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SHORT REPORT

Short Report: Exploring the Effect of Prenatal Fatty Acid Supplementation on Wheeze and Asthma in Black American Children

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Background: Black American children are at higher risk for developing asthma than White children. Identifying potential scalable preventive interventions that can reduce the racial disparities in asthma prevalence and associated morbidity and mortality are needed. We leveraged data from an RCT of prenatal supplementation with docosahexaenoic acid (DHA) in Black American women, to explore whether prenatal fatty acid supplementation is associated with offspring wheeze and asthma.

Methods: Data were from the Nutrition and Pregnancy Study (NAPS), a double-blind RCT of prenatal DHA supplementation in Black women targeting stress regulation during pregnancy. A subset of mothers (n = 83) completed a standardized questionnaire on offspring wheeze and asthma when children were between 0.5 and 5.5 years of age. DHA levels were measured from venous blood and reported as percent of total fatty acids.

Results: Of the 83 mothers providing data on child wheeze and asthma, 57 (68.7%) had been randomized to active DHA and 26 (31.3%) to placebo. Mothers and research staff were blind to group assignment. Comparison at the group assignment level yielded a relative reduction of 32% in the rate of wheeze or asthma among offspring of mothers assigned to active DHA compared to offspring of mothers assigned to placebo (OR = 1.6 [95% CI = 0.50–5.09], p = 0.426). DHA levels measured at 25–29 and 33–37 weeks of gestation differed as a function of offspring wheeze or asthma (t = 2.21, p = 0.015 and t = 2.54, p = 0.007, respectively).

Conclusion: These preliminary data suggest that increasing prenatal levels of DHA could be considered as a potential prevention for asthma in Black American children.

Keywords: Asthma, omega-3 fatty acids, pregnancy, Black American

Introduction

Asthma is a chronic inflammatory lung disease that currently affects an estimated 8.4% of children in the United States, resulting in over 600,000 emergency department (ED) visits and over 75,000 hospitalizations each year.[1] For decades, the burden of asthma in the US has fallen disproportionately on Black children living in low-income communities, for whom the prevalence, rates of hospitalization, morbidity, and mortality far exceeds those of their White peers.[2,3] Black children have 2–3 times higher rates of hospitalization and ED visits compared with White children, and a nearly 5-fold increase in asthma-related mortality.[4,5] Data from studies in Chicago show that asthma prevalence in predominantly Black neighborhoods is nearly double the prevalence in predominantly White neighborhoods.[6]

Several observational and randomized controlled trials (RCT), most of which have been comprised largely of White participants, have shown that prenatal fatty acid supplementation is associated with a reduction in offspring wheeze and asthma. Results from one of the largest RCTs of prenatal fatty acid, which was conducted in White women in Denmark, showed a 30% reduction in the risk for asthma in the supplemented group compared to the placebo group.[7] To date, research on fatty acids and asthma in youth living in the US also has largely been focused on White children. An

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exception is the Conditions Affecting Neurocognitive Development and Learning in Early Childhood (CANDLE) study in which two-thirds of the participants identified as Black.[8] In the CANDLE study, omega-3 fatty acid levels measured from maternal venous blood collected during the second trimester and quantified as quartiles were associated with a decreased risk for child asthma. Potential effects of maternal race on the association between prenatal omega-3 fatty acids and child asthma were controlled for statistically.[8] Additional research is needed to provide further evidence or lack thereof of the protective effects of prenatal fatty acids on asthma in Black American youth. Testing the association within racial groups and specification of blood levels at which protection may be increased is warranted to begin laying a foundation for implementation science.

In the present study, we compare maternal omega-3 fatty acid levels for children with and without wheeze or asthma by using data from a completed RCT of prenatal docosahexaenoic acid (DHA) supplementation in Black American women living in urban, under-resourced environments. We build on the existing research in several ways. First, all our maternal participants identified as Black, and therefore even in a relatively small sample we can explore the protective effects of DHA for Black families specifically. Second, DHA levels were assessed repeatedly during pregnancy, providing a preliminary examination of the impact of timing and level of increase in DHA on asthma risk in the offspring. Third, because data on maternal DHA levels were derived from an RCT, the supplementation dosage is known, thereby guiding the next step in developing a program of prevention science. Our objectives are to: 1) test whether the rate of infant wheeze and asthma in the offspring of mothers assigned to the DHA supplementation group is lower than the rate of infant wheeze and asthma in the offspring of mothers assigned to placebo; and 2) test whether maternal prenatal DHA blood levels differ as a function of offspring wheeze and asthma and if so, at what point in gestation are differences observed.

Methods

We conducted a case–control study, comparing children with and without asthma on maternal prenatal fatty acid levels using a subset of participants from the Nutrition and Pregnancy Study (NAPS), a double-blind RCT of prenatal DHA supplementation in Black women (NCT02647723). The primary outcome for the NAPS RCT was maternal perceived stress. For the RCT, 168 healthy pregnant, Medicaid-insured women (ages 18 to 34 years), reporting <2 servings of sea fish per week, were recruited at 10–17 weeks of gestation and randomly assigned in a 2:1 ratio to receive 450 mg DHA or placebo. Women were excluded from participating in the RCT if they reported known medical complications, regular use of steroid medications, alcohol, cigarettes, or illegal substances, use of blood thinners or anti-coagulants, or allergies to iodine, soy, or strawberry. The University of Chicago Institutional Review Board approved all study activities (IRB #15-0392; approved on 06/09/2015). All participants in the study provided informed consent, in accordance with the Declaration of Helsinki.

