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MATERNAL SERUM DOCOSAHEXAENOIC ACID AND SCHIZOPHRENIA SPECTRUM DISORDERS IN ADULT OFFSPRING

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Abstract

It is believed that during mid-to-late gestation, docosahexaenoic acid (DHA), an n-3 fatty acid, plays an important role in fetal and infant brain development, including neurocognitive and neuromotor functions. Deficits in several such functions have been associated with schizophrenia. Though sufficient levels of DHA appear to be important in neurodevelopment, elevated maternal DHA levels have also been associated with abnormal reproductive outcomes in both animal models and humans. Our objective was to assess whether a disturbance in maternal DHA levels, measured prospectively during pregnancy, was associated with risk of schizophrenia and other schizophrenia spectrum disorders (SSD) in adult offspring. In order to test the hypothesis that abnormal levels of DHA are associated with SSD, a case-control study nested within a large, population-based birth cohort, born from 1959 through 1967 and followed up for SSD from 1981

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Contributors: Dr. Brown conceived the study. Drs. Quesenberry, Hibbeln, Deckelbaum and Schaefer contributed to the study design, and Drs. Quesenberry and Schaefer participated in the selection of cases and controls. Dr. Hibbeln performed the laboratory analyses, Drs. Harper, Brown and Quesenberry conducted the statistical analysis, and Drs. Harper, Brown, and Hibbeln interpreted the data. Drs. Harper, Brown, Hibbeln, Schaefer, and Deckelbaum wrote the initial draft of the manuscript. All authors contributed to and have approved the manuscript.

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through 1997, was utilized. Maternal levels of both DHA and of arachidonic acid (AA), an n-6 fatty acid, were analyzed in archived maternal sera from 57 cases of SSD and 95 matched controls. There was a greater than two-fold increased risk of SSD among subjects exposed to maternal serum DHA in the highest tertile (OR=2.38, 95% CI=1.19, 4.76, $p=0.01$); no such relationship was found between AA and SSD. These findings suggest that elevated maternal DHA is associated with increased risk for the development of SSD in offspring.

Keywords

docosahexaenoic acid; arachidonic acid; schizophrenia; prenatal

1. INTRODUCTION

Docosahexaenoic acid (DHA), an n-3 fatty acid which cannot be synthesized *de novo*, comprises approximately one-third of the structural fatty acids found in the brain's gray matter (Neuringer et al. 1988, O'Brien and Sampson 1965, Svennerholm 1968). Particularly high concentrations are found in the cerebral cortex, synapses, and retinal rod photoreceptors (Bazan and Scott 1990, Bowen and Clandinin 2002, Sarkadi-Nagy et al. 2003). During the second and third trimesters of pregnancy, a considerable and preferential accumulation of DHA accompanies the fetal brain's dramatic increase in size (Crawford et al. 1976, Neuringer et al. 1984); in healthy pregnancies, fetal accretion of long chain polyunsaturated fatty acids (LCPUFAs) reflects maternal status (Rump et al. 2001, Wijendran et al. 2000).

To date, most research has focused on possible benefits of DHA during gestation. In animal models, DHA facilitates neuronal development (Auestad and Innis 2000) and function (McNamara and Carlson 2006). Gestational dietary DHA deficiencies alter biosynthesis and function of dopamine in the brain (McNamara and Carlson 2006) and cause behavioral (Fedorova and Salem 2006) and neurocognitive disturbances in offspring (Greiner et al. 2001, Moriguchi et al. 2000, Wainwright et al. 1998). In humans, low maternal intake of seafood, a rich source of n-3 fatty acids, is associated with lower verbal IQ, diminished prosocial behavior, suboptimal fine motor ability, and impaired social and verbal development (Hibbeln et al. 2007). Several double-blind, randomized, placebo-controlled clinical trials revealed maternal supplementation with DHA or DHA-rich foods during pregnancy increased offspring neurocognitive functioning in a number of areas (Colombo et al. 2004, Dunstan et al. 2008, Helland et al. 2003, Judge et al. 2007b). Not all measures of cognition improved, however, and statistical correction for multiple tests was not always implemented, highlighting the need for replication of exploratory findings. Moreover, other studies have found no relationship between DHA levels at birth and cognitive performance in childhood (Bakker et al. 2003, Ghys et al. 2002).

