

# Increased $\alpha$ -Linolenic Acid Intake during Pregnancy is Associated with Higher Offspring Birth Weight

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## ABSTRACT

**Background:** The amount and type of fat in the maternal diet during pregnancy are important contributors to fetal growth. The importance of plant-based omega-3 fatty acid ( $\alpha$ -linolenic acid, ALA) intake in fetal growth has not been previously examined.

**Objective:** We sought to determine the association of maternal ALA intake during pregnancy with birth weight and body composition of the offspring.

**Methods:** Mothers and their newborn infants ( $n = 224$ ) were recruited from the Royal Prince Alfred Hospital, Australia. Maternal diet during pregnancy was assessed using a validated food frequency questionnaire. Plasma fatty acid composition was analyzed in a subset of mothers ( $n = 41$ ). Newborn body composition was assessed using air-displacement plethysmography. All analyses were adjusted for gestational age, sex, physical activity, and total energy intake.

**Results:** Dietary fatty acid intakes were positively associated with plasma phospholipid fatty acids for total omega-3 fatty acids ( $\beta = 0.452$ ,  $P = 0.003$ ), ALA ( $\beta = 0.339$ ,  $P = 0.03$ ), linoleic acid ( $\beta = 0.353$ ,  $P = 0.03$ ), eicosapentaenoic acid ( $\beta = 0.407$ ,  $P = 0.009$ ), and docosahexaenoic acid ( $\beta = 0.388$ ,  $P = 0.01$ ). Higher maternal intake of ALA (% total fat) was associated with higher offspring birth weight [189.7-g increase per 1% higher ALA (95% CI: 14, 365 g);  $P = .04$ ], although individually neither newborn fat mass nor fat-free mass was significant. Birth weight increased across tertiles of maternal ALA intake ( $P_{ANOVA} = 0.05$ ), with birth weight being 221 g (95% CI: 12, 429 g) higher in those with the highest maternal ALA intake compared with those with the lowest intake ( $P = 0.04$ ). Mothers of infants born small for gestational age ( $n = 32$ ) had a lower ALA intake than those born appropriate for gestational age ( $n = 162$ ) or large for gestational age [ $n = 21$ ];  $P = 0.05$ ].

**Conclusions:** In otherwise healthy women giving birth at a major tertiary hospital in Australia, intake of ALA during pregnancy is associated with higher offspring birth weight. This may have implications for dietary strategies aimed at optimizing fetal growth via modification of maternal diet. *Curr Dev Nutr* 2019;3:nzy081.

## Introduction

Low birth weight is a major cause of adverse perinatal outcomes (1) and is associated with increased morbidity and mortality in infancy and adulthood (2). Epidemiologic evidence indicates that birth weight is associated with adult heart disease and type 2 diabetes (3), such that those at each end of the fetal growth spectrum are at highest risk. Maternal nutrition in pregnancy is important for regulating fetal growth and development. The developing fetus requires substantial amounts of fatty acids to support rapid cellular growth and activity (4). The biggest determinant of fatty acid delivery to the fetus is the concentration in the



**Keywords:**  $\alpha$ -linolenic acid, birth weight, maternal diet, fatty acids

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Abbreviations used: AA, arachidonic acid; AGA, appropriate for gestational age; ALA,  $\alpha$ -linolenic acid; LGA, large for gestational age; n-3 PUFA, omega-3 polyunsaturated fatty acids; n-6 PUFA, omega-6 polyunsaturated fatty acids; SGA, small for gestational age.

maternal circulation (5), which is strongly related to habitual maternal fatty acid intake (6). Several studies have demonstrated that the quantity and quality of maternal dietary fat intake have profound health implications during and after pregnancy (7). The relative proportions of saturated (SFA), monounsaturated (MUFA), and polyunsaturated fatty acid (PUFA) intake are often used as a crude measure of diet quality, although specific individual fatty acids within each class can have differing effects on cardiometabolic health (8). The PUFA are classified into 2 series, the omega-6 (n-6) and the omega-3 (n-3) PUFA. Studies concerning dietary intake of PUFA have focussed mainly on the longer-chain PUFA, arachidonic (AA, 20:4 n-6), eicosapentaenoic (EPA, 20:5 n-3), and docosahexaenoic (DHA, 22:6 n-3) acids, because of their pleiotropic roles (9). Cohort studies support beneficial effects of EPA and DHA for increasing birthweight and length of gestation (10, 11); however, the potential effects of their metabolic precursors, linoleic acid (LA, 18:2 n-6), and  $\alpha$ -linolenic acid (ALA, 18:3 n-3) have rarely been examined. In developing countries, higher circulating levels of ALA in early pregnancy were linked to better birth outcomes (12), and inadequate maternal dietary ALA intake was associated with lower birth weights (13).