As part of the RCT, women provided venous blood samples at baseline and 17–21, 25–29, and 33–37 weeks of gestation. To measure DHA, blood samples were centrifuged for 10 minutes at 4° C at 3000 rpm, the plasma was removed, and the red blood cells were stored at −80°C until analyzed. Red blood cell phospholipids were separated from other lipids by thin-layer chromatography on a Hewlett-Packard model 6890 Gas Chromatograph and then transmethylated with boron triflouride in methanol (Sigma Chemical Company) to yield fatty acid methyl esters. Individual fatty acid methyl esters were separated and quantified by gas chromatography. Individual peaks were identified via comparison to authentic standards (Sigma Aldrich). DHA content was calculated on a µg/mL basis from the known amount of standard added and determination of response factors. Coefficients of variation for all fatty acid peaks were measured by analyzing quality control samples randomly distributed throughout the study samples. In this report, DHA is reported as percent of total fatty acids in red blood cells; $\log_{10}$ transformed DHA levels were used in analyses.

Delivery information, including infant sex, gestational age at birth, birthweight, maternal age at delivery, and delivery method, was abstracted from the electronic medical record or maternal report.

A subset of mothers who completed the RCT (n = 83; 49% of the RCT cohort) later reported on wheeze and asthma using the infant (n = 30) or early childhood version (n = 53) of the Airways Outcomes Questionnaire[9] via RedCap surveys sent by e-mail or text. The average age of the children at the time of the maternal report on asthma was 3 years (range = 0.5 to 5.5 years). History or current asthma was defined as an affirmative response to "Has your child ever had

asthma or been diagnosed with asthma?" History or current wheeze was defined as an affirmative response to "Has your child ever had wheezing or whistling in the chest?" Affirmative responses to either of these questions were used to identify a positive case of wheeze or asthma. This is an inclusive definition of infant wheeze or asthma, which was deemed appropriate given the exploratory nature of the study.

Of the 83 mothers providing data on child wheeze and asthma, 57 (68.7%) had been randomized to active DHA and 26 (31.3%) to placebo, which is consistent with the random assignment in a 2:1 ratio. Mothers and research staff were blind to group assignment at the time of the assessment of offspring asthma.

Odds ratio was computed to test whether the rate of infant wheeze and asthma in the offspring of mothers assigned to the DHA supplementation group was lower than the rate of infant wheeze and asthma in the offspring of mothers assigned to placebo. *T*-tests were conducted at baseline and 17–21, 25–29, and 33–37 weeks of gestation to test whether maternal prenatal DHA blood levels differ as a function of offspring wheeze and asthma.

Results

Among the 83 children in this analytic sample, 42 (50.6%) were boys and 41 (49.4%) were girls. The average gestational age at birth was 38 weeks (range = 28–42 weeks) and the average birthweight was 3160 grams (range = 1180–4640). Mothers were on average 26 years of age at delivery (range = 18–35 years), and most pregnancies resulted in vaginal (n = 57; 69%) deliveries at term (n = 74, 89%). We conducted t-tests to test for differences in DHA levels by infant sex, delivery mode and preterm birth. None of the tests yielded statistically significant differences. Test of associations using correlation coefficients with gestational age at birth, birthweight, and maternal age at delivery resulted in a significant association between maternal age at delivery and baseline, but not later DHA levels, which was therefore included as a covariate in analyses on baseline DHA levels and history of or current wheeze or asthma.

Fifteen of the 83 children (18.1%) were reported to have a history of or current wheeze or asthma according to maternal report; 10 children were reported to have a history of or current asthma, and 5 children were reported to have a history of or current wheeze, but no asthma. Wheeze and/or asthma was reported for six of the 26 children (23.1%) whose mothers were assigned to placebo and nine of the 57 children (15.8%) whose mothers received active supplement (Figure 1), a relative reduction of 32%. This difference was not statistically significant (OR = 1.6 [95% CI = 0.50–5.09], p = 0.426).