Potential concerns about high DHA levels during gestation have also surfaced. One *in vitro* study found that while modest levels of this LCPUFA protected placental cells against oxidative damage, high levels resulted in increased lipid peroxidation (Shoji et al. 2009). A study of pregnant women found that markers of oxidative damage were no higher in those taking DHA supplements than in controls (Shoji et al. 2006). However, high maternal serum PUFA concentrations, associated with a diet rich in marine foods, correlate with low birthweights, even after controlling for contaminants such as mercury and polychlorinated biphenyls (PCBs) (Grandjean et al. 2001, Oken et al. 2004, Thorsdottir et al. 2004). In addition, in pregnant and lactating rats, high doses of DHA impair neural transmission, as measured by auditory brainstem responses, in offspring (Church et al. 2008, Haubner et al. 2002). Because these responses are strongly associated with the degree of myelination of the

auditory brainstem, the authors have speculated that exposure to high levels of DHA during development may alter this process.

Schizophrenia is considered in large part a neurodevelopmental disorder, with origins dating as early as the prenatal period (Brown and Susser 2003). Several neurochemical disturbances and neurocognitive abnormalities associated with prenatal DHA deficiency, such as deficits in cortical maturation and attention (Colombo et al. 2004, Helland et al. 2003, Judge et al. 2007b, Kudas et al. 2002, Levant et al. 2004, McNamara and Carlson 2006, Zimmer et al. 2000), are also observed in patients with schizophrenia (Brown et al. 1996), though studies of prenatal DHA deficiency in humans are confounded by premature birth. This suggests that gestational DHA deficiency could contribute to the etiopathogenesis of SSD. Alternately, some outcomes observed in schizophrenia, including low birthweight, intrauterine fetal growth retardation, and impaired myelination, suggest that high levels of DHA could also play a role in pathogenesis of this disorder. We therefore postulated a curvilinear relationship between maternal DHA levels and SSD, with increased risk at both extremes of the distribution. In order to test our hypothesis, DHA levels were measured in archived maternal sera from a large birth cohort of well-characterized pregnancies followed up for schizophrenia. We focused on the second/third trimester of pregnancy, given that placental transfer of this LCPUFA increases substantially during this time in order to accommodate growth of the fetal brain. In order to assess the specificity of associations between maternal DHA and schizophrenia, levels of arachidonic acid (AA), another LCPUFA, were also examined. DHA and AA belong to two different biosynthetic families: the n-3 and n-6 fatty acids, respectively. They are present in similar concentrations in the brain, and it is thought that AA, as well as DHA, plays an important role in early neurodevelopment (Dijck-Brouwer et al. 2005, Zhao et al. 2009, In Press). Clinical studies examining the neurodevelopmental effects of n-3 and n-6 LCPUFA levels during pregnancy, however, have thus far tended to find benefits associated with supplementation by the former but not the latter (Helland et al. 2003, Judge et al. 2007a, Judge et al. 2007b), though it is also true that more attention has been focused on the effect of n-3 LCPUFAs (Colombo et al. 2004, Dunstan et al. 2008, Malcolm et al. 2003a, Malcolm et al. 2003b).

2. MATERIALS AND METHODS

2.1 Cohort Description

The study was based on the Prenatal Determinants of Schizophrenia (PDS) Study sample. The PDS study has been fully described in previous publications (Brown et al. 2004, Brown et al. 2007, Susser et al. 2000) and will only be summarized here. The cohort was derived from the Child Health and Development Study (CHDS), which recruited nearly all pregnant women receiving obstetric care from the Kaiser Permanente Medical Care Plan (KPMCP) in Alameda County, California from 1959–1966. Liveborn offspring (N=19,044) were automatically enrolled in this health plan. KPMCP membership was largely representative of the population of the California Bay Area at the time, with some underrepresentation of the extremes of income (van den Berg 1979, van den Berg et al. 1984). The cohort for the PDS study comprised the 12,094 live births who were members of KPMCP from January 1, 1981 (the year in which computerized registries became available) until December 31, 1997. Maternal characteristics between CHDS cohort members who remained in KPMCP and those who left before 1981 were similar; the vast majority of those who left did so before age 10, well before the risk period of schizophrenia (Susser et al. 2000).

