

**GESTATIONAL WEIGHT GAIN AND OFFSPRING COGNITION**

BY

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## ABSTRACT

**Background:** Two thirds of US women are not gaining the recommended weight during pregnancy (1) and 50% of women giving birth in the US are either overweight or obese (2). While little is known about the effect of gestational weight gain (GWG) on offspring cognition, previous research has shown that BMIs >24.9 may lead to impaired cognitive outcomes.

**Objective:** To determine whether below or above recommended GWG has negative effects on cognition of the offspring and to determine whether pre-pregnancy BMI status affects offspring cognitive outcomes.

**Design:** Pre-pregnant weight and GWG data were collected from a subset of women (n=221) enrolled in a phase III clinical trial from 2006-2010. The offspring of these women underwent habituation tests at ages 4, 6, and 9 months. We used both self-reported pre-pregnancy weight and first clinic visit weight to determine GWG (inadequate, appropriate, or excessive) and weight status (normal or overweight/obese) categories. Underweight status was removed from data analysis due to few subjects in that category. All statistical analyses used mixed models.

**Results:** When self-reported pre-pregnancy weight was used to calculate GWG, several statistically significant three way interactions were found. However, these interactions lacked validity due to small sample sizes. There was one statistically significant relationship between GWG category and percentage of looking in sustained attention (SA) (p-value: 0.047). No statistically significant results were found when GWG was calculated based on weight at the first clinic visit.

**Conclusion:** Women who gained weight appropriately during pregnancy had offspring with greater percentage of looking spent in SA. This finding suggests a more sophisticated level of information processing in infants of women who gained appropriately when compared to infants of women who gained inadequately or excessively. No clear associations were found between maternal weight status and offspring cognition in infancy. The effect of pre-pregnancy weight status may not manifest itself during infancy or be detectable on tests of habituation in infancy. If further research conducted, it might be beneficial to use a later measure of cognition.

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## Chapter 1

### BACKGROUND AND JUSTIFICATION

In 2009 the Institute of Medicine (IOM) (currently the National Academy of Medicine) published revised GWG guidelines (3). Previous GWG guidelines focused primarily on pregnancy outcomes such as gestational diabetes mellitus, preeclampsia, stillbirths, and other conditions (3). However, in addition to addressing pregnancy outcome, the new guidelines added long-term health outcomes of the offspring (i.e. asthma, obesity, and cognitive impairment) as a reason for appropriate GWG (3). Indeed the IOM specifically addressed neurodevelopment as an area potentially affected by GWG (3). This is surprising because in 2009 when the guidelines were published, no studies examining GWG's effect on cognition of the offspring were available (3). The IOM recommended that more research be conducted. Since the publication of the 2009 guidelines seven studies have been published examining the effect of GWG on offspring cognition. Two of these studies were published on inadequate GWG and five on excessive GWG. The published results of inadequate GWG on offspring cognition are conflicting. One study saw decreased cognitive functioning (4) while the other saw no significant results (5). The results of excessive GWG on offspring cognition were more in agreement. Four studies showed at least some negative effect of excessive GWG on offspring cognition (6-9) while one observed no significant effect (10).

## **Statement of Purpose**

The purpose of my thesis is to assess the correlation between GWG and infant cognition. In addition, I will examine the relationship between pre-pregnancy weight status and offspring cognition. I hope to determine whether the effect on offspring cognition of both GWG and weight status by Body Mass Index (BMI) manifest themselves at an early age. Additional research will help to improve the GWG guidelines further and determine the need for GWG interventions. Also, additional research could help reinforce the importance for women to reach a normal weight status before pregnancy onset and lend support for pre-pregnancy weight loss interventions

## **Research Questions**

Primary research question

- Is maternal GWG during singleton, full-term pregnancy related to early cognitive performance of the offspring as measured by attention at ages 4, 6, and 9 months?

Secondary research question

- Is maternal weight status at the onset of pregnancy –normal weight or overweight/obese – related to early cognitive performance of the offspring as measured by attention at ages 4, 6 and 9 months?

## Chapter 2

### LITERATURE REVIEW

#### Introduction

The IOM has established guidelines for inadequate, appropriate, and excessive GWG. In 2009 the IOM updated the GWG guidelines. The guidelines recommended a range of weight gain based on pre-pregnancy weight status, determined by BMI. See table below (3).

<b>BMI (kg/m<sup>2</sup>)</b>	<b>Recommended GWG (lbs)</b>
<18.5	28-40
18.5-24.9	25-35
25.5-29.9	15-25
≥30.0	11-20

The IOM defined lower than recommended weight gain as “inadequate” and greater than recommended weight gain as “excessive”. To establish GWG guidelines, the IOM conducted research and identified areas in maternal and fetal health affected by weight gain. Offspring neurodevelopment was identified as an area potentially affected by GWG. The IOM stated that the effect of inadequate GWG on offspring cognition was especially of concern. However, it stressed that data were limited and more research be conducted on the effect of both inadequate and excessive GWG on offspring neurodevelopment. (3)

A limited amount of research exists regarding the impact of inadequate and excessive GWG on offspring cognition. However, additional research is needed to add to the body of literature to improve the weight gain guidelines further. Improved guidelines may help to prevent future GWG related offspring cognitive impairments. The purpose of this review of literature is to summarize the current knowledge on GWG and offspring cognition and to examine the need for further research. In addition, since maternal pre-pregnancy BMI is the determinant of GWG recommendations, I will also examine independently the effect of maternal BMI status on offspring cognition.

### **Infant Habituation**

Infant habituation is an early cognitive test that is based on the infant's attention. Habituation tests are widely used to record perceptual and cognitive capabilities of infants (11). In a test of visual habituation, infant looking duration towards a stimulus is recorded. The stimulus is then repeatedly shown to the infant in a series of distinct trials. As the stimulus is repeatedly shown, looking time decreases. Decreased looking time indicates a decrease in the orienting reflex (a response to a nonthreatening but unfamiliar stimulus) (12). The decrease in attention shows that encoding and information processing to the stimulus have occurred. In combination with looking time, heart rate (HR) is commonly used to more precisely identify the distinct phases of looking (13, 14). The use of HR to measure habituation allows looking to be divided into distinct phases (15). The first phase is orienting (OR). During this phase, HR is accelerated and initial processing of the stimulus begins (16). The second phase is sustained attention (SA). This phase is characterized by decrease in HR and encoding

of the stimulus (16). The final phase of habituation is attention termination (AT). In the AT phase the look is sustained, however, HR decline has ended (16)

It should be noted that it was originally presumed that looking time decreased linearly throughout the first year. However, recently this has been shown not to be true. A review of literature by Colombo noted three distinct phases (11). The first phase is an increase in brief looking between ages 8-10 weeks (17, 18), followed by a substantial decrease in looking time from that point until after 6 months of age (19, 20), and finally a plateau or slight increase subsequently through 12 months (21, 22).