Accordingly, we sought to determine the association of maternal fatty acid intakes during pregnancy with birth weight. We assessed whether individual n-3 and n-6 PUFA in the maternal diet are associated with offspring birth weight and body composition. We particularly focused on n-3 ALA, given the paucity of evidence available, hypothesizing that maternal intake of ALA would “normalize” fetal growth.

## Methods

### Participants

A total of  $n = 224$  mothers and their newborn infants were recruited from the maternity wards of Royal Prince Alfred Hospital, Sydney, Australia, between April 2015 and September 2016, as part of a study investigating newborn body fatness and vascular health in the offspring (“Body Fatness and Blood Vessel Health in Babies”—Protocol No. X14-0356). Eligible participants included singleton newborns  $\geq 34$  completed weeks of gestation that had body composition measured by air-displacement plethysmography (PEA POD, COSMED) within 24 h of birth. Infants from a multiple birth, or those with major congenital abnormalities, and those that required respiratory support were excluded from the study. All participating mothers provided written informed voluntary consent. Additional consent for maternal blood collection was obtained from  $n = 41$  mothers. Approval for the study was granted by the Human Research Ethics Committee of the Sydney Local Health District (HREC/14/RPAH/478).

### Newborn body composition and anthropometry

Newborn fat mass, fat-free mass, and body fat percentage were measured using air-displacement plethysmography (PEA POD, COSMED), as part of routine clinical practice (14). Birth weight, length, and head circumference were measured clinically and obtained from medical records. Weight was measured with the integrated PEA POD scales to the nearest gram, and head circumference to the nearest 0.1 cm using disposable infant paper tapes. Length was measured with a length board

to the nearest 0.1 cm (Easy-Glide Bearing infantometer, Perspective Enterprises). Gestational age (weeks) was calculated from the date of last menstrual period and early pregnancy ultrasound.

Newborns were categorized as small for gestational age (SGA; birth weight <10th percentile for gestational age and sex), appropriate for gestational age (AGA; birth weight from 10th to 90th percentile for gestational age and sex), and large for gestational age (LGA; birth weight >90th percentile for gestational age and sex), using Australian national birth weight percentile charts (15).

### Maternal characteristics and assessment of dietary fat intake

Maternal data including prepregnancy weight, height, age, health, medical history, and lifestyle information were collected using standardized questionnaires and from online medical records. Physical activity in the third trimester of pregnancy was assessed using the Pregnancy Physical Activity Questionnaire, validated for pregnancy (16), in which women were asked to recall physical activity in the last trimester of pregnancy. Dietary intake during the entire course of pregnancy was assessed using a validated electronic food frequency questionnaire (Dietary Questionnaire for Epidemiological Studies v2, Cancer Council, Victoria, Australia) (17). Mothers were asked to specifically think about their dietary intake during the entire course of pregnancy when completing the food frequency questionnaire. For the current analysis, we excluded data from mothers that did not complete the food frequency questionnaire ( $n = 11$ ), leaving a total of  $n = 213$  for analysis.

### Maternal plasma phospholipid fatty acid analysis

Venous blood samples were collected into EDTA tubes and refrigerated. Blood samples were centrifuged within 30 min of collection, at  $1300 \times$  RCF for 10 min to obtain plasma. Plasma samples were stored at  $-80^\circ\text{C}$  until analysis. Plasma phospholipids were extracted, and fatty acid composition was determined according to a modification in the method of Lepage and Roy using an acetyl chloride methylation procedure (18). Fatty acid methyl esters were quantified using gas chromatography (Shimadzu GC-2010 Plus system). The identity of each fatty acid peak was ascertained by comparison of the peaks retention time with those of synthetic standards of known fatty acid composition (Nu Check Prep). The relative amount of each fatty acid was quantified by integrating the area under the peak and dividing by the total area for all fatty acids, and reported as the percentage of total fatty acids.

### Statistical analysis

Statistical analyses were performed using SPSS (v22; IBM Corp.). Descriptive data are presented as mean  $\pm$  SD for continuous variables and  $n$  (%) for categorical variables. Preliminary assumption testing was conducted to check for normality, linearity, outliers, and homogeneity of variance with no serious violations observed for all test variables. Maternal total fat intake (g/day) and individual fatty acid intake (g/day) were converted to proportion of energy intake (%) and proportion of total fat intake (%), respectively. Pregnancy physical activity data were assigned an intensity value in metabolic equivalent of task (MET) based on values found in the compendium of physical activity (16). Each activity was classified by intensity: sedentary (<1.5 METs), light (1.5 to <3.0 METs), moderate (3.0–6.0 METs), or vigorous (>6.0 METs).

