetal HR was significantly lower in the supplemented group when compared to unsupplemented. (32 wks, $p = .01$, 36 wks, $p = .02$, 38 wks, $p = .03$). Overall HRV (SD2) and the SD1:SD2 ratio did not differ between groups (data not shown). There was no difference in short-term HRV (SD1) at 24 and 28 weeks GA but at 32 weeks, short-term variability was higher in the supplemented group and this persisted to term. The difference was significant at 36 weeks ($p = .02$) (Fig. 2).

These are preliminary data and, as such, have several limitations. This was a convenience sample of women who

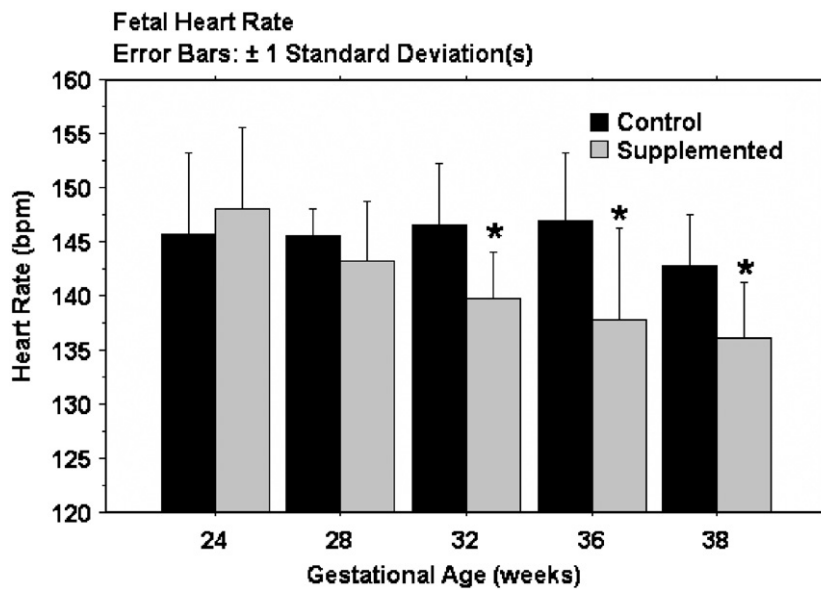


Fig. 1. Mean fetal HR (± 1 SD) in control (unsupplemented) and supplemented groups across gestational age. Mean HR for the supplemented group begins to diverge from the control group at 32 weeks and is consistently and significantly lower at 32, 36 and 38 weeks.

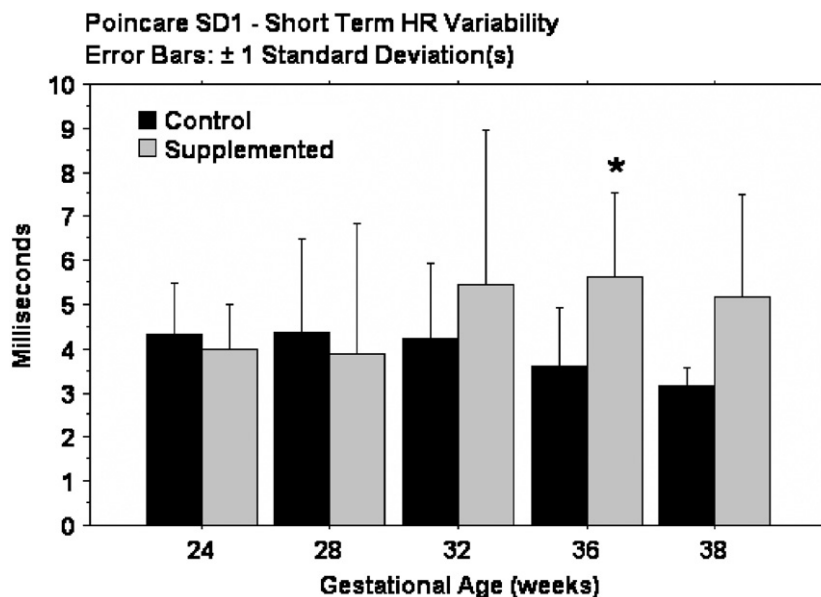


Fig. 2. Short term heart rate variability. There is no group difference in Poincare SD1, a measure of short term heart rate variability, between 24 and 28 weeks GA. At 32 weeks, short term HRV is higher in the supplemented group, significant at 36 weeks.

consumed DHA or DHA/EPA supplements during the 2nd and 3rd trimester of pregnancy, drawn from a larger pool of women with uncomplicated, singleton pregnancies. DHA intake was not controlled or monitored, there was no placebo group and we have no measure of maternal DHA status in either group. However, our preliminary, observational findings suggest that maternal DHA or DHA/EPA supplementation during pregnancy may result in lower fetal HR and higher cardiac vagal control and a larger, controlled study is planned.

4. Summary and conclusions

There were three aims of this paper. The first was to propose a hypothesis that sought to integrate the effects of DHA seen in both the cardiovascular and cognitive realms. This was done by invoking mechanisms common to the ANS which serves both vital physiological functions as well as fundamental steps in the initiation of information processing. Second, we sought to develop this hypothesis by reviewing the literature on the effects of DHA and links between ANS, DHA and cognitive function. Finally, we provided new data showing possible relations between prenatal DHA or DHA/EPA supplementation and fetal cardiac measures that are consistent with the hypothesis. We realize that we have made a series of preliminary arguments here, but it is our hope that this paper will spur researchers to consider the involvement of the ANS as a basic system that is affected by DHA as well as a mechanism through which DHA affects both physiological and behavioral outcomes. Furthermore, we hope that researchers will also seek to include measures of autonomic function in studies of DHA supplementation and status in the future.

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