While infant habituation has been studied for over 50 years and is widely used as a test of early cognition, its predictability is not well understood. The connection between infant cognition and later cognition is complex (23). It is noted that habituation is likely not in itself a component of intelligence but rather a “building block” for cognitive development during childhood (23).

### **Inadequate GWG and Offspring Cognition**

In the 2009 guidelines, the IOM expressed concern for inadequate GWG and offspring neurodevelopment. The concern stemmed from previous data on the effect of ketonemia/ ketonuria (atypically high concentrations of acidic ketones in the blood/ urine) on offspring neurodevelopment as a result of maternal fasting or weight loss during pregnancy (3). Inadequate GWG can negatively affect cognition of the offspring. Gage et al.(4) conducted a large prospective cohort study in the United Kingdom (UK) from 1990 until the present to assess the relationship between GWG and academic achievement at ages 4, 8, and 16 years. The sample size was large (5,836 at 4 years; 5,191 at 8 years, and 7,339 at 16 years). Race/ethnicity was not specified. The results

of this study showed that inadequate GWG was associated with lower school entry exam scores at age 4 and decreased final exam scores at age 16 years (4). However, no significant results were found for IQ at age 8 on the Wechsler Intelligence Scale for Children (WISC). The strengths of this study include that it has a large sample size. Also, while it was conducted in the UK, it utilized the 2009 IOM GWG guidelines.

Hinkle et al.(5) also examined the effect of inadequate GWG on offspring IQ at age 5 years. The outcome measure was the Wechsler Preschool and Primary Scales of Intelligence Revised (WIPPSI-R). This prospective cohort study had a sample size of 344. Women who were obese at pre-pregnancy were excluded from the study and 82.3% of the women in the sample were normal weight. There were no significant effects of GWG after adjusting for covariates. The study sample was very narrowly defined (normal weight, Scandinavian woman). However, like the study by Gage et al, the IOM's guidelines were used.

It should be noted that both Gage et al (age 8) and Hinkle et al. (age 5) used the same outcome measure, the WISC and both studies found no effect of inadequate GWG.

### **Excessive GWG and Cognition**

In addition to inadequate GWG, excessive GWG has been hypothesized to be associated with decreased cognitive functioning. However, the data are limited and, like inadequate GWG, most investigations have yielded null findings. The effect of excessive GWG on cognition of the offspring at age 4 and 7 years was assessed in a large prospective cohort study by Keim et al. based in Columbus, Ohio between the years 1959 and 1973 (9). The sample size was 31,968 individuals, including 8,704

siblings and was equally divided between children of European and African descent. The cognitive tests performed were the Stanford-Binet Intelligence scale and Graham-Ernhart Block Sort test at age 4 and the WISC and Wide Range Achievement Test (WRAT) at age 7 years. After adjusting for covariates, results were largely null except for one outcome in which excessive GWG was associated with a lower WRAT spelling test at age 7 years. Keim et al's study (9) is notable because it was the first to assess GWG and offspring cognition using siblings as a reference to control for familial effects. The strengths of this study include the large and diverse sample, and sibling-paired model help to validate the outcomes.

Pugh et al. (7) recently published a study examining the relationship between excessive GWG and cognition of the offspring at ages 6, 10, and 14 years. The design was a prospective cohort conducted in Pittsburgh, PA between 1983 and 1986. The cohort was originally designed to examine the outcome of substance use during pregnancy. Women were included in the cohort if they either drank 3+ drinks of alcohol per week or smoked 2+ joints of marijuana per month during the first trimester. The sample sizes included 542 at age 6, 557 at age 10, and 468 at age 14; the sample was equally divided between African-American and Caucasian participants. The tests of cognition used were the WRAT-R test at age 6 and 10, The Stanford-Binet Intelligence Scale 4<sup>th</sup> edition and Child Behavior Checklist (CBCL) at age 10, and the Wechsler Individual Achievement Test (WIAT) at age 14. Excessive GWG was associated with decreased reading and spelling scores at ages 6, 10, and 14 years. The primary limitation of this study is that it was from a cohort with exposures that were potentially

problematic for cognitive function. While the effect of substance use was statistically accounted for as a confounder, it could diminish the strength of the results.

The same cohort was used in two additional studies by Pugh et al. The first study's aim was to assess the relationship between excessive GWG and Attention Deficit/Hyperactive Disorder (ADHD) at age 10 using the Conner's Continuous Performance test, the CBCL, and teacher report forms (10). The second study's aim was to assess the relationship of excessive GWG on executive function and IQ at age 10 (6). This study measured IQ using the Stanford-Binet Scale 4<sup>th</sup> edition and measured executive function using the Wisconsin Card Sort test and part B of the Trail Making test. The ADHD study yielded no significant results (10). The second study, however, did find a significant association. While no association was found between GWG and IQ at 10 years of age, excessive GWG was associated with decreased executive function at 10 years old.

The effect of maternal obesity and GWG on offspring IQ at age 7 years was studied by Huang et al (8). It should be noted, however, that the study was designed to determine the effect of pre-pregnancy BMI status on IQ rather than the effect of GWG. Thus, the methods and results on the effect of GWG on IQ are limited. Compared to the offspring of normal weight women who gained near optimal levels, the offspring of obese women who gained >40 lbs had a 6.5 point lower IQ ( $p < 0.01$ ). This is after controlling for the effect of obesity alone on IQ score. Also, normal weight women who gained between 21-25 lbs were used as a reference group during data analysis. This is the reason for the comparison made above. While this single result is interesting, the data analysis/ methodology on GWG and IQ should have been more complete. The



article presented an image showing the relationship between IQ and GWG. From looking at the plots it appeared that excessive GWG not only affects the obese sample, but other weight status categories as well, however, none of the statistical values were listed in the article.

Little is known about the effect of excessive GWG on offspring cognition and the available research has limitations. The three studies by Pugh et al (6, 7, 10) have a sample with many variables that could influence cognition adversely making interpretation of their results difficult and not necessarily generalizable. The research by Huang et al (8) focused on an obese population, also limiting generalizability. However, the study by Keim and Pruitt (9) had few limitations. It included a larger sample size and innovative statistical methods.

### **Maternal Weight Status at Pregnancy Onset and Offspring Cognition**

In addition to GWG, maternal weight status at pregnancy onset has also been shown to affect offspring cognition. While substantial literature exists on the impact of high maternal pre-pregnancy weight status and offspring cognition, little data exists assessing underweight status. Only two articles address the relationship between low maternal weight status at pregnancy onset and offspring cognition.