**TABLE 1** Baseline characteristics by birth-weight-for-gestational age percentiles<sup>1</sup>

	Total (n = 213)	SGA (n = 30)	AGA (n = 162)	LGA (n = 21)	P <sup>2</sup>
<b>Maternal</b>					
Age, years	33.5 ± 4.4	32.7 ± 4.4	33.5 ± 4.3	34.9 ± 4.7	0.19
Prepregnancy BMI, kg/m <sup>2</sup>	23.6 ± 4.9	22.3 ± 3.2	23.7 ± 5.3	25.3 ± 4.2	0.10
Height, cm	164.6 ± 6.6	161.9 ± 7.6*	164.5 ± 6.2	169.2 ± 7.5*	<0.01
Weight, kg	63.7 ± 13.8	58.5 ± 10.70*	64.0 ± 14.4*	71.5 ± 13.0*	<0.01
Maternal obesity	18 (8)	1 (3)	15 (9)	2 (9)	0.59
Gestational diabetes, n (%)	35 (16)	4 (13)	28 (17)	3 (14)	0.70
Hypertension/pre-eclampsia, n (%)	10 (6)	0	10 (6)	0	0.19
Maternal smoking, n (%)	7 (4)	0	7 (4)	0	0.93
Fish oil supplementation during pregnancy, n (%)	22 (10)	4 (13)	16 (10)	2 (10)	0.84
Pregnancy multivitamin supplementation, n (%)	191 (89)	29 (96)	143 (88)	19 (90)	0.38
Iron supplementation, n (%)	92 (43)	14 (46)	69 (42)	9 (43)	0.92
Folate supplementation, n (%)	41 (19)	3 (10)	35 (21)	3 (14)	0.28
Vitamin D supplementation, n (%)	98 (46)	17 (56)	74 (46)	7 (33)	0.26
Vitamin C supplementation, n (%)	32 (15)	3 (10)	26 (16)	3 (14)	0.69
Calcium supplementation, n (%)	12 (5)	0	11 (6)	1 (4)	0.32
Magnesium supplementation, n (%)	12 (5)	1 (3)	9 (5)	2 (9)	0.64
Total energy expenditure, MET*h/wk	269.8 ± 143.6	244.19 ± 140.6	270.7 ± 146.6	299.35 ± 126.3	0.39
Sedentary activity, MET*h/wk	90.54 ± 38.8	80.3 ± 43.1	93.5 ± 37.2	83.6 ± 44.3	0.17
Light activity, MET*h/wk	109.1 ± 55.2	105.5 ± 52.0	108.3 ± 55.5	119.6 ± 58.8	0.64
Moderate activity, MET*h/wk	90.1 ± 84.7	73.1 ± 77.5	92.4 ± 87.8	95.8 ± 69.8	0.52
Vigorous activity, MET*h/wk	1.4 ± 3.5	2.7 ± 5.0	1.3 ± 3.3	0.4 ± 0.7	0.54
Total energy intake, kJ/day	7858 ± 3463	9133 ± 5229	7617 ± 3039	7897 ± 3198	0.08
Fat, %E	38.1 ± 4.7	37.4 ± 6.8	38.3 ± 4.3	37.4 ± 3.9	0.51
Protein, %E	19.6 ± 3.4	20.0 ± 2.7	19.6 ± 2.9	18.9 ± 1.8	0.52
Carbohydrates, %E	40.5 ± 5.3	40.7 ± 7.9	40.2 ± 4.9	41.8 ± 3.5	0.42
<b>Newborn</b>					
Gestational age, wk	38.6 ± 1.6	38.7 ± 1.2	38.6 ± 1.7	38.8 ± 1.6	0.85
Sex (male/female), n	99/114	17/13	69/93	13/8	0.10
Birth weight, g	3317 ± 533	2685 ± 247*	3313 ± 400*	4212 ± 437*	<0.001
Fat mass, g	377 ± 301	146 ± 83*	367 ± 196*	832 ± 623*	<0.001
Fat-free mass, g	2913 ± 455	2541 ± 244*	2911 ± 420*	3501 ± 364*	<0.001
Length, cm	49.3 ± 2.5	48.11 ± 2.72*	49.21 ± 2.16 <sup>†</sup>	52.26 ± 2.44* <sup>†</sup>	<0.001
Head circumference, cm	34.4 ± 1.5	33.30 ± 0.98*	34.46 ± 1.36*	36.32 ± 1.14*	<0.001
Body fatness, %	10.62 ± 4.8	5.42 ± 2.89*	10.88 ± 4.4*	16.01 ± 2.96*	<0.001