Maternal blood was drawn during pregnancy in the majority (91.6%) of subjects, without a specific requirement for fasting. The serum obtained was handled and stored in accord with a uniform, strict protocol involving immediate freezing and archiving at –20 degrees C in a single biorepository.

2.2 Cases and Controls

These methods are presented in detail elsewhere (Brown et al. 2004, Susser et al. 2000) and are therefore only briefly summarized here. The main outcome was schizophrenia and other schizophrenia spectrum disorders (SSD), defined as: schizophrenia, schizoaffective disorder, delusional disorder, psychotic disorder not otherwise specified, and schizotypal personality disorder. Case ascertainment and screening were based on computerized record linkage between the identifiers of the CHDS and KPMCP from inpatient, outpatient, and pharmacy registries. Diagnostic assessments were obtained with the Diagnostic Interview for Genetic Studies (DIGS), and consensus diagnoses were obtained following review by three experienced research psychiatrists/psychologists and reviews of medical records. All subjects provided written informed consent for human investigation. The study protocol was approved by the Institutional Review Boards of the New York State Psychiatric Institute and KPMCP.

Of 71 cases, 66 had prenatal serum drawn. Three subjects had no remaining sera available for this study, leaving 63 cases with at least one sample. Fifty-seven cases had second and third trimester sera, defined as > 98 gestational days. Of these, 36 cases had schizophrenia, 10 had schizoaffective disorder, and 11 had other schizophrenia spectrum disorders. Therefore, 81% of cases with second and third trimester prenatal sera had either schizophrenia or schizoaffective disorder.

All controls were selected from the CHDS cohort. The 71 cases already diagnosed and 318 subjects with major psychiatric disorders other than schizophrenia were excluded. Controls for the present study were matched to cases on: membership in KPMCP at the time of first treatment for schizophrenia, date of birth ($\pm$ 28 days), sex, number of maternal blood samples drawn during the index pregnancy, number of weeks after the last menstrual period of the first maternal blood draw during the index pregnancy ($\pm$ 4 weeks), and gestational age at which sera were drawn. For each case, 1–2 controls met these criteria (N controls=95).

2.3 Laboratory assay

Serum samples were thawed, weighed, and homogenized in methanol-hexane, and methylated in acetyl chloride according to the method of Lepage and Roy (1986). The within- and between- day imprecisions for fatty acid concentration measurements were 3.26 $\pm$ 1.2% and 2.95 $\pm$ 1.6%, respectively. All assays were performed blind to case/control status.

2.4 Statistical analysis: Nested Case-Control Design

In accord with standard practice, DHA and AA levels were expressed as the percentage composition among total fatty acids quantified (Bakker et al. 2003, Ghys et al. 2002). DHA and AA measurements were classified in tertiles, with cut-off points as defined among controls. The middle tertile served as the reference group.

Point and interval estimates of odds ratios were obtained by fitting conditional logistic regression models for matched sets. Statistical significance was judged at $\alpha = 0.05$, two-tailed. A number of potential confounders were considered. Analyses were conducted examining various demographic covariates and SSD status, using T, Wilcoxon 2-Sample, or χ^2 tests as appropriate, and each covariate and DHA/AA tertiles. Associations between prenatal risk factors for SSD identified previously in this sample and DHA/AA tertiles were also examined, using χ^2 or ANOVA tests, as appropriate. Covariates were included in models if they were associated with both the exposure and SSD outcome at $p < 0.10$ (Rothman and Greenland 1998).

3. RESULTS

3.1 Overview

The results for maternal serum DHA/AA by tertile and by case-control status, respectively, are presented in Table 1.

3.2 Demographics

No demographic variables were associated with both case-control status and LCPUFA levels (Tables 2, 3). Although there was a trend for decreased maternal education in cases (χ^2 : 5.1, $p=0.08$), there was no relationship between maternal education and DHA/AA levels. Gestational age at blood draw was correlated with both DHA (χ^2 : 11.0, $p<0.01$) and AA levels (χ^2 : 7.8, $p=0.02$), but was not significantly related to case versus control status. Likewise, maternal race and AA were correlated (χ^2 : 28.9, $p<0.01$), but no significant differences between cases and controls were found. Finally, no relationship between maternal psychosis and DHA/AA levels was found; only one of the mothers in the sample was diagnosed with this disorder.