The first of these was a secondary data analysis assessing the correlation between maternal pre-pregnancy BMI and offspring cognition at ages 5 and 7 years (24). The data for this study were obtained from a nationally representative prospective cohort study conducted in the UK (n=19,517). The outcome measures were subscales of the British Ability Scales second edition (BAS-II) at both 5 and 7 years and an additional number skills test at age 7. The results showed that being underweight (BMI

16-18.5 kg/m<sup>2</sup>), overweight (BMI 25-30 kg/m<sup>2</sup>), or obese ( $\geq 30$  kg/m<sup>2</sup>) were all associated with decreased cognitive outcomes of the offspring at ages 5 and 7 year when compared to normal weight women (BMI 18.5-25 kg/m<sup>2</sup>).

The second article is a prospective cohort study conducted in the US examining the effect of maternal pre-pregnancy BMI on child neurodevelopment at 2 years of age (25). The sample is also nationally representative and made up of 6850 2-year-olds. The cognitive test performed was the Bayley Short Form-Research Edition. The results for this study were the same as the UK study. When compared with offspring of normal weight mothers, children with mothers who were underweight, overweight, or obese pre-pregnancy had lower scores on the Mental Development Index.

Unlike low maternal pre-pregnancy BMI, much research exists on the relationship between high maternal BMI's and offspring cognition. Studies of high maternal BMI have examined effects based on, non-psychosocial and psychosocial cognitive outcomes. The non-psychosocial cognitive outcomes will be discussed first.

Three of these articles have been previously reviewed in this paper. The first is the study by Huang et al (8) which found that maternal obesity resulted in lower IQ scores at age 7. The results also showed that women with a BMI of 20 kg/m<sup>2</sup> had offspring with the highest IQ scores. Pugh et al (7) found that there was an inverse relationship between academic achievement scores at ages 6, 10, and 14 years and pre-pregnancy BMI  $>22$ kg/m<sup>2</sup>, and in a second article (6) it was seen the maternal obesity was associated with a 3.2 point lower IQ score at age 10.

In addition to these articles, one additional study is worthy of discussion. A prospective cohort study examined the effect of maternal obesity on offspring cognition

between 60 and 83 months(26). The study was conducted in the US and had a sample size of 3,412 children. The cognitive test performed was the Peabody Individual Achievement Test (PIAT). The results showed a significant association between pre-pregnancy obesity and lower PIAT scores that remained significant even after accounting for confounders (e.g., income and maternal education).

Psychosocial development has also been seen to be affected by high maternal weight status during pregnancy onset. The results of an article previously discussed by Pugh et al (10) showed that maternal obesity is correlated with increased offspring problem behaviors at age 10 years measured using the CBCL

Using data from a previous prospective cohort study, Jo et al (27) examined pre-pregnancy BMI status and child psychosocial development at age 6 years. The sample contained 1311 mother-child pairs. The cognitive test performed was the Strengths and Difficulties Questionnaire. The results showed that children of obese class I and II ( $BMI > 35 \text{ kg/m}^2$ ) mothers had increased odds of emotional symptoms, peer problems, total psychosocial difficulties, ADHD diagnosis, autism, or developmental delay diagnosis and more often received special services when compared to normal weight women.

In an additional study, the effect of maternal pre-pregnancy BMI and child ADHD symptoms at age 6-8 years were examined (28). The study was a population based cohort study conducted in the US. A total 174 children were examined for ADHD symptoms using the CBCL. The results showed that children of obese mothers had significantly higher prevalence and severity of ADHD symptoms when compared to both overweight and normal weight mothers. In addition, the findings showed a 2.8-fold

increase in the prevalence of ADHD among children of obese mothers versus non-obese mothers.

While there is a substantial amount of data on maternal pre-pregnancy obesity and offspring cognition, data for low maternal weight status is lacking.

## **Conclusion**

Methods to assess infant cognition have been established and are widely used. Therefore, it is possible to assess the relationship between GWG/ pre-pregnancy weight and infant cognition. The limited available research shows either a null or positive correlation between inadequate or excessive GWG and offspring cognition. More research needs to be conducted to increase the knowledge on this topic. The data on maternal weight status at pregnancy onset and offspring cognition is also limited. While a substantial amount of literature exists on women who enter pregnancy while obese, little is available on those who enter pregnancy underweight. Further research will help to improve GWG recommendations to prevent future neurological harm due to improper GWG and maternal weight status before pregnancy.

## **Chapter 3**

### **METHODS**

#### **Overview**

The purpose of my thesis will be to assess the relationship between a) GWG and b) pre-pregnancy weight status on offspring cognition assessed by infant habituation at ages 4, 6, and 9 months. The proposed design is a secondary data analysis of the Kansas University Docosahexaenoic acid (DHA) Outcomes Study (KUDOS). Data on maternal GWG, pre-pregnancy weight, and infant attention has previously been collected at part of this study. KUDOS was a phase III randomized controlled trial (RCT) initiated in 2006 and conducted at the University of Kansas Medical Center. The primary KUDOS study was completed in two phases. The first phase of the trial compared two doses of DHA during pregnancy (600mg vs. 0mg) to gain knowledge about the safety and value of administration on pregnancy outcomes. The subjects who were in the intervention group were provided with 3 500-mg capsules containing a total of 600mgs of DHA, while the control group received 3 500-mg of placebo capsules filled with vegetable oil. Both groups were instructed to take the 3 capsules daily from the enrollment until delivery. The second phase of the trial consisted of postnatal visits to examine the effect of maternal DHA supplementation on cognition and vision. Phase two had 5 postnatal visits between 4 and 18 months of age that assessed various behavioral outcomes.

The specific aims of the KUDOS study were to 1) determine whether RBC-phospholipid- DHA can be significantly increased by supplementation 2) assess the effect of DHA supplementation on duration of gestation 3) evaluate adverse events in

women and infants in the treated and placebo groups 4) evaluate the effect of maternal DHA supplementation on visual evoked potential acuity in infancy and 5) evaluate the effect of DHA supplementation on the development of fundamental measures of cognitive function in infancy. I used data collected in both the first and second phases of KUDOS to examine the effect of GWG and pre-pregnancy weight status on offspring cognition.

### **Sample**

Women were screened as eligible for KUDOS if they were between 16 - 35.99 years old, English speaking, between 8 – 20 weeks gestation age, planning to deliver in the Kansas City metropolitan area, and had a telephone contact. Women were excluded from the study if they were pregnant with multiple fetuses, had a BMI  $\geq$  40, diabetes mellitus, blood pressure  $\geq$ 140 mm Hg, or other serious health conditions that were deemed likely to affect fetal development (i.e. HIV, hepatitis, and cancer).

### **Research Setting**

The study was conducted at the University of Kansas Medical Center. Participants were from the Kansas City metropolitan area and were recruited at the obstetrics clinics at the University of Kansas Medical Center (Kansas City, KS), Truman Medical Center (Kansas City, MO), and St. Luke's Hospital (Kansas City, KS). The study enrolled participants between January 2006 and November 2009. Women were screened as eligible (2188) and 350 consented to be enrolled in the study. Of this 350, 301 participants completed the study through delivery. From the 301 women who delivered, 158 of the offspring completed 4 month visits, 170 completed 6 month visits,

and 156 completed 9 month visits. All postnatal follow-up visits were conducted at the University of Kansas Medical Center.