<sup>1</sup>Data are presented as means ± SDs and n (%), total n = 213, except for maternal BMI, n = 199 (SGA, n = 27; AGA, n = 154; LGA, n = 18), maternal height, n = 210, maternal weight, n = 209, sedentary activity, n = 199 (SGA, n = 28; AGA, n = 150; LGA, n = 21), light activity, n = 202 (SGA, n = 28; AGA, n = 153; LGA, n = 21), moderate and vigorous activity, n = 202 (SGA, n = 28; AGA, n = 153; LGA, n = 21). AGA, appropriate for gestational age; LGA, large for gestational age; MET, metabolic equivalent of task; SGA, small for gestational age.

<sup>2</sup>P values reflect the significance level between birth weight groups using ANOVA for continuous variables and the Pearson chi-square and Kruskal–Wallis test for dichotomous variables. Values with a common superscript (\*, †) are significantly different using post hoc multiple-comparison Tamhane's test.

This provided an energy expenditure for each activity expressed in MET\*h/wk. Total energy expenditure was derived from the sum of all activities listed in the Pregnancy Physical Activity Questionnaire. Associations between intake of maternal dietary fatty acids and newborn anthropometry, body composition, and maternal fatty acid composition were determined using multivariable linear regression adjusting for newborn gestational age, sex, pregnancy physical activity, and maternal total energy intake. Maternal dietary fatty acids were analyzed individually in the regression models. Categorical analysis of maternal ALA intake tertiles (33rd percentile, 1.179% total fat; 67th percentile, 1.336% total fat) was assessed using 1-factor ANOVA and post hoc Tukey tests. These percentiles translated into intakes of 0.96 g and 1.10 g ALA/day, respectively. Categorical analysis of birth weight percentiles and preterm and full-term groups was assessed using a post hoc multiple-comparison Tamhane test, Pearson chi-square test, independent-samples Kruskal–Wallis test, and Mann–Whitney U-test.

A probability level of  $P < .05$  was adopted throughout to infer statistical significance.

## Results

### Descriptive statistics

Characteristics of mothers and infants in the study are presented in **Table 1**. Mothers had a mean age of 33.5 y, 6% had hypertension or pre-eclampsia, 16% were diagnosed with gestational diabetes, and 4% continued to smoke during pregnancy. There were no differences in pregnancy physical activity, vitamin or fish oil supplementation during pregnancy, maternal total energy intake, or energy from fat, protein, or carbohydrates between mothers of the SGA, AGA, and LGA groups (**Table 1**) or between mothers of preterm infants (<37 weeks of gestation, n = 31) and full-term infants (n = 182, data not shown).

**TABLE 2** Association of dietary fat intake and fatty acid composition in plasma phospholipids<sup>1</sup>

	$\beta$	SE	P
Polyunsaturated fatty acids			
C18:2 n-6, linoleic acid	0.353	0.158	0.026
C18:3 n-3, $\alpha$ -linolenic acid	0.339	0.154	0.032
C20:2n-6, eicosadienoic acid	-0.278	0.200	0.079
C20:3 n-6, homo- $\gamma$ -linolenic acid	-0.432	0.192	0.005
C20:4 n-6, arachidonic acid	0.274	0.209	0.088
C20:5 n-3, eicosapentaenoic acid	0.407	0.139	0.009
C22:5 n-3, docosapentaenoic acid	0.135	0.196	0.405
C22:6 n-3, docosahexaenoic acid	0.388	0.148	0.013
Total	0.249	0.151	0.122
Total n-3 fatty acids	0.452	0.135	0.003
Total n-6 fatty acids	0.292	0.148	0.068
Saturated fatty acids			
Total	0.397	0.140	0.011
Monounsaturated fatty acids			
Total	-0.107	0.081	0.509

<sup>1</sup>Values are  $\beta$ -regression standardized coefficients and standard errors (SE) from linear regression models, n = 41.

The mean total gestational age of newborns was 38.6 wk, and no significant differences in gestational age or sex were observed between the birth weight groups ( $P = 0.85$  and  $P = 0.10$ , respectively).

**Dietary fatty acid intake and composition of plasma phospholipid fatty acids**

The associations of maternal dietary fatty acid intake with fatty acid incorporation into plasma phospholipid fractions are presented in **Table 2**. Direct positive associations between dietary fatty acids and their plasma phospholipid equivalents were observed for total n-3 PUFA and the individual PUFAs, ALA, EPA, DHA, and LA.