3.3 DHA, AA, and other prenatal risk factors for SSD

No association was found between DHA/AA tertiles and maternal pre-pregnant BMI, hemoglobin or homocysteine levels, or serological evidence of infection (Table 4). However, a positive correlation between AA tertile and BMI was identified ($\chi^2=9.20$, $p=0.01$).

3.4 Maternal DHA and AA levels for SSD cases and controls

Subjects with mothers in the lowest DHA tertile had the same risk of developing SSD as the middle (reference) tertile (OR=1.00, 95% CI=0.38, 2.67, $p=0.29$, Table 5). However, subjects with mothers in the highest DHA tertile experienced a greater than two-fold increased risk of developing SSD, compared to the middle tertile (OR=2.38, 95% CI=0.99, 5.70, $p=0.05$). Since the risk of developing SSD was nearly identical in the lowest and middle tertiles, a second analysis was performed in order to evaluate the risk associated with membership in the highest tertile vs the lower two tertiles. A similar effect was observed, with an increase in the lower limit of the confidence interval and a reduction in the p-value (OR=2.38, 95% CI=1.19, 4.76, $p=0.01$).

When examining the relationship between AA and SSD, both an unadjusted model and a model adjusting for maternal BMI were tested. In the unadjusted model, subjects with mothers in the lowest AA tertile had virtually the same risk of developing SSD as the middle (reference) tertile (OR=1.11, 95% CI=0.44, 2.78, $p=0.82$), and there was also no increased risk for offspring of mothers in the highest AA tertile (OR=1.74, 95% CI=0.77, 3.96, $p=0.19$). The results were similar in the adjusted model, both for the lowest tertile (OR=1.01, 95% CI=0.34, 3.05, $p=0.98$) and the highest (OR=1.26, 95% CI=0.44, 3.65, $p=0.67$).

4. DISCUSSION

A greater than twofold increased risk of schizophrenia and other schizophrenia spectrum disorders (SSD) was observed among offspring whose mothers had elevated DHA levels. To our knowledge, this is the first evidence of an association between maternal serum DHA levels in pregnancy and risk of SSD, or any adult-onset disorder in offspring. The effect was not accounted for by several potential confounders, and it was not observed for AA.

There is no straightforward interpretation as to why higher maternal levels of DHA were associated with greater risk of developing SSD in this population. Some studies in humans suggest that high levels of DHA can result in increased oxidative damage (Calzada et al. 2010, Guillot et al. 2009), which in turn has been linked to increased risk for SSD (Gysin et al. 2007, Prabakaran et al. 2004, Tosic et al. 2006). However, there is also evidence that the net effect of higher levels of DHA in humans is to reduce oxidative damage (Mori et al. 2000, Mori et al. 2003). It is possible that higher DHA may have been a surrogate marker for the consumption of seafood with unusually high levels of contaminants, such as mercury or PCBs (Torpy et al. 2006). Some individuals in our sample may have been genetically predisposed to greater oxidative stress or contaminant sensitivity, resulting in neurodevelopmental abnormalities associated with SSD risk. Finally, the effect of high maternal DHA levels upon neural transmission in a rat model suggests that myelin-related changes occur (Church et al. 2008, Haubner et al. 2002), and myelin-related changes in the brain have also been associated with schizophrenia (Prabakaran et al. 2004, Tkachev et al. 2007). A recent report that neonatal levels of vitamin D which would be considered high, but not toxic, were associated with increased schizophrenia risk (McGrath et al. 2010) indicates that the neurodevelopmental benefits of nutrients, such as DHA, may have upper limits.

Though we posited that low maternal levels of DHA would also result in increased risk of developing SSD in offspring, no evidence for such a relationship was found in this study. The level of DHA necessary to facilitate optimal brain development is poorly understood, but the possibility that dietary DHA is not necessary for women who consume a normal balance of linoleic acid and α -linolenic acid, the precursor of DHA, has been raised (Innis 2007). Perhaps even the levels found in the lowest tertile of this sample were adequate for normal brain development, at least in regard to SSD.