## **Ethics**

The Human Subjects Committee (HSC#10186) at the University of Kansas Medical Center approved this study. All participants completed an informed consent form at enrollment (see Appendix A). Research and the informed consent protocol complied with the Declaration of Helsinki and were approved by the Institutional Review Boards and Human Subjects Committees at The University of Kansas Medical Center (Kansas City, KS); the University of Missouri – Kansas (Truman Medical Center); and St. Luke’s Hospital (Kansas City, MO). All participants were informed about their privacy protection under the Health Insurance Portability and Accountability Act (HIPPA). All members of the research team followed university confidentiality policies, Privacy Protection for Research Subjects, and held certification with NIH Human Subjects protection and HIPPA. All participant data was stored in a secure location, accessible only by research personnel. Participants were given a random identification number at enrollment. This number along with the mother’s initials was used for identification of the offspring during postnatal visits to maintain confidentiality of the participants.

## **Procedures**

This study design is a retrospective cohort study using secondary data analysis of data obtained in the KUDOS trial. The purpose is to assess the possible association between GWG and pre-pregnancy weight status on cognition of the offspring.

Pre-pregnancy and full-term maternal weights were previously collected as part of the KUDOS study. Pre-pregnancy weight status was obtained both through medical records documenting weight at first OB appointment and through self-reported pre-pregnancy weight at enrollment. Full-term pregnancy weight was obtained using last recorded weight prior to delivery found in medical records. First appointment weight was used to determine both pre-pregnancy BMI status and to calculate GWG.

After delivery the infants returned for postnatal visits at 6 weeks, and 4, 6, 9, 10, and 18 months. Trained personnel performed Infant habituation tests at visits 4, 6, and 9 months. During this test, the infants were seated in a darkened quiet room and shown images of adult human faces on a screen. The phases of looking [orienting (OR), sustained attention (SA), and attention termination (AT)] were measured. In addition, peak look, total look duration, average looking time, and trials to habituation were recorded. Heart rate was measured along with looking to more clearly identify each phase of attention. The stimulus was repeatedly shown to the infant. Overtime, the infant's look duration began to decrease indicating encoding/learning had taken place. All tests of infant habituation were video recorded. The videos were later coded by two trained observers to distinguish the phases of looking and amount of time spent in each phase. Heart rate was used to assess the quality of attention during looking. During habituation, events such as infant fussiness, parental interference, and mechanical errors made some of the data unusable: 76% of the data at 4 months, 87% of the data at 6 months, and 82% of the data at 9 months was considered usable.



## Analysis of Data

GWG was calculated in two ways, using first clinic weight and using self-reported pre-pregnancy weight. The two GWG values were compared as mean  $\pm$  SD, while minimum and maximum values are also reported. GWG was analyzed as a categorical variable (using IOM guidelines). Pre-pregnancy weight status was analyzed as a categorical variable using 3 of the 4 weight status categories (normal, overweight, and obese). The underweight category was excluded from data analysis due to the sample being small ( $n=3$  for 1<sup>st</sup> clinic visit weight and  $n=7$  for self-reported weight). Infant gender and age were used as fixed effects during data analysis. Looking times were analyzed using both proportion and amount of time spent in each category. In addition, peak look, average looking, and total looking were analyzed. Mixed models method was used for all statistical analysis comparing either GWG or pre-pregnancy weight status to looking times. Differences with caregiver Peabody Picture Vocabulary Test (PPVT) scores, and maternal DHA supplementation were confounded. Smoking status during pregnancy, maternal age, and race were found to have no effect on offspring looking, and were not included in the model as covariates. All data was analyzed with SPSS Statistical 22.0 software. Data was considered significant if  $p$ -value  $\leq 0.05$ .

## Chapter 4

### RESULTS

#### Subject Characteristics

Of the 350 women who were enrolled in the KUDOS study a subset 221 women were evaluated to assess the possible association between GWG and pre-pregnancy weight status on infant cognition. Women were included in the subset if their offspring attended at least one of the study visits at 4, 6, and 9 months. See TABLE 1 for a summary of maternal characteristics and TABLE 2 showing both self-reported and first clinic visit weights of the mothers.

TABLE 1. Summary of Maternal Characteristics <sup>1</sup>

	Mean ± SD	Min - Max
Race (%white / %black / %other)	68/30/2	
Age at enrollment (y)	26.08 ± 4.74	16.06 - 35.97
PPVT	99.38 ± 15.15	67-140
Smoking during pregnancy (%n/%y)	65/35	

<sup>1</sup>Two hundred and twenty-one values for race, age, and smoking status. Two hundred and ten PPVTs were completed. 191 were completed by mothers, 18 by fathers, and 1 by grandmother.

TABLE 2. Comparison of Self-Reported and First Clinic Visit Weights

	Mean $\pm$ SD	Min - Max
BMI Category (%) <sup>1</sup>		
Self-Reported	4/46/31/19	
First Clinic Visit	1/35/35/29	
BMI Self-Reported (kg/m <sup>2</sup> )	25.66 $\pm$ 4.99	15.1 - 39.96
BMI First Clinic Visit (kg/m <sup>2</sup> )	27.2 $\pm$ 5.19	16.53 - 42.56
GWG Category (%) <sup>2</sup>		
Self-Reported	9/23/68	
First Clinic Visit	21/29/49	
GWG Self-Reported (lbs)	37.64 $\pm$ 15.44	-13 - 93
GWG First Clinic Visit (lbs)	28.52 $\pm$ 12.59	-6 - 59