Maternal DHA blood levels across pregnancy were available for 76 participants. DHA blood levels were not significantly different at baseline, controlling for maternal age (10–16 weeks of gestation) or at 17–21 weeks of gestation between children with and without wheeze and/or asthma. DHA levels measured at 25–29 and 33–37 weeks of gestation differed as a function of offspring wheeze or asthma (t = 2.21, p = 0.015 and t = 2.54, p = 0.007, respectively) (Figure 2). The percent of DHA in maternal blood was on average 7.0% and 6.9% at 25–29 and 33–37 weeks of gestation,

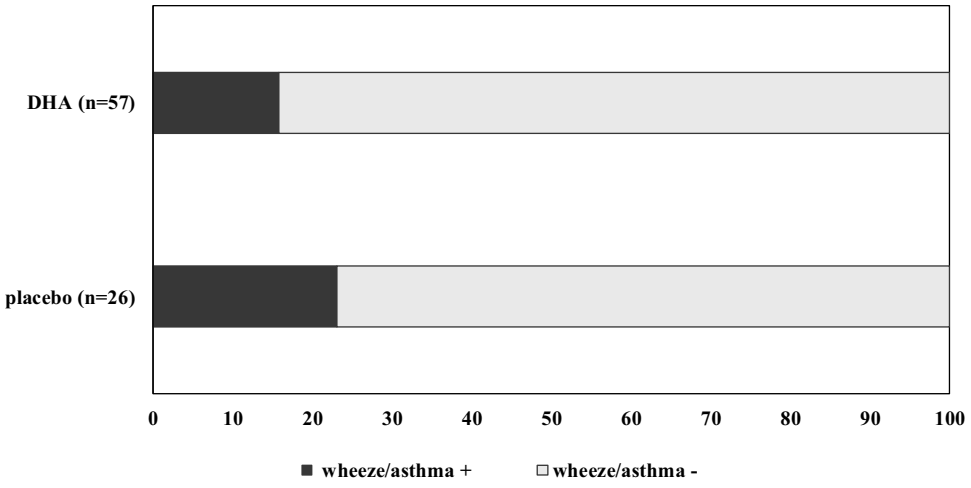

Figure 1 Percent of offspring with (+) and without (-) a history of or current wheeze/asthma among the group of mothers received docosahexaenoic acid (DHA) or placebo during pregnancy.

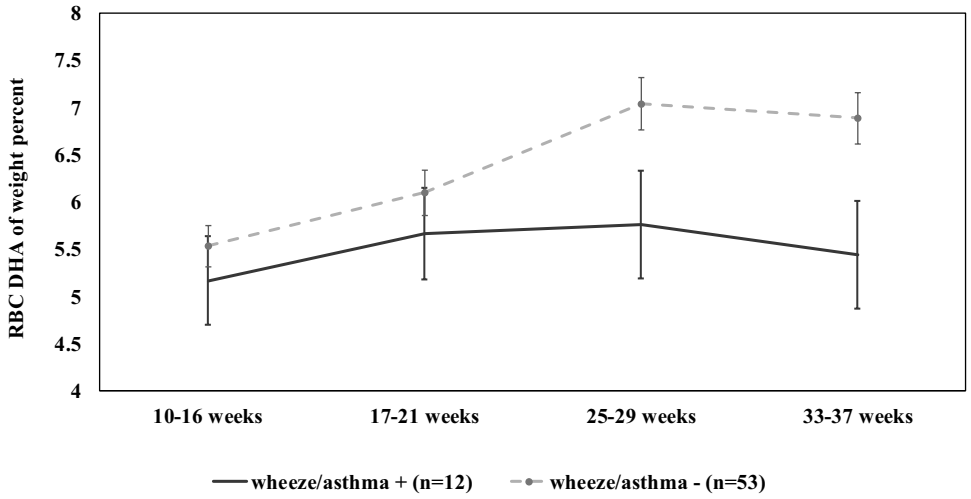

Figure 2 Maternal blood levels of docosahexaenoic acid (DHA) across pregnancy for offspring with (+) and without (-) a history of or current wheeze/asthma.

respectively, for mothers of children without wheeze or asthma compared to 5.8% and 5.4% for mothers of children with wheeze or asthma.

Discussion

The present study extends the current literature on the potential protective effects of prenatal DHA levels on offspring airway health. Comparison at the group assignment level yielded a relative reduction of 32% in the rate of wheeze or asthma among offspring of mothers assigned to active DHA compared to offspring of mothers assigned to placebo. This reduction is clinically meaningful, although not statistically significant, and is directly comparable to the statistically significant reduction observed in a large trial conducted in Denmark.[7] Adherence, dietary intake, and individual differences in metabolism can impact blood levels of DHA. Thus, the results showing statistically significant differences in prenatal blood levels of DHA between offspring with and without wheeze or asthma are compelling; with levels of DHA close to 7% in the third trimester appearing to offer protection. These results are consistent with data indicating that DHA levels > 5% are needed to support the health of pregnant women and the fetus.[10]

We note several limitations including use of maternal report to identify wheeze and asthma cases and the relatively small sample size, both of which limit the scope of the study. These limitations are offset to a degree by the use of a standardized and widely used maternal report measure[9] and the relative homogeneity of the participants on several dimensions including race, perinatal health, and living environment. In summary, these are preliminary data that suggest that increasing prenatal levels of DHA could be considered as a potential prevention for asthma in Black American children.

Abbreviations

RCT, randomized controlled trial; DHA, docosahexaenoic acid; NAPS, Nutrition and Pregnancy Study; mg, milligrams.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically

reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

Dr Christina Ciaccio reports personal fees from Genentech, stock options from Siolta and Clostrabio, outside the submitted work. The other authors have no other conflicts of interest to disclose.

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