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Original Research

The Effect of Prenatal Docosahexaenoic Acid Supplementation on Offspring Fat Mass and Distribution at 24 Months Old

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A B S T R A C T

Background: Excessive gestational weight gain (GWG) is related to increased offspring fat accrual, and increased fat mass (FM) is related to obesity development. Prenatal DHA supplementation has been linked to lower levels of offspring FM; however, conflicting data exist.
Objectives: This study aimed to determine if there is a protective effect of prenatal DHA supplementation on offspring fat accrual and adipose tissue deposition at 24 mo in offspring born to females who gain excessive weight compared with nonexcessive weight during pregnancy. We also explored if the effect of DHA dose on FM differed by offspring sex.
Methods: Infants born to females who participated in the Assessment of DHA on Reducing Early Preterm Birth randomized controlled trial (ADORE) were recruited. In ADORE, females were randomly assigned to either a high or low prenatal DHA supplement. Offspring body composition and adipose tissue distribution were measured using dual-energy x-ray absorptiometry (DXA). GWG was categorized as excessive or not excessive based on clinical guidelines.
Results: For total FM, there was a significant main effect for the DHA dose ($P = 0.03$); however, the dose by GWG status was nonsignificant ($P = 0.44$). Therefore, a higher prenatal DHA dose was related to greater offspring FM (622.9 g greater) and unrelated to GWG status. When investigating a DHA dose by sex effect, a significant main effect for DHA dose ($P = 0.01$) was detected for central FM. However, no interaction was detected ($P = 0.98$), meaning that both boys and girls had greater central FM if their mother was assigned to the higher DHA dose.
Conclusions: Greater prenatal DHA supplementation was associated with greater offspring FM and adipose tissue distribution at 24 mo. It will be important to understand if these effects persist into childhood.
This trial was registered at clinicaltrials.gov as NCT03310983.

Keywords: pregnancy, infancy, DHA, body composition, programing, adipose tissue distribution, excessive gestational weight gain

Introduction

High rates of overweight and obesity in United States children and adolescents [1] continue to be identified, necessitating an understanding of targets and windows of opportunity for intervention. During the first 1000 d, there is a rapid expansion in the number and size of adipocytes [2,3], resulting in varying amounts of adipose tissue. At birth, the differences in weight are largely due to variations in adipose tissue, because fat-free mass (FFM) is relatively stable [4,5]. Excessive gestational weight gain (GWG) is a known risk factor related to greater total fat mass (FM) and central FM in newborns [6,7], children [8,9], and adults [10]. There is a strong relationship between excessive GWG and offspring obesity development [11,12], diabetes, and cardiovascular disease [13,14]. Therefore, mitigating the effect of excessive GWG on offspring outcomes is critical.

Abbreviations: ALA, α-linolenic acid; ADORE, Assessment of DHA on Reducing Early Preterm Birth randomized controlled trial; COPSAC, Copenhagen Prospective Studies on Asthma in Childhood; DRI, dietary reference intake; DOMInO, DHA to Optimize Mother Infant Outcome; DHQ-II, Diet History Questionnaire II; DXA, dual-energy x-ray absorptiometry; FAME, fatty acid methyl esters; FM, fat mass; FFM, fat-free mass; GDM, gestational diabetes mellitus; GWG, gestational weight gain; GAINS, Growth and Adiposity in Newborns Study; HEI, healthy eating index; NCI, National Cancer Institute; NDS-R, Nutrition Data System for Research; RBC, red blood cell; RCT, randomized control trial.

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Increased maternal intake of PUFAs has been related to lower offspring FM and central adiposity in cross-sectional studies [15–18], whereas some have found no benefit [19]. It is hypothesized that an n-3 PUFA like DHA influences adipocyte development by preventing stem cells from maturing into adipocytes [20–23], downregulating the expression of genes involved in lipogenesis (fatty acid synthase, lipoprotein lipase, and stearoyl-CoA desaturase-1), and upregulating the expression of genes involved in β oxidation (acetyl Co-A oxidase) [24,25]. Although prenatal supplements are commonly consumed by pregnant females, only 1.5% of pregnant females report taking a prenatal supplement that includes DHA, totaling 1.18 g/mo for DHA + EPA, well below the recommended 6–9 g/mo [26] for DHA + EPA. DHA status is lower in United States females than in other developed countries [27–29], with DHA red blood cell (RBC) concentrations ranging from 4.3% to 5.0 % [28,30,31] compared with ≥6% reported by others [32–34]. In the United States, pregnant females and females of reproductive age consume ~60 mg DHA per day [35,36] and synthesize very little DHA (~40 mg) from α-linolenic acid (ALA; 18:3n-3) consumed in other foods [37,38]. This falls well below the expert recommendation of 200 mg/d of DHA during pregnancy, as no dietary reference intake (DRI) exists [39].

Only 2 randomized clinical trials have evaluated the effect of prenatal DHA supplementation on offspring adiposity using a direct measure of body composition [40–42]. The DHA to Optimize Mother Infant Outcome (DOMInO) trial found no between-group differences in offspring body composition at 3 and 5 y [40] or 7 y [43]; however, they found increased central adiposity at 3 y old only. Additionally, a follow-up of the Copenhagen Prospective Studies on Asthma in Childhood (COPSAC) found in offspring exposed to prenatal DHA supplementation, a higher mean BMI from birth to 10 y old and a higher odds ratio of being overweight and having increased body fat at 10 y old [44]. These data suggest that prenatal DHA supplementation may impact offspring central and total adiposity during early childhood that is detected later in midchildhood.

To the best of our knowledge, no study has investigated if DHA supplementation mitigates the risk of greater offspring adiposity accrual associated with excessive GWG. Therefore, this study aimed to determine if the prenatal dose of DHA (1000 mg/d compared with 200 mg/d) interacted with GWG status (excessive or not excessive) to influence total infant FM at 24 mo. The secondary aim was to determine if the prenatal dose of DHA interacted with offspring sex to influence infant central FM at 24 mo.

Methods

To answer the proposed research questions, offspring born to females who were enrolled in the Assessment of DHA on Reducing Early Preterm Birth randomized controlled trial (ADORE; NCT02626299) were invited to enroll in the Growth and Adiposity in Newborns Study (GAINS; NCT03310983). The study methods for each trial are described below.

Study overview of the ADORE trial

The ADORE (HD083292; NCT0262299) study protocol [45] and primary results [46] have been published. An overview of the study and methods are briefly discussed. The primary purpose of the ADORE trial was to determine if high or low prenatal DHA supplements (1000 mg/d or 200 mg/d, respectively) influenced early preterm birth (<34 weeks of gestation). ADORE was a randomized, double-blind, controlled phase III clinical trial of DHA supplementation during the last 2 trimesters of pregnancy. ADORE study enrollment occurred at 3 sites (Kansas City, KS; Columbus, OH; and Cincinnati, OH), whereas the GAINS study only enrolled offspring from Kansas City, KS. The inclusion and exclusion criteria are listed in the ADORE protocol [45]. Females aged ≥18 y and in their 12th to 20th week of gestation were eligible for enrollment. At the Kansas City site, 489 pregnant participants were enrolled. The study was approved by the HSC (00003455), and informed consent was obtained before completion of any study activities.

Fatty acid analysis

Maternal blood taken at enrollment and birth and cord blood were analyzed for red blood cell (RBC) phospholipid fatty acid content. RBCs were separated from plasma and buffy coat by centrifugation (3000 × *g*, 10 min; 4°C), frozen, and stored under nitrogen at −80°C until analysis. Phospholipids from erythrocytes were isolated according to a modified Folch method [28], fractionated by thin-layer chromatography, transmethylated with boron trifluoride-methanol, and the resulting fatty acid methyl esters (FAME) were separated and quantified using a gas chromatograph (Varian 3900; Varian Inc.) with a capillary column (100 m; SP-2560, Sigma Aldrich) and a chromatography workstation (Star 6.41; Agilent) for peak integration and analysis [28]. Individual peaks were identified by comparison with qualitative standards (PUFA 1 and PUFA 2; Sigma Aldrich), and a preweighed standard mixture (Supelco 37 Component FAME mix; Sigma Aldrich) was used to adjust fatty acids for area or weight to calculate the final weight percent of total fatty acids.