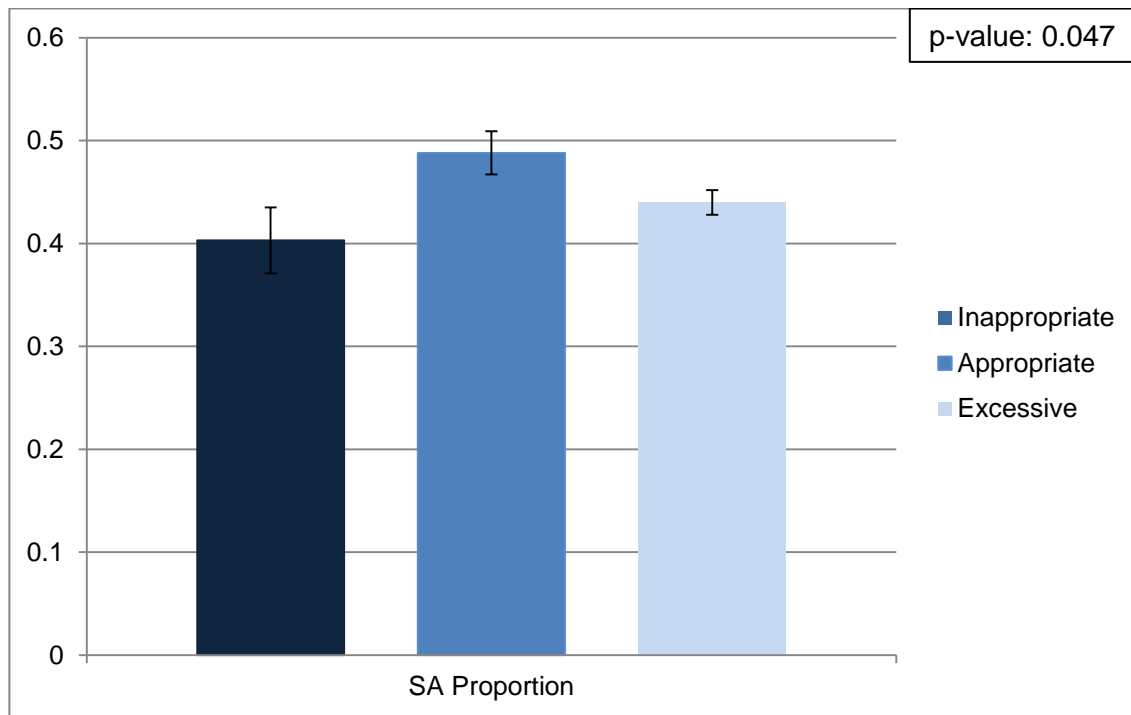
<sup>1</sup>Underweight/normal/overweight/obese

<sup>2</sup>Inadequate/appropriate/excessive GWG

## GWG and Cognition

Using self-reported pre-pregnancy weight, we found a statistically significant relationship between proportion of looking in SA and GWG (P-value: 0.047). See FIGURE 1. The proportion of looking in SA reflects the amount of time actively engaging in learning and information processing of the stimulus. This analysis averaged SA in each GWG category across all 3 ages tested (4, 6 and 9 months). As part of normal development, the percentage of looking spent in SA commonly decreases as the infant ages. However, it should be noted that SA maintenance throughout the first year of life has been associated with increased cognitive outcomes during childhood (29) We did not find an interaction between infant age and GWG category (p-value: 0.780). No other significant or near significant results were seen between GWG and offspring cognition.

**FIGURE 1.** Proportion of Looking in SA as a Function of GWG Category



\*Standard error = 0.032 (inadequate), 0.021 (appropriate), and 0.012 (excessive)

No significant associations were found between GWG and infant looking at 4, 6, or 9 months when using first clinic visit weight.

### **Pre-pregnancy BMI and Cognition**

When using self-reported weight to determine weight status before pregnancy, several three-way interactions were seen. However, these results are invalid due to small cell sizes.

No significant association was observed between pre-pregnancy weight status and infant looking at 4, 6, and 9 months when using first clinic visit weight.

## Chapter 5

### DISCUSSION

#### **GWG and Cognition**

According to the 2015 national vital statistics report of birth data, it is estimated that 48% of women gain excessively, 32% gain appropriately, and 21% gain inadequately (1). Compared with the national average, the women in this study had similar GWG values. When calculated using self-reported pre-pregnancy weight, 68% gained excessively, 23% gained appropriately, and 9% gained inadequately. Based on their weight at the first clinic visit, 49% gained excessively, 29% gained appropriately, and 21% gained inadequately. With at least two-thirds of pregnant women not gaining the recommended amount of weight, this is a public health concern.

Previous research has shown that either excessive or inadequate GWG may affect cognition of the offspring (4, 6-9). However, all prior studies examined the effect of GWG on cognition at an older age of the offspring. In this study, when examining the effect of GWG on offspring cognition during infancy, only one association was found. It was seen that women who gained appropriately during pregnancy had offspring with a greater percentage of looking in SA (p-value: 0.047). This association was seen only when GWG was calculated using self-reported weight, but not when using first clinic visit weight. While one might question the reliability of self-reported pre-pregnancy weight, almost all previous research studying the impact of GWG or maternal BMI status on offspring cognition have used self-reported weights. Using self-reported weight seems to be standard. The only exception I found was Buss et al (28) who used first clinic visit weight. Because women were enrolled between 2 and 5 months of

pregnancy, the use of weight at the first clinic visit should have resulted in a highly variable GWG between the onset of pregnancy and first clinic visit among the subjects.

Even though only one variable was found to be significantly related to GWG, it should be noted that proportion of looking in SA attention is a main variable of interest when analyzing habituation data. Proportion of looking in SA reflects the amount of time actively engaging in learning and information processing of the stimulus. It appears that the effect of GWG on cognition may manifest itself during infancy.

### **Pre-pregnancy BMI and Cognition**

According to the 2014 national vital statistics report, approximately 3.8% of women who gave birth in the US were underweight, 45.9% were normal weight, 25.6% were overweight, and 24.8% were obese (2). Thus, one in every two women who delivers in the US is either overweight or obese. Also, the number of overweight and obese women in the US is likely increasing (30). When using self-reported weight 4% of our subjects were underweight, 46% were normal weight, 31% were overweight, and 19% were obese. In comparison, using the first clinic visit weight, 1% were underweight, 35% were normal, 35% were overweight, and 29% were obese. The proportions using self-report are more closely aligned with national statistics, suggesting that self-report is a better representation of weight status at the start of pregnancy.

The research shows consistent evidence that obesity negatively effects offspring cognition (6-8, 24-28), however, as noted previously the studies have been done in populations with little overweight/obesity and the literature is weighted heavily toward a group of subjects considered at risk for drug and alcohol use. However, little is known

about the effect of being underweight (24, 25). Due to the evidence supporting the association between obesity and decreased cognition, I hypothesized that there would be a significant association between obesity and infant attention. However, our results do not support a link between weight status and infant cognition. In addition, due to the large amount and strength of previous research showing the negative connection between obesity and offspring cognition, I question whether little association truly exists or whether the observed effect on cognition is not able to be seen until a later age. The effects of maternal pre-pregnancy BMI may not manifest itself during infancy. Thus, infant attention tests may not be suitable for this study.

There were several statistically significant three way interactions found for weight status and infant attention, but no clear connection was seen. This could be due to the fact that subgroups were very small when divided by GWG and gender. Results were only seen when self-reported weights were used, but not first clinic visit weight. As discussed above, self-reported weight is more in line with national statistics for weight status at the beginning of pregnancy, however, it would be preferable to have a measured weight at the start of pregnancy.

More research does seem worthwhile using infant attention as an outcome. There will also be the opportunity to explore these issues at older ages, because we have age-appropriate cognitive assessments out to 6 years of age.