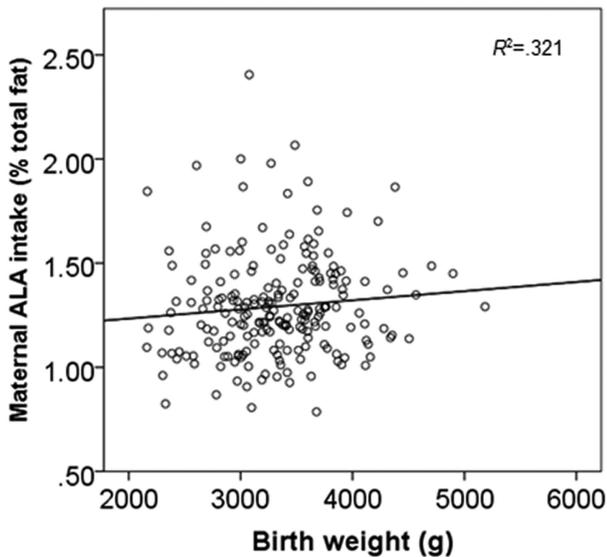
**Maternal dietary fatty acid intake and birth weight and offspring body composition**

Maternal intakes of total SFA, MUFA, and PUFA (% total fat) were not associated with offspring birth weight or body composition (**Table 3**). Maternal intake of ALA (% total fat) was associated with higher offspring birth weight (**Figure 1**) such that each 1% higher ALA intake (% total fat) was associated with a 189.7-g higher birth weight [95% CI: 14, 365 g];  $P = .04$ ] (**Table 3**). This association remained when excluding  $n = 22$  mothers that reported taking fish oil supplementation during pregnancy [ $\beta = 182.4$  g (95% CI: 0.5, 364 g);  $P = 0.05$ ] (data not shown). There were no differences in birth weight, newborn body composition, or maternal dietary fatty acid intake in mothers that reported fish oil supplementation (data not shown). To exclude effects of prematurity, the association between increased maternal ALA intake with higher offspring birth weight remained when excluding  $n = 31$  infants that were born preterm [ $\beta = 292.9$  g (95% CI: 87.4, 498.5 g);  $P = 0.05$ ] but was weakened when excluding mothers that were diagnosed with hypertension, pre-eclampsia, or gestational diabetes [ $\beta = 171.5$  g (95% CI: -18, 360 g);  $P = 0.08$ ] and when adding prepregnancy BMI to the adjusted model [ $\beta = 115.2$  g (95% CI: -154, 385 g);  $P = 0.40$ ] (data not shown). Categorical analysis of dietary ALA intake showed an increase in birth weight with increasing ALA with a 221-g [(95% CI: -429, -12 g);  $P = .04$ ; **Table 4**] difference in

**TABLE 3** Associations of maternal dietary fatty acid intake with birth weight and newborn body composition (% total fat)<sup>1</sup>

Fatty acids	Birth weight (g)		Fat mass (g)		Fat-free mass (g)		Body fatness (%)	
	$\beta$	P	$\beta$	P	$\beta$	P	$\beta$	P
Saturated fatty acids	1.8 (-10, 13)	0.76	-1.6 (-9, 6)	0.67	2.0 (-9, 13)	0.72	0.05 (-0.07, 0.2)	0.45
Monounsaturated fatty acids	4.7 (-23, 32)	0.73	-4.6 (-22, 13)	0.61	-4.0 (-28, 21)	0.75	-0.1 (-0.4, 0.1)	0.29
Polyunsaturated fatty acids	-2.3 (-16, 15)	0.98	6.4 (-4, 16)	0.21	-0.9 (-15, 13)	0.90	0.01 (-0.2, 0.2)	0.94
Total n-6 fatty acids	1.46 (-16, 19)	0.87	9.2 (-2, 21)	0.11	-1.1 (-17, 15)	0.88	0.02 (-0.2, 0.2)	0.79
C18:2n-6, linoleic acid	1.6 (-16, 19)	0.86	9.3 (-2, 21)	0.11	-1.0 (-17, 15)	0.90	-0.02 (-0.2, 0.2)	0.79
C20:4n-6, arachidonic acid	-826.9 (-1991, 338)	0.16	-333.1 (-1092, 425)	0.39	-751.9 (-1810, 307)	0.16	-0.8 (-13, 11)	0.89
Total n-3 fatty acids	69.4 (-44, 182)	0.23	28.4 (-45, 102)	0.45	56.6 (-47, 160)	0.28	0.8 (-0.3, 2)	0.17
C18:3n-3, $\alpha$ -linolenic acid	189.7 (14, 365)	0.04	90.3 (-24, 205)	0.12	124.2 (-36, 285)	0.13	1.3 (-0.5, 3.1)	0.15
C20:5n-3, eicosapentaenoic acid	-21.8 (-475, 432)	0.93	-25.6 (-320, 269)	0.86	42.8 (-369, 455)	0.84	1.6 (-3, 6)	0.49
C22:6n-3, docosahexaenoic acid	-18.6 (-253, 216)	0.88	-21.8 (-174, 131)	0.78	18.5 (-194, 231)	0.86	0.7 (-2, 3)	0.59