Gestational weight gain

GWG was calculated by subtracting the self-reported prepregnancy body weight from the last body weight measured in the outpatient clinic (from the electronic medical record) before delivery. In the clinic, body weight was measured in light clothing with shoes removed. To accurately categorize weight gain status, we accounted for gestational age at the last recorded clinic visit. Using the recommended rate of weight gain range for the third trimester [47], we calculated a personalized range for each participant. The personalized range was used to classify GWG according to the 2009 IOM GWG guidelines as excessive or not excessive [47].

Maternal dietary intake

Maternal dietary intake was measured at enrollment. The National Cancer Institute (NCI) Diet History Questionnaire II (DHQ-II) food frequency questionnaire was completed by each English-speaking non-Latina female. Data collected from the DHQ-II was analyzed using Diet*Calc Analysis software to generate dietary intake of nutrients and food groups. The DHQ-II was not developed or validated in a population of Latina adults. Therefore, to accurately assess and represent dietary intake in our Latina population, 24-h dietary recalls were completed. A trained research staff fluent in Spanish collected the recall information using the multiple-pass method. Spanish-speaking and

English-speaking Latina females did not complete the DHQ-II and instead completed 3 24-h dietary recalls, 2 during weekdays and 1 on the weekend. The recalls were entered into the Nutrition Data System for Research (NDS-R, version 2017) for macro- and micronutrient analysis.

Study overview of the GAINS proposal

Infants born to females who participated in the ADORE randomized controlled trial (RCT) were invited to enroll in the GAINS study (DK118220; NCT03310983). The GAINS study protocol has been published [48]. The primary aim of GAINS was to determine if the prenatal dose of DHA (1000 mg/d or 200 mg/d) interacted with GWG (excessive or nonexcessive) to influence total infant FM at 24 mo. The secondary aim was to determine if the prenatal dose of DHA (1000 mg/d or 200 mg/d) interacted with sex (male or female) to influence infant central FM at 24 mo. The study was approved by the HSC (0000140895) and informed consent was obtained before the completion of any study activities.

Anthropometrics

Body weight was assessed using a calibrated scale (Detetco Scales) throughout the study duration. Length was measured using an infant length board (Shorr Productions), and beginning at 18 mo, standing height was measured using a wall-mounted stadiometer (Accu-Hite; Seca Corp.). Subjects removed their shoes and were centered on the stadiometer. Height was recorded to the nearest 0.1 cm. Two measurements were taken, and the average was recorded.

Dual-energy x-ray absorptiometry to measure total body fat and adipose tissue distribution

Dual-energy x-ray absorptiometry (DXA, encore software version 13.60; Prodigy) was used to measure body composition and regional adipose tissue distribution. Using specific anatomic landmarks as previously described [48], regions including the arms, legs, and trunk were demarcated (arm fat, leg fat, and trunk fat). Infants were placed in an immobilizer to prevent movement and ensure body positioning to allow for the identification of landmarks and regions. One rater analyzed all scans and determined if movement was detected that would have invalidated the results. These scans were marked as unusable. Calculations were completed for total FM, represented by total body less head. Regional adipose tissue distribution was represented by the central (trunk) and peripheral (arms plus legs).

Dietary intake of the child

One multiple-pass 24-h dietary recall was administered to the child's caregiver and collected by trained research staff at each visit to characterize energy and nutrient intake. The 24-h recalls accurately estimate dietary intake [49,50] and contain less reporting bias than diet records [49,51]. The recalls were entered into NDS-R version 2017 for macro- and micronutrient analysis. Specific details on the current method of infant feeding were collected (e.g., breastfeeding, formula), and the introduction of solids was assessed at each study visit.

Power calculation

Details for the power calculation were provided in the GAINS study protocol [48]. Briefly, a power calculation was completed to ensure an adequate sample size to address the primary aim: to determine if the effect of GWG status (excessive or not excessive) is modified by the prenatal dose of DHA (1000 mg/d or 200 mg/d) to influence total infant FM at 24 mo of age. The data used for the power analysis was from pilot data in offspring exposed to high or low prenatal DHA doses. The change in FM (g) was assessed in early infancy, and a mean difference of −168 compared with 304 g was found between groups, with a within-group standard deviation of 442 g. Based on the power calculation, we found that a total sample size of 120 was required to answer the primary aim, resulting in a power of 0.815. Allowing for 20% attrition, the sample size increased to 150.

Statistical analysis

The primary aim was to determine if the prenatal dose of DHA (1000 mg/d or 200 mg/d) interacts with GWG status (excessive or not excessive) to influence total infant FM at 24 mo. Using univariate analysis of covariance (ANCOVA), the primary analysis tested the DHA dose effect (high or low) in excessive GWG compared with that in not excessive GWG. The secondary aim determined if the prenatal dose of DHA interacts with offspring sex to influence infant central FM at 24 mo. Using ANCOVA, secondary analysis tested the DHA dose effect in males compared with that in females. Both the primary and secondary aims included testing for the following confounding variables to be included in an adjusted model: maternal age, maternal race/ethnicity, education, prepregnancy BMI, GWG, ever smoker, marital status, parity, healthy eating index (HEI), prenatal RBC ω-6 concentrations, maternal RBC DHA concentrations at ADORE enrollment and delivery, offspring HEI, offspring sex (aim 1 only), offspring age at the time of DXA scan, and offspring gestational age at birth. Because of the limitations of the sample size, we could not include all confounders in the adjusted model. To determine which confounders to include in the adjusted analysis, each confounder was individually added to the unadjusted models (DHA dose, GWG status or offspring sex, and the interaction) and was included by defining a significance level for entry into the model of $P < 0.1$. All analyses were performed using participants who completed the 24-mo study visit and had usable total FM data from the DXA scan. Data of participants who withdrew, were lost to follow-up, or did not have a usable scan were treated as missing and excluded from the analysis. We used PROC GLM in SAS 9.4 for all analyses.

The GAINS trial was powered using an analysis of variance model for the continuous outcome of total FM. The model tested the interaction between GWG status (excessive or not excessive) and DHA dose (1000 mg/d or 200 mg/d), allowing us to investigate if the high dose supplement of DHA reduced infant FM compared with the low-dose supplementation and specifically, if this reduction was greater in offspring exposed to excessive GWG. The original power was quoted as 81.5% [48]; however, the power dropped to 52% with the attained sample size.

Results

Figure 1 presents the consort diagram for the ADORE and GAINS studies, and Table 1 presents the participant characteristics. Of the 489 ADORE participants who enrolled at KUMC [46], 448 continued to be followed up at the time of delivery. Of