### **Further Research**

While few conclusive results were found during this study, further research should be conducted to assess both the effect of GWG and pre-pregnancy BMI on cognition. I recommend that GWG and weight status be explored in relation to

measures of cognition that have been obtained on this cohort up to age 6 years. With such a high prevalence of excessive GWG and overweight/obese status, it is important to determine if there are negative effects on offspring cognition.

### **Limitations**

Both self-reported weight and first clinic visit weight were used for data analysis. Due to a large variation in the gestation age (GA) at first clinic visit, it is likely that first clinic visit weights are not an accurate measure of GWG. The GA at first visit ranged from 4 weeks – 23 weeks with a mean of 11 weeks and standard deviation of 3.85. Due to an estimated optimal weight gain of 1lb/wk after week 13, this would likely underestimate weight gain of those participants who had their first clinic visit during their second trimester. On the other hand, self-reported weight is likely a limitation, because it is common for individuals to underestimate their weight. A further limitation is that we could not use self-reported weight in all cases and had to use first clinic weights for 29 (13% of total women) because some women could not recall a pre-pregnancy weight.

This is the first study, to my knowledge, to assess the association between GWG and pre-pregnancy weight status on infant cognition. All previous research has assessed either child or adolescent cognition. Thus, we are unable to compare the results of this study to the work of other researchers.

Due to such a small sample of underweight women (n=7 for self-report and n=3 for first clinic visit) in our cohort, data analysis was not possible in that BMI group.



## **Chapter 6**

### **SUMMARY**

With estimates of only one third of US women gaining recommended weight during pregnancy (1) and 50% of pregnant women being overweight or obese (2), it becomes a public health concern. While this study found little significant relationship between GWG or pre-pregnancy BMI on offspring cognition, previous research has observed significant findings of obesity on cognitive outcomes. The effects of GWG and pre-pregnancy BMI may not manifest themselves during infancy or be able to be detected on tests of habituation.

Future research to evaluate the effect of GWG and pre-pregnancy weight status should be conducted using cognitive outcomes assessed from 18 months to 6 years that have already been collected on this cohort.

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APPENDIX A

CONSENT FORM FOR KU DHA OOUTCOMES STUDY (KUDOS)

CONSENT FORM  
The Effects of DHA on Pregnancy and Infant  
Outcome (Kansas University DHA Outcomes  
Study or KUDOS)

Sponsor: NIH (1R01  
HD047315)

INTRODUCTION

As a pregnant woman who is between 8 and 20 weeks of gestation, you are being invited to enroll in a research study of a nutrient (DHA) that is a component of normal brain and important for brain development. The centers involved in the study are the University of Kansas Medical Center in Kansas City, Kansas, St. Luke's Hospital in Kansas City Missouri, and Truman Medical Center in Kansas City, Missouri. If you decide to enroll in this study, your baby will participate in research procedures at the University of Kansas Medical Center. Dr. Susan Carlson is the main investigator for this study. A total of 350 pregnant women will be enrolled in this study between October 2005 and January 2010.

*You do not have to participate in this research study. It is important that before you make a decision to participate, you read the rest of this form. You should ask as many questions as you need to understand what will happen if you participate in the study.*

BACKGROUND

Docosahexaenoic acid (DHA) is a fat that is found in very large amounts in the brain. DHA is important for how my baby sees and learns. Breast milk and, since 2002, US formulas contain DHA. Many studies have shown that DHA in the diet helps the baby's vision, attention, and ability to learn. In this way, DHA is considered an important nutrient for babies after they are born.

DHA may also be important before babies are born. Four studies found that women's DHA during pregnancy was related to higher infant/child function. These studies are called observational studies, meaning that the women's normal DHA status was studied in relation to development of the baby/child. There is only one study that gave women DHA during pregnancy and measured development of their babies/children. That study showed higher IQ at 4 years of age in children whose mothers took fish oil capsules during the last 6 months of pregnancy. (Fish oil contains a lot of DHA). However, because women in the study also consumed DHA while they were breastfeeding they provided more DHA to their babies after they were born. Therefore, the study does not prove that giving DHA before babies are born will help their development. There are no studies that have varied DHA intake only during pregnancy. You and your child are being asked to participate in such an experimental study.

## PURPOSE

The purpose of this study is to determine if a dietary supplement of DHA during pregnancy will help babies be born at the right time and help their development. If you decide to be in the study, you will have a 50-50 chance of receiving capsules with the supplement of DHA or ordinary food oil, which does not contain any DHA.

## PROCEDURES

If you choose to enroll yourself and your infant in this study, the investigators will record some information from your medical record about your pregnancy and medical history. They will also ask you a few questions about foods that you usually eat. You will have a blood sample collected from a vein in your arm. One-half teaspoon of blood will be drawn. The blood will be used to measure DHA in your blood as well as other nutrients. You will be asked to provide a current address and phone number where you can be contacted. .

**During** pregnancy: You will be randomly assigned (like flipping a coin) to capsules with DHA-oil or ordinary food oil (which does not contain any DHA). The DHA-oil is the same oil that is used in US infant formulas and has been fed safely to millions of infants.

You will be given enough capsules each month to take 3 capsules each day and you agree to try to consume all 3 capsules. If you consume all 3 capsules, you will consume 600 mg of DHA. The capsules are relatively small and you should find them easier to swallow than many nutrient supplements. They are orange-flavored, so if you burp (common in pregnancy and in the first week of taking any nutrient supplement), the taste should not be unpleasant. You do not need to take the capsules at any specific time as they are a nutrient and not a drug. However, you should decide upon a regular time to take them so that taking the capsules will become a habit and you won't forget. For example, you might wish to take them just before you go to bed or when you have your first beverage of the day.

Neither you nor the investigators will know which capsules you have been assigned to. On the day you enroll for the study, we will send you home with your first bottle of capsules. About 30 days later (early enough so that you do not run out of capsule), you will receive another bottle of capsules in the mail. **AT THAT TIME, YOU AGREE TO PLACE THE FIRST BOTTLE WITH ANY REMAINING CAPSULES IN THE ENVELOPE AND DROP IT INTO THE MAIL.**

This process will be repeated each month until your baby is born and you will continue to take 3 capsules per day until your baby is born. Each time you receive a new bottle, you will mail back the bottle that you have been using and that day will open and begin using the new bottle.



The investigators will contact you by phone at least once per month. They will ask about capsule intake and they will ask how you are doing. Maintaining contact with our study personnel on a monthly basis is very important.

**IF YOUR PHONE NUMBER OR ADDRESS CHANGES AT ANY TIME DURING THE STUDY, YOU WILL LET THE INVESTIGATORS KNOW BY CALLING 913-588-3781 AND LEAVING A MESSAGE.**

**Delivery:** After you are admitted to the hospital to deliver, you should telephone study personnel or ask the person at admitting to telephone them. You will be given a cell phone number today to call. Once you deliver your baby, the investigators will visit you in the hospital to collect data about your delivery and your baby's health. A sample of your baby's cord blood will be collected after delivery by nurses at the hospital and given to the investigators. A nurse will also draw a small blood sample (one-half teaspoon) from you while you are in the hospital. The blood samples will be used to measure DHA and other nutrients. The investigators will visit you, and give you an appointment for your baby's first follow-up visit at KUMC.