<sup>1</sup>Values are unstandardized  $\beta$ -regression coefficients (95% CI) from linear regression models, and represent the increase in the outcome variable (e.g., birth weight in grams) per unit increase in the exposure (dietary fatty acid intake). Adjusted for newborn gestational age, sex, pregnancy physical activity, and maternal total energy intake.



**FIGURE 1** Association of maternal ALA intake with offspring birth weight. ALA,  $\alpha$ -linolenic acid.

birth weight between the highest and lowest groups of maternal ALA intake. No significant associations were observed between ALA intake and either fat mass or fat-free mass, although both were in the same direction as for the association with birth weight. Conversely, maternal ALA intake differed between birth weight groups with mothers of infants born SGA consuming less ALA than those born AGA and LGA ( $P = 0.04$ , **Table 5**). This observed percentage increase in ALA intake (% total fat) across the birth weight groups may have been at the expense of n-6 AA intake (% total fat) with reported decreases in AA intake (% total fat) across the lowest to the highest birth weight groups [0.11 compared with 0.09 compared with 0.08 AA (% total fat); SGA compared with AGA compared with LGA respectively;  $P = 0.10$ ]. However, there was no association of n-6 AA intake with birth weight, nor were there any significant associations observed for the longer-chain n-3 PUFA or n-6 PUFA with birth weight. Interestingly, maternal ALA intake was also lower in infants born preterm than in those born full-term [1.12 compared with 1.30 ALA (% total fat) respectively;  $P = 0.04$ , **Table 6**]. No differences were observed in maternal total energy intake or for other individual fatty acids in any of the birth weight or preterm groups (**Tables 5 and 6**).

**TABLE 4** Differences in birth weight by tertiles of maternal ALA intake per day<sup>1</sup>

ALA intake tertile (% total fat, g/day)	Reference	Mean difference	P
Lowest (<1.19%, <0.96 g of ALA)	Middle	-104.0 (-311, 103)	0.46
Middle (1.19–1.34%, 0.96–1.10 g of ALA)	Highest	-116.7 (-323, 90)	0.38
Highest (>1.34%, >1.10 g of ALA)	Lowest	220.7 (12, 429)	0.04

<sup>1</sup>Data are presented as mean differences (95% CIs) between each tertile of ALA intake (% total fat, g/day). ALA,  $\alpha$ -linolenic acid.

## Discussion

Birth weight is causally associated with risk of noncommunicable diseases in adulthood (19) with a 200-g increase in birth weight being consistent with a 2–4% lower risk of heart disease in adulthood, and a 4–7% lower risk of type 2 diabetes (20, 21). We studied the association of fatty acid intakes, particularly ALA, on offspring birth weight and newborn body composition. Our study found that maternal ALA intake is associated with offspring birth weight, such that a 1% higher ALA intake (% total fat) was associated with an estimated 197-g increase in birth weight. Furthermore, analysis of dietary intake by birth weight percentile groups revealed that mothers of SGA infants reported the lowest intake of ALA during pregnancy compared with the AGA and LGA groups.

The mechanisms by which maternal fatty acids affect fetal growth are not clear. Both n-3 and n-6 fatty acids are mechanistically linked with fetal growth, through oxygen support, energy storage, cell membrane function, and regulation of inflammation (22).

Although the n-3 EPA and DHA along with n-6 AA are fundamental structural components in cellular membranes, n-3 and n-6 PUFA have opposing effects on key physiological pathways. EPA and AA compete for the same cyclooxygenase enzyme to serve as precursors for active eicosanoids that have profound effects on biological responses. Consumption of an n-6 PUFA-enriched diet produces potent proinflammatory and prothrombotic eicosanoids, whereas a diet with a more balanced intake of n-6 and n-3 PUFA produces eicosanoids that are less inflammatory and less immunosuppressive (23), which is important for both maternal and fetal health (24). These long-chain PUFA are synthesized from their precursors, LA and ALA, the 2 essential fatty acids that are required for human health but cannot be synthesized endogenously. ALA does not accumulate in body tissues to any appreciable amounts and is converted to EPA and then to DHA, whereas LA is converted to AA, through enzymatic chain elongation and desaturation (25). The estimated fractional conversion of ALA to EPA and DHA is modest, whereas the conversion efficiency is not known in fetal metabolism, and it is reported to be 4% in healthy adults (26). It is possible that increased ALA intake can saturate this process, indeed, higher intakes of ALA have been shown to increase EPA and DHA in plasma and cell lipids (27, 28). Specifically, in pregnancy, the levels of DHA and AA increase in cord blood in relation to circulating levels of ALA and LA in maternal blood (29). Alternatively, these long-chain PUFAs can be directly sourced from the diet. EPA and DHA are found in high amounts in fish and marine oils, whereas AA is abundant in animal sources.