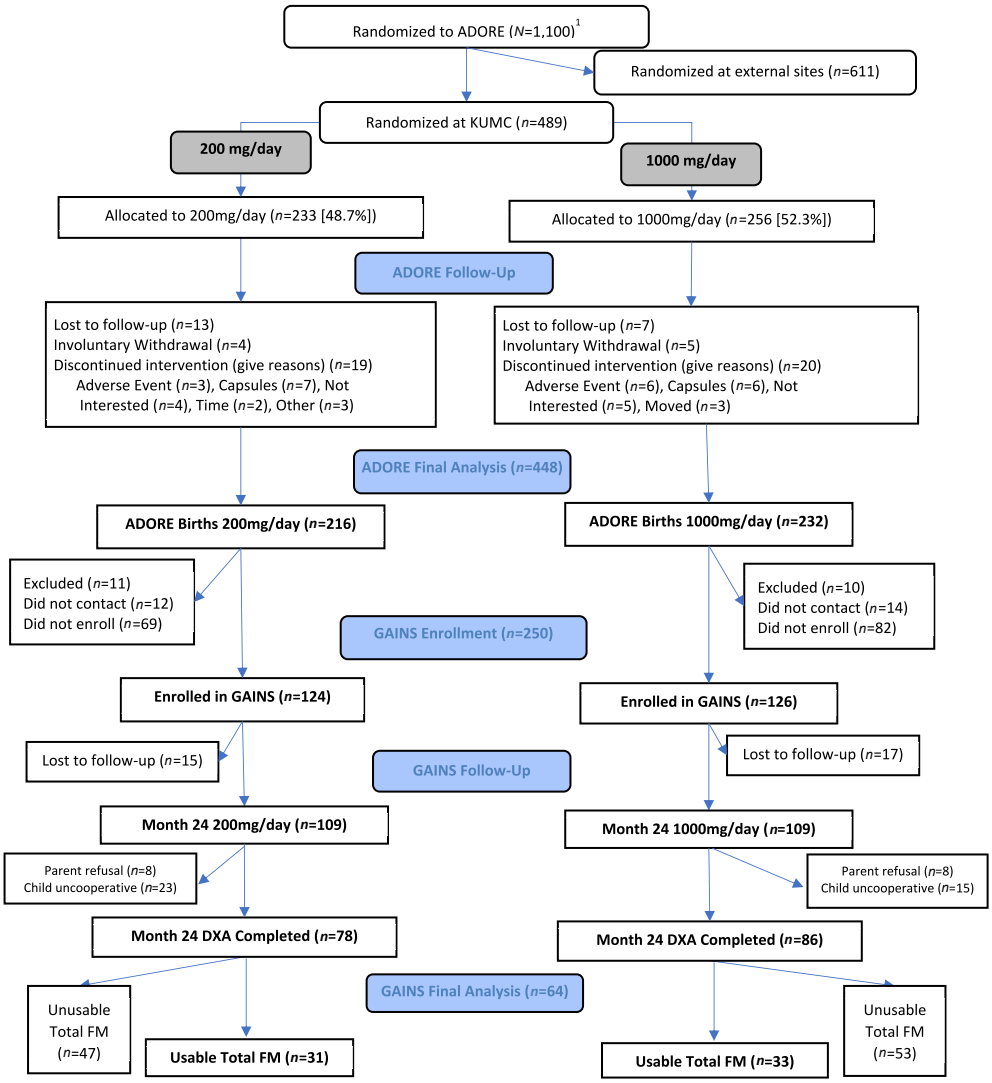

FIGURE 1. Consort diagram. ADORE, Assessment of DHA on Reducing Early Preterm Birth randomized controlled trial; DXA, dual-energy x-ray absorptiometry; FM, fat mass; GAINS, Growth and Adiposity in Newborns Study.

the 448 ADORE females who could be enrolled in GAINS, 297 were screened for eligibility and 250 were enrolled (55.8%). There were 124 females who enrolled and received 200 mg/d DHA and 126 females who enrolled and received 1000 mg/d DHA. Based on the a priori definition of adherence determined by the ADORE study [46], 90.9% of the females with data included in the primary aim were adherent.

Table 2 presents delivery and birth characteristics. Eleven participants were missing either their prepregnancy BMI or their last prenatal weight; therefore, their GWG status could not be calculated. The observed rates of excessive GWG were 62.8% (76/121) and 69.5% (82/118) for low- and high dose DHA, respectively. A total of 52% of the offspring were male; newborns had a mean gestational age of 38.8 wk (SD = 1.4) and a mean birth weight of 3347.4 g (SD = 481.4). Table 3 provides descriptive characteristics for offspring measurements at the 24-mo visit by group randomization. No between-group differences were found for any of the reported characteristics. There were 218 infants who completed a 24-mo visit; however, 16 parents refused the DXA scan and 38 children were uncooperative, resulting in 164 DXA scans available. For total FM, 100 scans were unusable because of movement during the scan, resulting in 64 usable scans. Supplementary Table 1 compares the offspring characteristics at the 24-mo visit for unusable or usable data. No between-group differences were found for any characteristics. In those with usable DXA data ($n = 64$), Table 4 compares scans of offspring characteristics at the 24-mo visit by DHA dose. The DHA dose received was closely balanced for those with usable data, with 48.4% receiving 200 mg/d and 51.6% receiving 1000 mg/d. For the 218 infants who completed a 24-mo visit, the mean body weight was 12,684.6 g (SD = 1627.4) and 12,983.6 g (SD = 2071.2) for the low and high DHA doses, respectively. For the 64 infants who had usable 24-mo total FM data, the mean weights were 12,407.7 g (SD = 1491.3) and 13,203.0 g (SD = 2092.3) for the low and high DHA doses, respectively. Offspring in the high DHA dose group had higher total FM and FFM.

Table 5 presents offspring body composition estimates by DHA dose and GWG status. All estimates presented in the tables are for the adjusted models, including the covariates listed in the footnotes. There was no difference in results between the adjusted and unadjusted models. For the model examining total FM, there was a significant main effect for the DHA dose ($P = 0.03$); however, the

TABLE 1
Maternal baseline characteristics for GAINS enrollees

	200 mg/d $N = 124$ (49.6%)	1000 mg/d $N = 126$ (50.4%)	Total $N = 250$
Age at ADORE enrollment, y	30.4 ± 5.1	31.4 ± 5.6	30.9 ± 5.4
DHA mean % of RBC total fatty acids (SD)	6.5 (1.7)	6.1 (1.6)	6.3 (1.6)
Marital status, *n* (%)			
Married/Partnered	92 (74.2)	95 (75.4)	187 (74.8)
Other[1]	32 (25.8)	31 (24.6)	63 (25.2)
Maternal race and ethnicity, *n* (%)			
American Indian or Alaskan Native	1 (0.8)	0 (0)	1 (0.4)
Asian	0 (0.0)	5 (4.0)	5 (2.0)
Black or African-American	13 (10.5)	9 (7.1)	22 (8.8)
Hispanic	42 (33.9)	53 (42.1)	95 (38.0)
White	65 (52.4)	58 (46.0)	123 (49.2)
Biracial: Asian, White	1 (0.8)	0 (0)	1 (0.4)
Biracial: Black, White	2 (1.6)	0 (0)	2 (0.8)
Multiracial: Black, American indian, White	0 (0.0)	1 (0.8)	1 (0.4)
Maternal education, *n* (%)			
Less than high school graduate	18 (14.5)	28 (22.2)	46 (18.4)
HS graduate or GED	19 (15.3)	21 (16.7)	40 (16.0)
Some college or tech school	23 (18.6)	21 (16.7)	44 (17.6)
Bachelor's degree obtained	45 (36.3)	30 (23.8)	75 (30.0)
Master's degree obtained	16 (12.9)	21 (16.7)	37 (14.8)
Doctorate	3 (2.4)	5 (4.0)	8 (3.2)
Family income, *n* (%)			
<$15,000	17 (13.7)	18 (14.3)	35 (14.0)
$15,000–$24,999	18 (14.5)	20 (15.9)	38 (15.2)
$25,000–$49,999	24 (19.4)	29 (23.0)	53 (21.2)
$50,000–$99,999	26 (21.0)	21 (16.7)	47 (18.8)
$100,000–$149,999	23 (18.6)	25 (19.8)	48 (19.2)
≥$150,000	16 (12.9)	11 (8.7)	27 (10.8)
Unknown	0	2 (1.6)	2 (0.8)
Ever smoker, yes *n* (%)	27 (21.8)	28 (22.2)	55 (22.0)
6 mo prior, yes *n* (%)	14 (11.3)	10 (7.9)	24 (9.6)
Current smoker, yes *n* (%)	3 (2.4)	4 (3.2)	7 (2.8)
Pregnancy history, *n* (%)			
Primagravida	36 (29.0)	33 (26.2)	69 (27.6)
Prior preterm birth	19 (15.3)	14 (11.1)	33 (13.2)
Prior early preterm birth (<34 wk)	8 (6.5)	3 (2.4)	11 (4.4)
Parity, mean (SD)	2.5 (1.6)	2.8 (1.7)	2.7 (1.7)
	$N = 120$	$N = 121$	$N = 241$
Diet quality, HEI, mean (SD)	62.2 (10.1)	62.7 (11.2)	62.5 (10.7)
	$N = 123$	$N = 123$	$N = 246$
Prepregnancy BMI, kg/m^2, mean (SD)	28.0 ± 6.7	29.2 ± 8.1	28.6 ± 7.4
Normal weight, *n* (%)	46 (37.4)	41 (33.3)	87 (35.4)
Overweight, *n* (%)	41 (33.3)	34 (27.6)	75 (30.5)
Obese, *n* (%)	36 (29.3)	48 (39.0)	84 (34.2)

Abbreviations: ADORE, Assessment of DHA on Reducing Early Preterm Birth randomized controlled trial; BMI, body mass index; HEI, healthy eating index; RBC, red blood cell.
[1] divorced ($n = 4$), separated ($n = 3$), unmarried/single ($n = 56$).

dose by GWG status was nonsignificant ($P = 0.44$). This suggests that a higher prenatal DHA dose was related to higher offspring FM (622.9 g greater), and this effect was found regardless of excessive or not excessive GWG. We hypothesized that in offspring exposed to excessive GWG, a high dose of prenatal DHA supplementation would reduce infant FM compared with low-dose supplementation. However, we found higher FM in infants exposed to the high prenatal DHA dose, with no difference based on GWG status. Regarding adipose tissue distribution, a significant main effect was found for the DHA dose for central FM ($P = 0.003$); however, the dose by GWG status interaction was nonsignificant ($P = 0.53$). For the covariates included in both models, an increase in age at the DXA scan and Hispanic ethnicity of offspring resulted in higher masses.