We found no evidence that maternal DHA levels were associated with previously described prenatal risk factors for SSD, including elevated maternal BMI (Schaefer et al. 2000), low hemoglobin (Insel et al. 2008) and high homocysteine levels (Brown et al. 2007), or evidence of exposure to toxoplasma or influenza (Brown and Derkits 2010). Thus, although nutritional deficiencies often accompany one another and infections can alter nutrient levels, elevated maternal DHA appears to be operating independently of these other putative prenatal determinants. While high DHA levels, as a percentage of fatty acids, were associated with increased SSD risk, there was no increase in their concentrations (data available on request), suggesting that the amount of DHA relative to other fatty acids is most relevant, rather than the absolute quantity of DHA. This is in accordance with a body of research which has found that the relative amounts of fatty acids in the serum, rather than their concentrations, are more pertinent to health (Bradbury et al. 2010, Ma et al. 1993).

Interpretation of our results may be complicated by the fact that LCPUFA levels were examined in maternal, rather than fetal, blood. Maternal LCPUFAs are preferentially sequestered and transported across the human placenta by binding to fatty acid transport proteins (Dutta-Roy 2000, Koletzko et al. 2007, Larque et al. 2006). Diminished transport function could result in increased maternal and decreased fetal DHA levels, potentially altering fetal brain development and accounting for the observed findings. The plausibility of transport defects contributing to our findings is supported by reports of a decreased ratio of fetal to maternal plasma DHA in intrauterine growth retardation (IUGR) (Cetin et al. 2002) and increased levels of maternal erythrocyte DHA in tandem with decreased fetal levels in gestational diabetes (Wijendran et al. 2000). Several more recent studies question whether impaired transport is associated with these common pregnancy complications, however. One study showed that plasma levels of DHA in mothers and fetuses with IUGR were not significantly different from those in controls (Alvino et al. 2008). Another study

demonstrated that DHA levels in mothers with gestational diabetes were comparable to those in controls and that low fetal levels appear to result from increased utilization or altered metabolism of this LCPUFA by the fetus, rather than from abnormal transport (Ortega-Senovilla et al. 2009). Thus, while it is unclear at present whether the association between elevated maternal levels of DHA and SSD could be accounted for by low fetal DHA levels resulting from impaired fatty acid transport, this explanation could reconcile our results with studies demonstrating an association between lower fetal DHA levels and less optimal cognitive outcomes (Carlson 2009).

Though the LCPUFAs in this study were measured in decades-old sera, the levels appeared reasonable when compared to those from fresh samples; mean values of 1.6–5.0% for DHA and 4.6–10.0% for AA have been reported for late pregnancy in North America and the UK, where significant variability has been found between sites (Cheruku et al. 2002, Innis and Elias 2003, Montgomery et al. 2003). LCPUFAs appear to degrade faster in red blood cells from patients with schizophrenia vs those from controls, when samples are frozen at –20 C (Fox et al. 2003). In this study, however, we found no evidence of more rapid degradation in maternal samples corresponding to case offspring; levels were actually higher in these sera. Only one of the mothers from whom serum was drawn was diagnosed with psychosis, and the corresponding DHA level fell in the middle tertile.

Several additional potential limitations must be considered. First, analyses of serum LCPUFA levels were carried out on non-fasting samples. Because intake of fish rich in n-3 fatty acids was very low in North America over 45 years ago, when the sera were obtained (Madden et al. 2009), this is not likely to be a serious confounder. Moreover, variations in serum fatty acid levels due to the presence or absence of fasting would likely be similar between mothers of cases and controls. Second, in order to rule out the possibility that our results could have been confounded by the presence of seafood contaminants, it would be desirable to assay for these analytes in future studies. Finally, it has been shown that higher levels of estrogen are associated with higher DHA levels (Kitson et al. 2010). Because little is known about the effects of prenatal estrogen levels upon SSD risk, it would be informative to examine maternal estrogen levels in relation to SSD in future work, in order to assess whether this hormone could contribute to the increased risk observed in this study.