Cohort studies have supported the beneficial effects of the long-chain n-3 PUFA, EPA, and DHA for fetal growth with evidence for a dose-dependent relation between marine food intake in pregnancy and infant birth weight (10), as well as a reported association between low consumption of marine foods in early pregnancy with preterm delivery and low birth weight (11). Conversely, an inverse association of n-6 AA intake with birth weight has been reported (30, 31). However, the potential effects of their respective metabolic precursors, LA and ALA, have rarely been examined.

Inadequate intake of maternal ALA in an Indonesian population, but not EPA or DHA, has been reported to be associated with lower offspring birth weight (13). Infants born to women with an ALA intake

**TABLE 5** Comparison of dietary fatty acid intake in mothers of different birth weight-for-gestational age groups<sup>1</sup>

Fatty acids (% total fat)	SGA (n = 30)	AGA (n = 162)	LGA (n = 21)	P
Saturated fatty acids	41.70 ± 4.65	42.10 ± 5.59	42.79 ± 4.63	0.73
Monounsaturated fatty acids	34.83 ± 2.16	35.01 ± 4.54	34.64 ± 1.89	0.18
Polyunsaturated fatty acids	13.45 ± 3.69	13.45 ± 4.11	13.64 ± 3.59	0.92
Total n-6 fatty acids	11.58 ± 3.38	11.70 ± 3.62	11.86 ± 3.60	0.98
C18:2n-6, linoleic acid	11.47 ± 3.39	11.61 ± 3.62	11.79 ± 3.61	0.98
C20:4n-6, arachidonic acid	0.11 ± 0.06	0.09 ± 0.05	0.08 ± 0.03	0.10
Total n-3 fatty acids	1.83 ± 0.64	1.84 ± 0.49	1.78 ± 0.35	0.60
C18:3n-3, α-linolenic acid	1.18 ± 0.30	1.27 ± 0.32	1.43 ± 0.37	0.05
C20:5n-3, eicosapentaenoic acid	0.17 ± 0.19	0.15 ± 0.14	0.14 ± 0.10	0.92
C22:6n-3, docosahexaenoic acid	0.36 ± 0.36	0.33 ± 0.27	0.29 ± 0.21	0.86
n-6/n-3 ratio	8.43 ± 9.70	6.88 ± 3.27	6.52 ± 2.08	0.96

<sup>1</sup>Data are presented as means ± SDs. *P* values reflect the significance level between birth weight groups using the Kruskal–Wallis test. AGA, appropriate for gestational age; LGA, large for gestational age; SGA, small for gestational age.

lower than the recommended 820 mg/day had birth weights that were 114 g lower than those of other infants (13). Another study evaluating *n* = 1838 pregnant women in Southern India, a population with diets predominately low in SFA and n-3 PUFA but high in n-6 LA, showed that higher intakes of ALA (>0.3%E) and at least 40 mg/day of long-chain n-3 PUFA in early pregnancy were associated with higher birth weight and lower incidence of SGA (32). Similarly, in our cohort, mothers of SGA infants reported the lowest ALA intake. Interestingly, we also found that mothers of LGA infants reported the highest ALA intake during pregnancy. Thus, maternal ALA intake may be more beneficial to improve fetal growth in those at risk of being born SGA. It has been suggested that dietary or supplemental n-3 PUFA during critical periods of development may be of particular benefit with regard to cardiovascular disease risk secondary to being born SGA (33, 34). Although pre-emptive at this stage, our findings may suggest a role for maternal ALA intake as a means to improve the fetal growth profile in pregnancies identified as being at risk of fetal growth restriction.