Table 6 presents offspring adipose tissue distribution estimates by DHA dose and offspring sex. For central FM, 40 scans were unusable because of movement during the scan, resulting in 124 usable scans. A significant main effect for DHA dose ($P = 0.01$) was detected; however, the dose by offspring sex interaction was nonsignificant ($P = 0.98$). This suggests that a higher prenatal DHA dose was related to higher central FM, and this was found in both boys and girls. All estimates presented in the tables are for the adjusted models, including the covariates listed in the footnotes. There was no difference in results between the adjusted and unadjusted models. For the covariates included in both models, an increase in age at the DXA scan and Hispanic ethnicity of offspring resulted in higher masses.

TABLE 2
Maternal delivery and offspring birth characteristics

	200 mg/d $N = 124$ (49.6%)	1000 mg/d $N = 126$ (50.4%)	Total $N = 250$
Labor type, *n* (%)			
Spontaneous	25 (20.2)	27 (21.4)	52 (20.8)
Augmented	19 (15.3)	12 (9.5)	31 (12.4)
Induced	60 (48.4)	76 (60.3)	136 (54.4)
No labor/scheduled c-section	20 (16.1)	11 (8.7)	31 (12.4)
Delivery type, *n* (%)			
Vaginal	91 (73.4)	97 (77.0)	188 (75.2)
C-section	33 (26.6)	29 (23.0)	62 (24.8)
GDM diagnosis, *n* (%)	21 (17.0) N=121	29 (23.0) N=118	50 (25.0) N=239
GWG, kg, mean (SD)	13.4 (6.6)	13.8 (8.4)	13.6 (7.5)
Excessive GWG, *n* (%)	76 (62.8) $N = 120$	82 (69.5) $N = 122$	158 (66.1) $N = 242$
Mother's prepregnancy DHA Mean % RBC[1]	8.0 (1.7)	10.5 (3.1)	9.2 (2.8)
Preterm birth, *n* (%)	11 (8.9)	6 (4.8)	17 (6.8)
Gestational age at birth, wk, mean (SD)	38.63 (1.51)	38.92 (1.35)	38.77 (1.43)
NICU admission, *n* (%)	12 (9.7)	9 (7.1)	21 (8.4)
Infant sex, male, *n* (%)	62 (50.0)	68 (54.0)	130 (52.0)
Infant birth weight, g, mean (SD)	3303.7 (505.1)	3390.3 (454.7)	3347.4 (481.4)
Infant birth length, cm, mean (SD)	50.3 (2.6) $N = 124$	50.5 (2.2) $N = 124$	50.4 (2.4) $N = 248$
Infant head circumference, cm, mean (SD)	34.0 (1.6)	34.2 (1.5)	34.1 (1.5)

Abbreviations: ADORE, ADORE, Assessment of DHA on Reducing Early Preterm Birth randomized controlled trial; GDM, gestational diabetes mellitus; GWG, gestational weight gain; RBC, red blood cell.
[1] $P < 0.001$, as ADORE participants were given different levels of DHA per day.

TABLE 3
Offspring descriptive characteristics by group randomization

	200 mg/d $N = 109$ (49.6%)	1000 mg/d $N = 109$ (50.4%)	Total $N = 218$
Age at visit, mo, mean (SD)	24.4 (0.6)	24.3 (0.5)	24.3 (0.6)
Weight, g, mean (SD)	12684.6 (1627.4)	12983.6 (2071.2)	12834.1 (1864.3)
Length, cm, mean (SD)	86.0 (2.9)	86.2 (3.2)	86.1 (3.0)
Head circumference, cm, mean (SD)	48.3 (1.5)	48.1 (1.4)	48.2 (1.5)
Weight percentile	55.5 (30.5)	61.4 (28.1)	58.4 (29.4)
Weight for length percentile	63.6 (29.1) $N = 102$	68.2 (27.7) $N = 103$	65.9 (28.4) $N = 205$
Abdominal circumference, cm, mean (SD)	47.0 (3.7)	47.8 (3.8)	47.4 (3.8)
Skinfolds, mm, mean (SD)	$N = 104$	$N = 108$	$N = 211$
Peripheral	11.8 (2.5)	11.7 (2.6)	11.7 (2.6)
Central	10.3 (2.6)	10.5 (2.6)	10.4 (2.6)

Discussion

This study aimed to understand if fetal exposure to a high dose of prenatal DHA supplementation can mitigate the effects of

TABLE 4
Usable DXA offspring descriptive characteristics by group

	200 mg/d $N = 31$ (48.4%)	1000 mg/d $N = 33$ (51.6%)	Total $N = 64$
Age at visit, mo, mean (SD)	24.2 (0.3)	24.3 (0.5)	24.3 (0.4)
Weight, g, mean (SD)	12407.7 (1491.3)	13203.0 (2092.3)	12817.8 (1855.6)
Length, cm, mean (SD)	85.5 (3.3)	86.5 (3.4)	86.0 (3.4)
Head circumference, cm, mean (SD)	48.0 (1.2)	48.2 (1.5)	48.1 (1.4)
Weight percentile	49.7 (30.3)	63.8 (29.7)	57.0 (30.3)
Weight for length percentile	62.4 (26.4)	70.2 (28.1)	66.4 (27.3)
Abdominal circumference, cm, mean (SD)	46.6 (3.9)	48.5 (3.6)	47.6 (3.8)
Skinfolds, mm, mean (SD)			
Peripheral	11.5 (2.8)	12.2 (2.6)	11.9 (2.7)
Central	9.7 (2.7)	11.1 (2.5)	10.4 (2.7)
Percentage body fat, %, mean (SD)	29.2% (3.6%)	31.1% (5.8%)	30.2% (4.9%)
Fat mass, g, mean (SD)	3024.3 (669.2)	3479.6 (1239.3)	3259.0 (1022.7)
Lean mass, g, mean (SD)	7045.6 (855.6)	7295.7 (1011.7)	7174.6 (934.9)
Peripheral fat mass, g, mean (SD)	1953.1 (407.3)	2183.6 (704.0)	2071.9 (586.7)
Trunk fat mass, g, mean (SD)	1071.2 (286.5)	1295.9 (551.3)	1187.1 (454.2)

TABLE 5
Estimated offspring body composition by group randomization and GWG status

	200 mg/d ($N = 31$)	1000 mg/d ($N = 28$[1])	Net difference 1000 vs. 200 mg/d	*P*
Aim 1: Fat mass, g, mean (95% CI)[2]				
Treatment	3050.7 (2697.3, 3404.1)	3673.6 (3248.6, 4098.7)	622.9 (66.9, 1178.9)	0.03
GWG				0.44
Not excessive ($n = 22$)	2874.3 (2346.7, 3402.0)	3708.5 (3013.9, 4403.1)	834.2 (-329.1, 1197.4)	
Excessive ($n = 37$)	3227.1 (2745.5, 3708.6)	3638.7 (3175.5, 4101.9)	411.6 (-456.0, 1279.3)	
Central fat mass, g, mean (95% CI)[2] rowhead				
Treatment	1085.3 (934.3, 1236.2)	1377.3 (1195.8, 1558.8)	292.0 (54.6, 529.5)	0.02
GWG				0.53
Not excessive ($n = 22$)	1009.8 (784.4, 1235.1)	1374.0 (1077.3, 1670.6)	364.2 (−132.6, 860.9)	
Excessive ($n = 37$)	1160.8 (955.1, 1366.4)	1380.6 (1182.8, 1578.5)	219.8 (−150.7, 590.4)	

Abbreviations: 95% CI, 95% confidence interval; DXA, dual-energy x-ray absorptiometry; GWG, gestational weight gain.
[1] 5 participants were missing their gestational weight gain; thus, could not defined.
[2] Covariates included: offspring ethnicity and age at DXA scan.