We conclude that elevated maternal serum DHA levels, as a percentage of total fatty acids, were associated with a greater than twofold increased risk of SSD among adult offspring. These results are based on direct, prospectively measured maternal serum DHA levels during pregnancy and derive from a well-characterized and representative birth cohort, continuously followed for SSD over the period of risk for the disorder. This work may inspire future studies with archived neonatal sera available for measurement of essential nutrients and neurodevelopmental risks. In particular, studies performed in areas with higher maternal seafood intake, such as Japan and Iceland (Hibbeln 2002), may prove particularly informative, as these populations with very high DHA intakes appear to have no greater risk for SSD.

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Table 1

Maternal DHA and AA levels categorized by tertile among schizophrenia cases and controls

Tertile (Range, % of Total Fatty Acids)	Cases		Controls	
	N, %	Mean, SD	N, %	Mean, SD
DHA	57	1.51 (0.46)	95	1.38 (0.41)
Lowest (≤ 1.14)	13 (22.8)	0.87 (0.17)	32 (33.7)	0.95 (0.18)
Middle (1.15 to 1.45)	12 (22.1)	1.32 (0.09)	31 (32.6)	1.34 (0.09)
Highest (>1.45)	32 (56.1)	1.83 (0.28)	32 (33.7)	1.85 (0.27)
AA	57	5.31 (1.50)	95	5.14 (1.35)
Lowest ≤ 4.35)	17 (29.8)	3.65 (0.82)	32 (33.7)	3.74 (0.49)
Middle (4.36 to 5.44)	13 (22.8)	4.80 (0.29)	31 (32.6)	4.90 (0.35)
Highest (>5.44)	27 (47.4)	6.60 (0.85)	32 (33.7)	6.47 (0.75)

Table 2

Demographics of schizophrenia and other schizophrenia spectrum disorder (SSD) cases and controls

Characteristic	Cases (n=57)	Controls (n=95)	Test Statistic ^a	P-value
Gestational Age ^b (Mean, SD), Days	154.3 (38.3)	153.9 (36.1)	w: 4368.5	0.98
Subject Sex ^b (N, % Male)	39 (68.4)	66 (69.5)	χ^2 : 0.02	0.89
Maternal Age (Mean, SD), Years	28.2 (6.5)	27.6 (6.1)	t: 0.58	0.56
Maternal Education (N, %)			χ^2 : 5.12	0.08
<H.S.	13 (25.0)	11 (12.6)		
H.S. Grad	24 (46.2)	37 (42.5)		
Some College/College Grad	15 (28.9)	39 (44.8)		
Maternal Race (N, %)			χ^2 : 1.02	0.60
White	28 (50.0)	48 (51.1)		
Black	24 (42.9)	35 (37.2)		
Other	4 (7.1)	11 (11.7)		
Maternal Smoking (N, %)	23 (45.1)	42 (49.4)	χ^2 : 0.24	0.63
Previous Pregnancies (N, %)	44 (77.2)	71 (76.3)	χ^2 : 0.01	0.91

^a w: Wilcoxon Two-Sample Test Statistic; t: T-test Statistic; χ^2 : χ^2 Test Statistic^b Cases and controls were matched on these factors

Table 3
Tests of association between various demographic characteristics of the study sample and DHA and AA tertiles