**Visit 1 (6 weeks of age):** The investigators will measure how your baby sees using a test that involves placing 3 electrodes directly on your baby's head. The process involves cleaning the area then placing a small amount of paste similar to toothpaste on the head. The electrodes are placed on top of the paste. The electrodes will be used to record your baby's brain waves while he/she is looking at pictures. Your child's weight, height and head circumference will be measured again and you will be asked questions about what your baby eats. If you are breastfeeding your baby, you will be asked to provide a teaspoon of breast milk to the investigator. The sample will be frozen and analyzed for fats that are found in the capsules. The visit should last about 40 minutes. You should arrive on time and allow that amount of time for the visit.

**Visit 2 (4 months of age):** The investigators will measure how your baby sees using the same test as before and another vision test. Your baby will wear a pair of plastic glasses during the second test. In another test, your child will be given an object to look at several times. The investigator will measure how long he/she looks at the object and how quickly he/she stops looking at the object. Your child will be video recorded during the test. Your baby's heart rate will be measured during the test. Your baby's height, weight and head circumference will be measured and you will be asked about what food your baby eats. Your baby will have a blood sample collected by either heel stick or drawn from a vein. If it is necessary to use a heel stick, the investigator may use a cream or spray that will numb the area before obtaining the sample. One-half teaspoon of blood will be drawn. The blood will be used to measure DHA and other nutrients. You should let the investigator know if your baby has been sick or not acting well

since his/her last visit. The visit will take 60-90 minutes.

Visit 3 (6 months of age): The investigators will measure how your baby sees using the test that requires him/her to wear a pair of plastic glasses. In another test, he/she will be given an object to look at several times (just like at 4 months of age). The investigator will measure how long he/she looks at the object and how quickly he/she stops looking at the object. Your child will be video recorded during the test. Your baby's heart rate will be measured during the test. Your baby's height, weight and head circumference will be measured. You will be asked questions about what your baby eats. You should let the investigator know if your baby has been sick or not acting well since his/her last visit. The visit should take 40 -60 minutes.

Visit 4 (9 months of age): Your baby will have both tests that measure how he/she sees. In another test, your child will be given an object to look at several times (just like at 4 and 6 months of age). The investigator will measure how long he/she looks at the object and how quickly he/she stops looking at the object and your baby's heart rate will be measured during the test. Your child will be video recorded during the test. Your baby's height, weight and head circumference will be measured. You will be asked questions about what your baby eats. You should let the investigator know if your baby has been sick or not acting well since his/her last visit. The visit should take about 40-60 minutes.

Visit 5 (10 months of age): During this visit your baby will be placed on your lap in front of a small table. A test will be completed with a small toy, foam block and 2 cloths that will be placed in front of your child. You will also take a short language test. The small toy will be given to your child to keep. In another test, your baby will be asked to take turns with the researcher building fun toys. After your baby has played for a moment with the pieces, the researcher will show him or her how to build the toy. Then, your baby will be given a turn to put the toy together. Your baby's turn will happen either immediately or after 10-minutes of play with other things. We will show your child objects in groups of 2 and 3 to see how long they look at the objects. Your child will be video recorded during the tests. You should let the investigator know if your baby has been sick or not acting well since his/her last visit. You will be asked questions about what your baby eats. The entire 10-month visit should last 70 minutes.

Visit 6 (12 months of age): The investigators will measure how your baby sees using both vision tests. Your child will be video recorded while playing with an interesting toy and the investigator will use the recording to measure some aspects of attention. We will show your child objects in groups of 2 and 3 to see how long they look at the objects. Your child's height, weight and head circumference will be measured. You will be asked questions about what your baby eats. You should let the investigator know if your child has been sick or not

acting well since his/her last visit. We will request your child's medical record from his/her doctor. The visit should take about 2 hours. It is important that your child be rested before the testing at this visit. If for some reason your baby cannot finish the tests that day – this may happen if he/she is unusually fussy or tired – you will be asked to return to finish the remaining tests within 7 days.

Visit 7 (18 months of age): The investigators will measure how your child sees using the test that he/she had while wearing plastic glasses. Your child will be video recorded while playing with an interesting toy and the investigator will use the recording to measure some aspects of attention. Your child will also be given a standardized test to measure mental and physical development. Your child's height, weight and head circumference will be measured. You will be asked questions about what your baby eats. You will be asked questions about the words your child uses and understands. You should let the investigator know if your child has been sick or not acting well since his/her last visit. The visit should take about 2 hours. It is important that your child be rested before the testing at this visit. If for some reason your child cannot finish the tests that day – this may happen if he/she is unusually fussy or tired – you will be asked to return to finish the remaining tests within 7 days.

## RISKS

Some redness, soreness, or bruising may occur at the site of blood sampling. There is also a very slight risk of infection.

You may experience burping from the capsules and find this unpleasant

There are no known risks of consuming the amount of DHA you will be provided if you receive the DHA. Even if you forget to take your capsules for one or two days, there is no known risk of deciding to "catch up" on the third day. The amount is smaller than pregnant

women in many countries eat every day. Nevertheless, you could develop a problem that has not been observed before.

## NEW FINDINGS STATEMENT

You will be informed if any significant new findings develop during the course of the study that may affect your willingness to participate or to allow your child to participate in this study.

## BENEFITS

You and your child may or may not benefit from participating in this study. If you receive the supplement, it may help your baby to be born at the right time and your baby's/child's development. If you will not get the supplement, your baby and you will not be getting any of those benefits. It is also possible that all

infants/children will get some benefit from being followed closely with developmental testing. It is hoped that additional information gained in this research study may be useful in understanding if DHA can help your baby be born at the right time and help your baby's vision, attention, and learning as he or she grows. You will receive a video recording of your infant doing the 4, 6, and 9 month looking test when the 12 month visit is complete

#### ALTERNATIVES

You do not have to participate in this study to be able to take DHA supplements while you are pregnant. You may purchase capsules containing DHA at local stores without a prescription (for example, Osco, Costco, Wal-Mart). There are also several brands of prenatal supplements with DHA available by prescription or over the counter. The prenatal capsules typically contain 200 mg of DHA each and are marketed to take one capsule/day as a DHA supplement.

#### COSTS

Capsules containing either DHA or food oil will be provided to you at no cost while you are participating in this study. You will not incur any costs because of your or your child's participation

#### PAYMENT TO SUBJECTS

If study investigators are able to communicate with you each month you will be given 2 bonus gift cards to either Wal-Mart or Target of \$25 each. The first gift card will be given to you half way through your treatment phase if communication is maintained at least one time each month during the first half of your treatment. The second gift card will be given at delivery if communication maintained at least one time each month during the second half of your treatment.