TABLE 6
Estimated trunk fat mass distribution by offspring sex

	200 mg/d ($N = 59$)	1000 mg/d ($N = 65$)	Net difference 1000 vs. 200 mg/d	P
Aim 2: Central fat mass, g, mean (95% CI)[1]				
Treatment	1073.1 (973.1, 1173.2)	1252.2 (1157.3, 1347.2)	179.1 (43.3, 314.9)	0.01
Infant sex				0.98
Female ($n = 58$)	1095.5 (944.6, 1246.4)	1276.4 (1140.8, 1412.0)	180.9 (−83.8, 445.6)	
Male ($n = 66$)	1050.7 (917.3, 1184.1)	1228.1 (1096.4, 1359.7)	177.3 (−70.0, 424.7)	

Abbreviations: 95% CI, 95% confidence interval; DXA, dual-energy x-ray absorptiometry.
[1] Covariates included: offspring ethnicity and age at DXA scan.

excessive GWG on offspring adiposity measured at 24 mo. We found that offspring exposed to a high dose of prenatal DHA supplementation had higher total FM, and this effect was independent of GWG status. Furthermore, exposure to a high dose of prenatal DHA supplementation was related to higher central FM, and this effect was also independent of GWG status. The second aim sought to understand if there were differences in regional adipose tissue distribution based on DHA dose and offspring sex. A higher prenatal DHA dose was related to higher central FM, and this was found independent of offspring sex. Therefore, our data suggest that fetal exposure to high dose prenatal DHA supplementation was related to increased FM and central FM.

Cross-sectional studies, studies using indirect measures of body composition (e.g., weight, length, and BMI), and RCTs investigating prenatal and postnatal supplementation have found mixed results for the benefit of DHA supplementation on offspring body composition [15–19,52,53]. However, only 2 follow-up studies have investigated the effect of only prenatal DHA supplementation (no postnatal) on offspring fat accrual using a direct method of body composition assessment [40,41]. The DOMInO trial provided 800 mg/d DHA (compared with control vegetable oil) during the second and third trimesters of pregnancy, with the initial aim to assess maternal depressive symptoms and offspring cognition [54]. The follow-up study measured offspring body composition using bioelectrical impedance in early childhood. No between-group difference in body composition was found in offspring aged 3 and 5 y old [40] or at 7 y old [43]. The DOMInO trial did find a negative effect of prenatal DHA supplementation on waist-to-hip ratio measured at 3 y old and insulin resistance measured at 5 y old [40]; however, an increased waist-to-hip ratio was not detected at the 5-y [40] or 7-y visits [43].

The COPSAC trial compared 2.4 g of fish oil supplementation (compared with control olive oil), which included 37% of DHA (888 mg/d DHA), starting at 24 weeks of gestation through delivery. Offspring BMI was reported from birth to 10 y old, and body composition and metabolic risk score were assessed at 10 y old. The trajectory of BMI from infancy to 10 y old was greater in the supplemented group, with an inflection of BMI at ~6 y old such that the increase of BMI in the supplemented group increased at a greater rate, suggesting a fetal programming effect. At 10 y old, children in the supplemented group had a higher mean BMI and a higher odds ratio of being overweight. These changes corresponded to an increase in the percentage body fat and total FM assessed at 10 y, suggesting a shift in body composition to a higher proportion of adiposity. A metabolic risk score was calculated that showed a significant difference between groups, with a more adverse metabolic profile in the offspring given prenatal DHA supplementation.

Our findings of increased offspring adiposity were contrary to our hypothesis but similar to results found in the DOMInO and the COPSAC trials. The DOMInO trial also found a negative effect of prenatal DHA supplementation on offspring central adiposity measured at 3 y [40]; however, in the DOMInO trial, this difference was no longer detected at the midchildhood visits [40,43]. Using data from the KUDOS prenatal DHA supplementation trial, our group found that exposure to a higher prenatal DHA dose (600 mg/d) was related to higher offspring FFM measured at 5 y old [55]; however, data on body composition during infancy and toddlerhood was not available for this cohort. In the COPSAC trial, adiposity was greater in offspring exposed to supplementation from birth to 10 y old. It may be that a higher dose of prenatal DHA is programming an overall bigger offspring size. Data from the GAINS and COPSAC trials suggests that the greater size results in a shift in body composition, with greater accrual in adiposity, which contradicts findings from the 5 y old KUDOS trial . It will be important to follow the GAINS cohort to understand if there is a relationship between exposure to a high dose of prenatal DHA supplement and an increase in offspring FM, FFM, or adipose tissue distribution, as increases in these outcomes have different relationships with disease risk [56,57]. However, data from COPSAC suggest that the programming of a bigger size results in greater fat accrual and a more adverse metabolic profile.

Notably, although the birth weights in GAINS for the low and high DHA groups were similar (3303.7 and 3390.3 g, respectively) at 24 mo, offspring born to females from the high DHA group weighed 822 g more than the low DHA group. This may suggest that offspring exposed to a high dose of prenatal DHA supplementation experienced faster growth than the low-dose group. A strong predictor of higher rates of FM accrual is rapid infant weight gain [58]. In the DOMInO trial, the high DHA group and control group had similar weights at birth and at 3-, 5-, and 7-y visits, suggesting similar growth rates between the groups. However, in the COPSAC trial, offspring born to females in the supplemented group had higher overall BMI z-scores from birth to 10 y old. Data on the growth rate of the KUDOS cohort has not been published. Therefore, differences found between the cohorts may be explained by the differences in growth rates. Additionally, rapid infant weight gain can interact with maternal obesity to further increase offspring adiposity [59]. The mean prepregnancy BMI of the DOMInO sample was 26.2 kg/m^2 with an upper end of 30.5 kg/m^2. In the ADORE cohort, the mean prepregnancy BMI was greater with a higher upper range (28.6 ± 7.4 kg/m^2), resulting in 34.2% of the sample having an obese prepregnancy BMI. The DOMInO trial also had lower rates of gestational diabetes mellitus (GDM) (5.2% compared with 11.3%). In contrast, in the COPSAC trial, the mean prepregnancy BMI of the supplemented group was relatively lean (24.8 ± 4.4 kg/m^2), and the rates of GDM were not reported. Maternal risk

factors related to increased offspring adiposity and rapid infant weight gain include maternal obesity and fetal exposure to GDM [60–62]. Therefore, the differences in weight change between GAINS and DOMInO trials, potentially driven by differences in maternal characteristics that prenatal DHA exposure may not be able to mitigate, may explain the differences in findings between the 2 studies. It will be important to explore the drivers of rapid weight gain in these cohorts in relation to adiposity accrual in future studies.

There are strengths and limitations of this study to consider. A strength is leveraging the follow-up of an NIH-funded RCT with a robust dataset including the measurement of many covariates. The use of DXA, a sophisticated body composition technique, is also a strength. Many prior studies relied on body weight for length or BMI measurements as surrogate markers of adiposity. BMI in adults is related to clinical outcomes; however, the predictive value and usefulness in infants, children, and adolescents is less clear [63]. The use of BMI in infants, children, and adolescents is complicated by inter-individual variability among children for periods of rapid growth for which BMI cannot distinguish changes in FM or lean mass. In infants and children, there is a 2-fold range of variation in fatness for a given BMI value [64]. The use of DXA allows for the assessment of body composition across infancy, childhood, and adulthood using the same technique and allows for the distinction of adipose tissue distribution, an important driver of disease risk and development. Use of the same body composition technique is important because there are differences in body composition values when using different techniques [65,66]. Therefore, it is important to use the same body composition methodology across all time points. It will be important to understand if the GAINS results change as the population ages. There are also some limitations to consider. Although we exceeded our recruitment goal of $N = 150$ with the enrollment of 250 participants into GAINS, acquiring usable total body DXA scans in toddlers proved to be challenging. We could obtain 124 (75.6%) usable trunk scans and 64 (39%) usable total body scans, resulting in a high rate of missing data for total FM. We anticipated a 20% missing data rate for total FM; however, our missing data rate for total FM was 61%, resulting in lower power than originally anticipated. Therefore, work is needed to develop protocols to improve DXA full-body scan acquisition in infants and toddlers. The ADORE trial only provided supplements during the prenatal period. Therefore, this analysis cannot provide evidence to inform the impact of prenatal and postnatal supplementation. Results from the Impact of Nutritional Fatty Acids during Pregnancy and Lacatation on Early Human Adipose Tisue Development (INFAT) study reported on the impact of prenatal and postnatal DHA supplementation, along with the reduction of n-6 fatty acids in the diet, and found no effect on offspring adiposity in infancy or at 5 y old [67,68]; however, this study population was at low risk for offspring obesity development, including a low maternal prepregnancy BMI and high maternal education.