Evidence from randomized clinical trials remains inconclusive and is restricted to maternal supplementation of EPA or DHA only; although positive associations with birth weight are reported, these are mediated by the increase in overall gestation rather than a direct effect on fetal growth (35, 36). Observed differences in birth size have been largely a function of differences in gestational age at birth (37). As different

processes underlie the duration of pregnancy and birth weight (38), the PUFA that prolong gestation do not necessarily augment fetal growth. Prostaglandins, inducing cervical ripening and uterine contractions, are synthesized from AA, whereas EPA and DHA compete to depress the synthesis of AA-derived prostaglandins potentially prolonging gestation (39). However, we did not find any associations between dietary EPA, DHA, or the n-6 PUFA and birth weight. In contrast, our results indicate a growth-promoting effect of ALA intake, with the increase in birth weight being independent of gestational age at birth. It is noteworthy that no specific function has been assigned to ALA itself other than serving as a source of energy or conversion to EPA and DHA. Therefore, any mechanisms of improvement in birth weight are most likely via desaturation and elongation to its longer-chain derivatives. Although conversion rates of ALA into the longer-chain EPA and DHA are modest with the estimated fractional conversion reported to be less than 5% (40), increased ALA intake has demonstrated to increase proportions of long-chain n-3 fatty acids in plasma and cell lipids to reproduce beneficial effects (28). However, ALA may itself exert beneficial effects. A systematic review and meta-analysis of both dietary and biomarker observational studies suggests that higher ALA exposure is associated with a lower risk of CVD (41). Although evidence from prospective human clinical trials is limited, enrichment of ALA in maternal diets has been shown to attenuate

**TABLE 6** Comparison of dietary fatty acid intake in mothers of infants born preterm and full term<sup>1</sup>

Fatty acids (% total fat)	Preterm (n = 31)	Full-term (n = 182)	P
Saturated fatty acids	42.01 ± 5.71	42.14 ± 5.33	0.88
Monounsaturated fatty acids	35.46 ± 2.35	35.25 ± 2.27	0.60
Polyunsaturated fatty acids	13.10 ± 4.08	13.54 ± 3.99	0.51
Total n-6 fatty acids	11.28 ± 3.70	11.78 ± 3.56	0.41
C18:2n-6, linoleic acid	11.17 ± 3.70	11.68 ± 3.55	0.38
C20:4n-6, arachidonic acid	0.11 ± 0.06	0.09 ± 0.05	0.26
Total n-3 fatty acids	1.73 ± 0.52	1.83 ± 0.55	0.36
C18:3n-3, α-linolenic acid	1.12 ± 0.43	1.30 ± 0.33	0.04
C20:5n-3, eicosapentaenoic acid	0.17 ± 0.11	0.15 ± 0.15	0.08
C22:6n-3, docosahexaenoic acid	0.37 ± 0.22	0.32 ± 0.28	0.09
n-6/n-3 ratio	6.87 ± 2.51	7.10 ± 5.22	0.89

<sup>1</sup>Data are presented as means ± SDs. *P* values reflect the significance level between groups using the Mann–Whitney *U*-test.

obesity associated insulin resistance in mice offspring (42) as well as to prevent liver lipid accumulation (43).

Although the basis for many of the proposed mechanisms is not fully understood, it has been established that the presence of n-3 PUFA as part of either a phospholipid molecule or triglycerol induces physical effects that change metabolic pathways (44). n-3 PUFAs improve membrane fluidity, increase flow mediated vasodilation, and are precursors for biosynthesis of lipid mediators involved in regulation including aspects of inflammation (23). All these may lead to a reduction in blood viscosity and an increase in the placental blood flow, thereby improving fetal growth. Thus, decreased maternal intake of n-3 PUFA may result in an inadequate supply to the fetus for optimal development.

We also demonstrated in a subset of mothers a positive association between reported fatty acid intakes and plasma fatty acids in phospholipid fractions, including for total PUFA, and most individual PUFA, including ALA. This strengthens our dietary recall data. Similar associations between dietary recall in pregnancy and fatty acid composition of maternal plasma phospholipids have been reported (45). Although we are not able to draw conclusions in relation to maternal blood fatty acids with birth weight outcomes, lower levels of maternal erythrocyte n-3 PUFA in low-birth-weight deliveries have been reported (46).

A limitation to our study is the small sample size, lack of prepregnancy data on diet and exercise, and that our results apply to a relatively healthy sample of pregnant women within a small demographic region. Future studies should seek to prospectively determine whether dietary modification focusing on ALA intake can optimize fetal growth in pregnancies considered clinically to be at risk of fetal growth restriction. Such hypothetical improvements in fetal growth profile may have long-term effects on risk of chronic disease in the offspring.

In conclusion, the current findings indicate that increased intake of ALA during pregnancy is associated with higher offspring birth weight. This may have implications for prevention strategies aimed at improving fetal growth via modification of maternal diet.

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