Additionally, if the study investigators are called after you are admitted for delivery you will be given your choice of a bonus gift card worth \$50 from either Wal-Mart or Target. You may make the call yourself or have someone else call for you. Study personnel will give you the gift card when they come to the hospital after your baby is born.

Once your baby is born, you will receive a check for \$50 after your baby completes each of the following visits: 6 weeks, 4 months, 6 months, 9 months, and 10 months. You will receive a check for \$100 after your child completes each of the following visits: 12 and 18 months.

The reimbursements are to cover the costs of transportation and to partially compensate you for your time required to participate in the study.

Your IOMe, address, social security number, and the title of this study will be given to the KUMC Research Institute. This is done so that the Research Institute can write a check for study payments. Payments are taxable income.

### IN THE EVENT OF INJURY

In the event you experience any serious health problem (hospitalization, life-threatening illness, or death) for any reason during your pregnancy, you should immediately seek treatment or help in the way you normally would as if you were not in a study. You should let Susan Carlson, Ph.D. know about any of these problems as soon as possible by calling her office (913-588-5359) or the study office (913-588-3781). A message may be left at both numbers. Dr. Carlson may also be reached at home (816-960-1805).

### INSTITUTIONAL DISCLAIMER STATEMENT

If you believe you have been injured as a result of participating in research at Kansas University Medical Center (KUMC), you should contact the Director, Human Research Protection Program, Mail Stop #1032, University of Kansas Medical Center, 3901 Rainbow Blvd., Kansas City, KS 66160. Compensation to persons who are injured as a result of participating in research at KUMC may be available, under certain conditions, as determined by state law or the Kansas Tort Claims Act.

Truman Medical Center (TMC) will provide medical attention to you if you suffer any injury or harm as a direct result of participating in this research project. TMC, your study doctor, and the sponsor of this study will decide, at their discretion, who should pay for the medical care. TMC will provide treatment to you in the event of any medical emergency while present at TMC, whatever the cause. Moreover, you will have the benefit of the coverage of any existing healthy insurance you own. Participation in this research study does not take the place of routine physical examinations or clinic visits to your personal physician. If you believe you have been injured as a result of participating in this study you are encouraged to contact the study investigator, Dr. Susan Carlson, at her work number, 913-588-5359.

The University of Missouri-Kansas City appreciates the participation of people who help it carry out its function of developing knowledge through research. Although it is not the University's policy to compensate or provide medical treatment for persons who participate in studies, if you think you have been injured as a result of participating in this study, please call the investigator, Dr. Susan Carlson at 913-588-5359 (work) or Sheila Anderman, IRB administrator of UMKC's Adult Health Sciences Institutional Review Board at 816-235-6150

### CONFIDENTIALITY AND PRIVACY AUTHORIZATION

Names of subjects or information identifying subjects will not be released without written permission unless required by law. Videotapes of your baby when he/she is looking at pictures and playing with toys will be used only by the investigators and their students and to make a videotape copy for you. The videotapes will be secured under lock and key like all other information that could be linked directly

to your child. The videotape of your child will not be shown without specific permission from you and even then would not identify your

child by IOMe. Efforts will be made to keep you and your child's personal information confidential. Researchers cannot guarantee absolute confidentiality. If the results of this study are published or presented in public, information that identifies you and/or your baby will be removed.

The privacy of you and your child's health information is protected by a federal law known as the Health Insurance Portability and Accountability Act (HIPAA). If you choose to participate in this study, you will be asked to give permission for researchers to use and disclose your and your baby's health information that is relevant to the study.

To perform this study, researchers will collect health information about me and my child from his/her and my medical records and from the study activities that are listed in the Procedures section of this consent form. My and my baby's study-related health information will be used at KU Medical Center by Dr. Carlson, members of the research team, Truman Medical Center, St. Luke's Hospital and the KU Hospital Medical Record Department, the KUMC Research Institute and officials at KUMC and at Truman Medical Center that oversee research, including the KUMC Human Subjects Committee, the IRB that governs St. Luke's Medical Center and Truman Medical Center and other committees and offices that review and monitor research studies.

Dr. Carlson and her team may share information about me and my baby with representatives of Martek Biosciences, the monitoring company who verifies study data, the laboratory that processes study lab samples, other business partners who help with the study, the U.S. Food and Drug Administration (FDA), and U.S. agencies that govern human research (if and when regulatory compliance issues arise). Martek Biosciences (Columbia, MD) donated the capsules for this study that is otherwise supported by the National Institute of Child Health and Human Development.

Some of the persons or groups that receive my and my baby's study information may not be required to comply with HIPAA privacy laws. My and my child's information may lose its federal protection if those persons or groups disclose it.

Permission granted on this date to use and disclose my health information remains in effect indefinitely. By signing this form I give permission for the use and disclosure of my and my child's information for purposes of the study at any time in the future.

If I enroll in the study, the investigators cannot tell me what capsule I was assigned to until the study ends. This may be after I have stopped taking the

capsules.

#### QUESTIONS

I have read the information in this form. Dr. Carlson or her associates have answered my question(s) to my satisfaction. I know if I have any more questions after signing this I may contact Dr. Carlson or one of her associates at (913) 588-5359. If I have any questions about my or my child's rights as a research subject, I may call (913) 588-1240 or write the Human Subjects Committee, University of Kansas Medical Center, 3901 Rainbow Blvd. MSN 1032, Kansas City, KS 66160.

#### SUBJECT RIGHTS AND WITHDRAWAL FROM THE STUDY

My and my child's participation in this study is voluntary and the choice to not participate or to quit at any time can be made without penalty or loss of benefits. Not participating or quitting will have no effect upon the medical care of treatment my child receives now or in the future at the University of Kansas Medical center. The entire study may be discontinued for any reason without my consent by the investigator conducting the study, by the sponsor of the study, or the FDA. My child's participation can be discontinued by the investigator or by the sponsor if it is felt to be in my child's best interest or if I do not follow the study requirements. If I choose to withdraw before my child is 18 months of age, I may be asked to answer questions about the study on the telephone.

If I want to cancel permission to use my or my child's health information, I should send a written request to Dr. Carlson. The mailing address is Susan Carlson, Ph.D., Dept. of Dietetics and Nutrition, MS 4013, 4019 Delp, University of Kansas Medical Center, 3901 Rainbow Boulevard, Kansas City, KS 66160. If I cancel permission to use my child's health information, the research team will stop collecting any additional information about me and my child.

Should the study be terminated prior to the completion of my pregnancy, neither the investigator nor the University of Kansas Medical Center will be under any obligation to provide me with DHA capsules used in the study.