In conclusion, the results of this study suggest that exposure to a high dose of prenatal DHA supplementation was related to greater offspring weight, including greater total FM at 24 mo. We also found that independent of offspring sex, higher prenatal DHA was related to greater offspring central adipose tissue deposition. This is the third study to find a relationship between prenatal DHA supplementation and increased offspring adiposity. It will be important to understand if our findings persist into childhood and if DHA exposure is related to obesity risk and development.

Author contributions

The authors' responsibilities were as follows – HRH, DKS, BG, and SEC: designed the project, developed the overall research plan, and provided study oversight; HRH: conducted the research; BG and AB: analyzed the data; HRH and AB: wrote the article; and all authors: read and approved the final manuscript.

Conflict of interest

HRH has a patent for the Infant Immobilizer for Medical Imaging pending at the University of Kansas Medical Center. All other authors report no conflicts of interest.

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Data availability

Data described in the manuscript, code book, and analytic code will be made available upon request pending application approval.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cdnut.2024.103771.

References

[1] C.D. Fryar, M.D. Carroll, J. Afful, Prevalence of overweight, obesity, and severe obesity among children and adolescents aged 2-19 years: United States, 1963–1965 through 2017–2018 [Internet], National Center for Health Statistics, 2020 [cited 8 February, 2021]. Available from: https://www.cdc.gov/nchs/data/hestat/obesity-child-17-18/obesity-child.htm.

[2] J.L. Knittle, K. Timmers, F. Ginsberg-Fellner, R.E. Brown, D.P. Katz, The growth of adipose tissue in children and adolescents. Cross-sectional and longitudinal studies of adipose cell number and size, J. Clin. Invest. 63 (2) (1979) 239–246, https://doi.org/10.1172/JCI109295.

[3] T.J. Boulton, M. Dunlop, J.M. Court, The growth and development of fat cells in infancy, Pediatr. Res. 12 (9) (1978) 908–911, https://doi.org/10.1203/00006450-197809000-00005.

[4] P.M. Catalano, E.D. Tyzbir, S.R. Allen, J.H. McBean, T.L. McAuliffe, Evaluation of fetal growth by estimation of neonatal body composition, Obstet. Gynecol. 79 (1) (1992) 46–50.

[5] H.R. Hull, J.C. Thornton, Y. Ji, A. Yu, K. Dorsey, D. Gallagher, et al., Higher infant body fat with excessive gestational weight gain in overweight women, Am. J. Obstet. Gynecol. 205 (3) (2011) 211 e1–e7, https://doi.org/10.1016/j.ajog.2011.04.004.

[6] H.R. Hull, J. Thornton, C. Paley, K. Navder, D. Gallagher, Maternal obesity influences the relationship between location of neonate fat mass and total fat mass, Pediatr, Obes. 10 (4) (2015) 245–251, https://doi.org/10.1111/ijpo.257.

[7] E.M. Carlsen, K.M. Renault, K. Nørgaard, L. Nilas, J.E.B. Jensen, L. Hyldstrup, et al., Newborn regional body composition is influenced by maternal obesity, gestational weight gain and the birthweight standard score, Acta Paediatr 103 (9) (2014) 939–945, https://doi.org/10.1111/apa.12713.

[8] S.R. Crozier, H.M. Inskip, K.M. Godfrey, C. Cooper, N.C. Harvey, Z.A. Cole, et al., Weight gain in pregnancy and childhood body composition: findings from the Southampton Women's Survey, Am. J. Clin. Nutr. 91 (6) (2010) 1745–1751, ajcn.2009.29128.