Characteristic	DHA			AA		
	Low	Middle	High	Low	Middle	High
Gestational Age At Blood Draw (Mean, SD), Days	169.5 (41.0)	153.0 (34.1)	144.0 (32.2)	165.7 (37.5)	152.8 (38.8)	145.4 (32.7)
χ^2 Test Statistic	11.0			7.8		
P-value	<0.01			0.02		
Gestational Age At Birth (Mean, SD), Days	278.5 (18.8)	281.6 (15.8)	280.1 (14.5)	279.6 (19.1)	278.7 (15.0)	281.4 (14.4)
χ^2 Test Statistic	1.7			0.4		
P-value	0.43			0.84		
Subject Sex (N, % Male)	33 (73.3)	25 (58.1)	47 (73.4)	37 (75.5)	28 (63.6)	40 (67.8)
χ^2 Test Statistic	3.4			1.6		
P-value	0.19			0.44		
Maternal Age (Mean, SD), Years	26.9 (5.0)	27.6 (6.4)	28.7 (6.9)	26.9 (5.5)	27.4 (6.8)	29.0 (6.4)
F Test Statistic	1.1			1.6		
P-value	0.35			0.20		
Maternal Education (N, %)						
<H.S.	8 (18.6)	4 (10.3)	12 (21.1)	8 (17.8)	7 (16.7)	9 (17.3)
H.S. Grad	17 (39.5)	18 (46.2)	26 (45.6)	18 (40.0)	21 (50.0)	22 (42.3)
Some College/College Grad	18 (41.9)	17 (43.6)	19 (33.3)	19 (42.2)	14 (33.3)	21 (40.4)
χ^2 Test Statistic	0.7			<0.1		
P-value	0.40			0.94		
Maternal Race (N, %)						
White	27 (60.0)	24 (55.8)	25 (40.3)	35 (71.4)	23 (52.3)	18 (31.6)
Black	13 (28.9)	15 (34.9)	31 (50.0)	6 (12.2)	17 (38.6)	36 (63.2)
Other	5 (11.1)	4 (9.3)	6 (9.7)	8 (16.3)	4 (9.1)	3 (5.3)
χ^2 Test Statistic	5.6			28.9		
P-value	0.23			<0.01		
Maternal Smoking (N, %)	23 (54.8)	19 (48.7)	23 (41.8)	21 (46.7)	24 (60.0)	20 (39.2)
χ^2 Test Statistic	1.6			3.9		
P-value	0.45			0.14		

Characteristic	DHA			AA		
	Low	Middle	High	Low	Middle	High
Previous Pregnancies (N, %)	38 (84.4)	31 (72.1)	46 (74.2)	35 (71.4)	36 (81.8)	44 (77.2)
χ^2 Test Statistic	2.2			1.4		
P-value	0.33			0.49		

Table 4
Tests of association between various previously described prenatal determinants of SSD in the study sample and DHA and AA tertiles

Characteristic	DHA			AA		
	Low	Middle	High	Low	Middle	High
Pre-pregnant BMI (Mean, SD), kg/m ² , N=115	22.3 (3.4)	22.9 (4.6)	23.5 (4.2)	21.7 (3.0)	22.4 (3.7)	24.5 (4.8)
χ^2 Statistic	1.9			9.2		
P-value	0.39			0.01		
Hemoglobin Levels During Pregnancy (Mean, SD), g/dL, N=110	11.3 (1.2)	11.4 (0.8)	11.3 (1.1)	11.4 (0.9)	11.3 (1.1)	11.2 (1.2)
χ^2 Statistic	0.5			1.2		
P-value	0.76			0.56		
Third Trimester Homocysteine Levels (Mean, SD), μ mol/L, N=137	11.5 (6.1)	11.0 (5.7)	11.4 (3.8)	11.1 (6.2)	12.1 (5.1)	11.0 (3.8)
F Statistic	2.0			3.1		
P-value	0.38			0.21		
Influenza and/or Toxoplasma Infection (N, %), N=148	6 (13.3)	10 (23.3)	16 (26.7)	9 (18.8)	10 (22.7)	13 (23.2)
χ^2 Statistic	2.8			0.4		
P-value	0.25			0.84		

Table 5

Results of conditional logistic regression analysis of maternal docosahexaenoic (DHA) and arachidonic acid (AA) and SSD (unless otherwise noted, n=152; 57 cases, 95 controls).

Tertile	Parameter Estimate	Standard Error	χ^2	Odds Ratio	95% CI	P-Value
DHA						
Lowest	0.003	0.50	0.00	1.00	0.38, 2.67	1.00
Middle (ref)	-	-	-	-	-	-
Highest	0.867	0.45	3.77	2.38	0.99, 5.70	0.05
Lowest and Middle (ref)	-	-	-	-	-	-
Highest	0.865	0.35	5.97	2.38	1.19, 4.76	0.01
AA						
Unadjusted model						
Lowest	0.104	0.47	0.05	1.11	0.44, 2.78	0.82
Middle (ref)	-	-	-	-	-	-
Highest	0.555	0.42	1.75	1.74	0.77, 3.96	0.19
Model adjusting for maternal pre-pregnant BMI (n=115; 51 cases, 64 controls)						
Lowest	0.013	0.56	<0.01	1.01	0.34, 3.05	0.98
Middle (ref)	-	-	-	-	-	-
Highest	0.233	0.54	0.19	1.26	0.44, 3.65	0.67