[9] J.L. Kaar, T. Crume, J.T. Brinton, K.J. Bischoff, R. McDuffie, D. Dabelea, Maternal obesity, gestational weight gain, and offspring adiposity: the exploring perinatal outcomes among children study, J. Pediatr. 165 (3) (2014) 509–515, https://doi.org/10.1016/j.jpeds.2014.05.050.
[10] R.M. Reynolds, C. Osmond, D.I.W. Phillips, K.M. Godfrey, Maternal BMI, parity, and pregnancy weight gain: influences on offspring adiposity in young adulthood, J. Clin. Endocrinol. Metab. 95 (12) (2010) 5365–5369, https://doi.org/10.1210/Jc.2010-0697.
[11] S.B. Sridhar, J. Darbinian, S.F. Ehrlich, M.A. Markman, E.P. Gunderson, A. Ferrara, M.M. Hedderson, Maternal gestational weight gain and offspring risk for childhood overweight or obesity, Am. J. Obstet. Gynecol. 211 (3) (2014) 259 e1, 0.1016/j.ajog.2014.02.030 259.e8.
[12] S.P. Mourtakos, K.D. Tambalis, D.B. Panagiotakos, G. Antonogeorgos, G. Arnaoutis, K. Karteroliotis, et al., Maternal lifestyle characteristics during pregnancy, and the risk of obesity in the offspring: a study of 5,125 children, BMC Pregnancy. Childbirth. 15 (2015) 66, https://doi.org/10.1186/s12884-015-0498-z.
[13] J.J. Reilly, J. Armstrong, A.R. Dorosty, P.M. Emmett, A. Ness, I. Rogers, et al., Early life risk factors for obesity in childhood: cohort study, BMJ 330 (7504) (2005) 1357, https://doi.org/10.1136/bmj.38470.670903.E0.
[14] T.J. Parsons, C. Power, O. Manor, Fetal and early life growth and body mass index from birth to early adulthood in 1958 British cohort: longitudinal study, BMJ 323 (7325) (2001) 1331–1335, https://doi.org/10.1136/bmj.323.7325.1331.
[15] N. Sanz, M. Diaz, A. López-Bermejo, C. Sierra, A. Fernandez, F. de Zegher, et al., Newborns with lower levels of circulating polyunsaturated fatty acids (PUFA) are abdominally more adipose, Pediatr, Obes. 9 (3) (2014) e68–e72, https://doi.org/10.1111/j.2047-6310.2013.00200.x.
[16] S.M. Donahue, S.L. Rifas-Shiman, D.R. Gold, Z.E. Jouni, M.W. Gillman, E. Oken, Prenatal fatty acid status and child adiposity at age 3 y: results from a US pregnancy cohort, Am. J. Clin. Nutr. 93 (4) (2011) 780–788, https://doi.org/10.3945/ajcn.110.005801.
[17] R.J. Moon, N.C. Harvey, S.M. Robinson, G. Ntani, J.H. Davies, H.M. Inskip, et al., Maternal plasma polyunsaturated fatty acid status in late pregnancy is associated with offspring body composition in childhood, J Clin. Endocrinol. Metab. 98 (1) (2013) 299–307, https://doi.org/10.1210/jc.2012-2482.
[18] A.J. Vidakovic, O. Gishti, T. Voortman, J.F. Felix, M.A. Williams, A. Hofman, et al., Maternal plasma PUFA concentrations during pregnancy and childhood adiposity: the Generation R Study, Am. J. Clin. Nutr. 103 (4) (2016) 1017–1025, https://doi.org/10.3945/ajcn.115.112847.
[19] I. Gonzalez-Casanova, A.D. Stein, W. Hao, R. Garcia-Feregrino, A. Barraza-Villarreal, I. Romieu, et al., Prenatal supplementation with docosahexaenoic acid has no effect on growth through 60 months of age, J. Nutr. 145 (6) (2015) 1330–1334, https://doi.org/10.3945/jn.114.203570.
[20] M. Korotkova, B. Gabrielsson, M. Lönn, L.A. Hanson, B. Strandvik, Leptin levels in rat offspring are modified by the ratio of linoleic to alpha-linolenic acid in the maternal diet, J. Lipid Res. 43 (10) (2002) 1743–1749, https://doi.org/10.1194/jlr.M200105-JLR200.
[21] M. Korotkova, B.G. Gabrielsson, A. Holmäng, B.M. Larsson, L.A. Hanson, B. Strandvik, Gender-related long-term effects in adult rats by perinatal dietary ratio of n-6/n-3 fatty acids, Am. J. Physiol. Regul. Integr. Comp. Physiol. 288 (3) (2005) R575–R579, https://doi.org/10.1152/ajpregu.00342.2004.
[22] H.K. Kim, M. Della-Fera, J. Lin, C.A. Baile, Docosahexaenoic acid inhibits adipocyte differentiation and induces apoptosis in 3T3-L1 preadipocytes, J. Nutr. 136 (12) (2006) 2965–2969, https://doi.org/10.1093/jn/136.12.2965.
[23] D. Gaillard, R. Négrel, M. Lagarde, G. Ailhaud, Requirement and role of arachidonic acid in the differentiation of pre-adipose cells, Biochem. J. 257 (2) (1989) 389–397, https://doi.org/10.1042/bj2570389.
[24] D.B. Jump, S.D. Clarke, A. Thelen, M. Liimatta, Coordinate regulation of glycolytic and lipogenic gene expression by polyunsaturated fatty acids, J. Lipid Res. 35 (6) (1994) 1076–1084, https://doi.org/10.1016/S0022-2275(20)40103-8.
[25] S.D. Clarke, D. Jump, Polyunsaturated fatty acids regulate lipogenic and peroxisomal gene expression by independent mechanisms, Prostaglandins Leukot. Essent. Fatty Acids. 57 (1) (1997) 65–69, https://doi.org/10.1016/S0952-3278(97)90494-4.
[26] C.L. Nochera, L.H. Goossen, A.R. Brutus, M. Cristales, B. Eastman, Consumption of DHA + EPA by low-income women during pregnancy and lactation, Nutr. Clin. Pract. 26 (4) (2011) 445–450, https://doi.org/10.1177/0884533611406133.
[27] M.S. Parra, L. Schnaas, M. Meydani, E. Perroni, S. Martínez, I. Romieu, Erythrocyte cell membrane phospholipid levels compared against reported dietary intakes of polyunsaturated fatty acids in pregnant Mexican women, Public Health Nutr 5 (6A) (2002) 931–937, https://doi.org/10.1079/PHN2002381.
[28] S.E. Carlson, J. Colombo, B.J. Gajewski, K.M. Gustafson, D. Mundy, J. Yeast, et al., DHA supplementation and pregnancy outcomes, Am. J. Clin. Nutr. 97 (4) (2013) 808–815, https://doi.org/10.3945/ajcn.112.050021.
[29] R. Yuhas, K. Pramuk, E.L. Lien, Human milk fatty acid composition from nine countries varies most in DHA, Lipids 41 (9) (2006) 851–858, https://doi.org/10.1007/s11745-006-5040-7.
[30] C.M. Smuts, M. Huang, D. Mundy, T. Plasse, S. Major, S.E. Carlson, A randomized trial of docosahexaenoic acid supplementation during the third trimester of pregnancy, Obstet. Gynecol. 101 (3) (2003) 469–479, https://doi.org/10.1016/s0029-7844(02)02585-1.
[31] K.M. Gustafson, S.E. Carlson, J. Colombo, H.W. Yeh, D.J. Shaddy, S. Li, et al., Effects of docosahexaenoic acid supplementation during pregnancy on fetal heart rate and variability: a randomized clinical trial, Prostaglandins Leukot, Essent. Fatty Acids 88 (5) (2013) 331–338, https://doi.org/10.1016/j.plefa.2013.01.009.
[32] R.S. Kuipers, M.F. Luxwolda, W.S. Sango, G. Kwesigabo, D.A. Dijck-Brouwer, F.A. Muskiet, Postdelivery changes in maternal and infant erythrocyte fatty acids in 3 populations differing in fresh water fish intakes, Prostaglandins Leukot, Essent. Fatty Acids 85 (6) (2011) 387–397, https://doi.org/10.1016/j.plefa.2011.06.004.
[33] S.J. Otto, A.C. van Houwelingen, A. Badart-Smook, G. Hornstra, Changes in the maternal essential fatty acid profile during early pregnancy and the relation of the profile to diet, Am. J. Clin. Nutr. 73 (2) (2001) 302–307, https://doi.org/10.1093/ajcn/73.2.302.
[34] V. Lakin, P. Haggarty, D.R. Abramovich, J. Ashton, C.F. Moffat, G. McNeill, et al., Dietary intake and tissue concentration of fatty acids in omnivore, vegetarian and diabetic pregnancy, Prostaglandins Leukot. Essent. Fatty Acids 59 (3) (1998) 209–220, https://doi.org/10.1016/S0952-3278(98)90065-5.
[35] J.T. Brenna, A. Lapillonne, Background paper on fat and fatty acid requirements during pregnancy and lactation, Ann. Nutr. Metab. 55 (1–3) (2009) 97–122, https://doi.org/10.1159/000228998.
[36] Y. Papanikolaou, J. Brooks, C. Reider, V.L. Fulgoni III, U.S. adults are not meeting recommended levels for fish and omega-3 fatty acid intake: results of an analysis using observational data from NHANES 2003–2008, Nutr. J. 13 (2014) 31, https://doi.org/10.1186/1475-2891-13-31.
[37] G.C. Burdge, Metabolism of alpha-linolenic acid in humans, Prostaglandins Leukot. Essent. Fatty Acids 75 (3) (2006) 161–168, https://doi.org/10.1016/j.plefa.2006.05.013.
[38] E.A. Emken, R.O. Adlof, R.M. Gulley, Dietary linoleic acid influences desaturation and acylation of deuterium-labeled linoleic and linolenic acids in young adult males, Biochim. Biophys. Acta. 1213 (3) (1994) 277–288, https://doi.org/10.1016/0005-2760(94)00054-9.
[39] Institute of Medicine, Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein, and amino acids [Internet], The National Academies Press, Washington, DC, 2005, https://doi.org/10.17226/10490. Last Accessed Nov 2023.
[40] B.S. Muhlhausler, L.N. Yelland, R. McDermott, L. Tapsell, A. McPhee, R.A. Gibson, et al., DHA supplementation during pregnancy does not reduce BMI or body fat mass in children: follow-up of the DHA to Optimize Mother Infant Outcome randomized controlled trial, Am. J. Clin. Nutr. 103 (6) (2016) 1489–1496, https://doi.org/10.3945/ajcn.115.126714.
[41] B.A. Foster, E. Escaname, T.L. Powell, B. Larsen, S.K. Siddiqui, J. Menchaca, et al., Randomized controlled trial of DHA supplementation during pregnancy: child adiposity outcomes, Nutrients 9 (6) (2017), https://doi.org/10.3390/nu9060566.
[42] R.K. Vinding, A. Sevelsted, D. Horner, N. Vahman, L. Lauritzen, C.P. Hagen, et al., Fish oil supplementation during pregnancy, anthropometrics, and metabolic health at age ten: a randomized clinical trial, Am. J. Clin. Nutr. 119 (4) (2024) 960–968, https://doi.org/10.1016/j.ajcnut.2023.12.015.
[43] K. Wood, E. Mantzioris, B. Lingwood, J. Couper, M. Makrides, R.A. Gibson, et al., The effect of maternal DHA supplementation on body fat mass in children at 7 years: follow-up of the DOMInO randomized controlled trial, Prostaglandins Leukot. Essent. Fatty Acids 139 (2018) 49–54, https://doi.org/10.1016/j.plefa.2017.09.013.

[44] H. Bisgaard, J. Stokholm, B.L. Chawes, N.H. Vissing, E. Bjarnadóttir, A-M.M. Schoos, et al., Fish oil-derived fatty acids in pregnancy and wheeze and asthma in offspring, N. Engl. J. Med. 375 (26) (2016) 2530–2539, https://doi.org/10.1056/NEJMoa1503734.
[45] S.E. Carlson, B.J. Gajewski, C.J. Valentine, L.K. Rogers, C.P. Weiner, E.A. DeFranco, et al., Assessment of DHA on reducing early preterm birth: the ADORE randomized controlled trial protocol, BMC Pregnancy Childbirth 17 (1) (2017) 62, https://doi.org/10.1186/s12884-017-1244-5.
[46] S.E. Carlson, B.J. Gajewski, C.J. Valentine, E.H. Kerling, C.P. Weiner, M. Cackovic, et al., Higher dose docosahexaenoic acid supplementation during pregnancy and early preterm birth: a randomised, double-blind, adaptive-design superiority trial, EClinicalMedicine 36 (2021) 100905, https://doi.org/10.1016/j.eclinm.2021.100905.
[47] Institute of Medicine (US) and National Research Council (US), Committee to Reexamine IOM Pregnancy Weight Guidelines, in: K.M. Rasmussen, A.L. Yaktine (Eds.), Weight gain during pregnancy: reexamining the guidelines [Internet], National Academies Press (US), Washington (DC), 2009. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20669500.
[48] H.R. Hull, B.J. Gajewski, D.K. Sullivan, S.E. Carson, Growth and adiposity in newborns study (GAINS): the influence of prenatal DHA supplementation protocol, Contemp. Clin. Trials. 132 (2023) 107279, https://doi.org/10.1016/j.cct.2023.107279.
[49] J.M. Conway, L.A. Ingwersen, B.T. Vinyard, A.J. Moshfegh, Effectiveness of the US Department of Agriculture 5-step multiple-pass method in assessing food intake in obese and nonobese women, Am. J. Clin. Nutr. 77 (5) (2003) 1171–1178, https://doi.org/10.1093/ajcn/77.5.1171.
[50] C.A. Blanton, A.J. Moshfegh, D.J. Baer, M.J. Kretsch, The USDA automated multiple-pass method accurately estimates group total energy and nutrient intake, J. Nutr. 136 (10) (2006) 2594–2599, 136/10/2594.
[51] J.R. Hebert, T.G. Hurley, D.E. Chiriboga, J. Barone, A comparison of selected nutrient intakes derived from three diet assessment methods used in a low-fat maintenance trial, Public Health Nutr 1 (3) (1998) 207–214. S1368980098000330.
[52] G.L. Li, H.J. Chen, W.X. Zhang, Q. Tong, Y.E. Yan, Effects of maternal omega-3 fatty acids supplementation during pregnancy/lactation on body composition of the offspring: a systematic review and meta-analysis, Clin. Nutr. 37 (5) (2018) 1462–1473, https://doi.org/10.1016/j.clnu.2017.08.002.
[53] A.B. Courville, O. Harel, C.J. Lammi-Keefe, Consumption of a DHA-containing functional food during pregnancy is associated with lower infant ponderal index and cord plasma insulin concentration, Br. J. Nutr. 106 (2) (2011) 208–212, https://doi.org/10.1017/S0007114511000961.
[54] M. Makrides, R.A. Gibson, A.J. McPhee, L. Yelland, J. Quinlivan, P. Ryan, DOMInO Investigative Team, Effect of DHA supplementation during pregnancy on maternal depression and neurodevelopment of young children: a randomized controlled trial, JAMA 304 (15) (2010) 1675–1683, https://doi.org/10.1001/jama.2010.1507.
[55] B.H. Hidaka, J.M. Thodosoff, E.H. Kerling, H.R. Hull, J. Colombo, S.E. Carlson, Intrauterine DHA exposure and child body composition at 5 y: exploratory analysis of a randomized controlled trial of prenatal DHA supplementation, Am. J. Clin. Nutr. 107 (1) (2018) 35–42, https://doi.org/10.1093/ajcn/nqx007.
[56] A.M. Sedlmeier, S.E. Baumeister, A. Weber, B. Fischer, B. Thorand, T. Ittermann, et al., Relation of body fat mass and fat-free mass to total mortality: results from 7 prospective cohort studies, Am. J. Clin. Nutr. 113 (3) (2021) 639–646, https://doi.org/10.1093/ajcn/nqaa339.
[57] P. Huai, J. Liu, X. Ye, W.Q. Li, Association of central obesity with all cause and cause-specific mortality in US adults: a prospective cohort study, Front. Cardiovasc. Med. 9 (2022) 816144, https://doi.org/10.3389/fcvm.2022.816144.
[58] M. Zheng, K.E. Lamb, C. Grimes, R. Laws, K. Bolton, K.K. Ong, et al., Rapid weight gain during infancy and subsequent adiposity: a systematic review and meta-analysis of evidence, Obes. Rev. 19 (3) (2018) 321–332, https://doi.org/10.1111/obr.12632.
[59] S.P. Gilley, K.K. Harrall, C. Friedman, D.H. Glueck, C.C. Cohen, W. Perng, et al., Association of maternal BMI and rapid infant weight gain with childhood body size and composition, Pediatrics 151 (5) (2023) e2022059244, https://doi.org/10.1542/peds.2022-059244.
[60] A. Andres, H.R. Hull, K. Shankar, P.H. Casey, M.A. Cleves, T.M. Badger, Longitudinal body composition of children born to mothers with normal weight, overweight, and obesity, Obesity (Silver Spring) 23 (6) (2015) 1252–1258, https://doi.org/10.1002/oby.21078.
[61] M.T. Tint, S.A. Sadananthan, S.E. Soh, I.M. Aris, N. Michael, K.H. Tan, et al., Maternal glycemia during pregnancy and offspring abdominal adiposity measured by MRI in the neonatal period and preschool years: the Growing Up in Singapore Towards healthy Outcomes (GUSTO) prospective mother-offspring birth cohort study, Am. J. Clin. Nutr. 112 (1) (2020) 39–47, https://doi.org/10.1093/ajcn/nqaa055.
[62] Z. Hu, F.A. Tylavsky, J.C. Han, M. Kocak, J.H. Fowke, R.L. Davis, et al., Maternal metabolic factors during pregnancy predict early childhood growth trajectories and obesity risk: the CANDLE study, Int. J. Obes. (Lond). 43 (10) (2019) 1914–1922, https://doi.org/10.1038/s41366-019-0326-z.
[63] J.C. Wells, M.S. Fewtrell, Measuring body composition, Arch. Dis. Child. 91 (7) (2006) 612–617, https://doi.org/10.1136/adc.2005.085522.
[64] J.C. Wells, A Hattori chart analysis of body mass index in infants and children, Int. J. Obes. Relat. Metab. Disord. 24 (3) (2000) 325–329, https://doi.org/10.1038/sj.ijo.0801132.
[65] J. Elberg, J.R. McDuffie, N.G. Sebring, C. Salaita, M. Keil, D. Robotham, et al., Comparison of methods to assess change in children's body composition, Am. J. Clin. Nutr. 80 (1) (2004) 64–69, https://doi.org/10.1093/ajcn/80.1.64.
[66] M.E. Heard-Lipsmeyer, H. Hull, C.R. Sims, M.A. Cleves, A. Andres, Evaluating body composition in infancy and childhood: a comparison between 4C, QMR, DXA, and ADP, Pediatr. Obes. 15 (6) (2020) e12617, https://doi.org/10.1111/ijpo.12617.
[67] C. Brei, L. Stecher, D. Much, M-T. Karla, U. Amann-Gassner, J. Shen, et al., Reduction of the n-6:n-3 long-chain PUFA ratio during pregnancy and lactation on offspring body composition: follow-up results from a randomized controlled trial up to 5 y of age, Am. J. Clin. Nutr. 103 (6) (2016) 1472–1481, https://doi.org/10.3945/ajcn.115.128520.
[68] H. Hauner, D. Much, C. Vollhardt, S. Brunner, D. Schmid, E-M. Sedlmeier, et al., Effect of reducing the n-6:n-3 long-chain PUFA ratio during pregnancy and lactation on infant adipose tissue growth within the first year of life: an open-label randomized controlled trial, Am. J Clin. Nutr. 95 (2) (2012) 383–394, https://doi.org/10.3945/ajcn.111.022590.