Fish Oil Supplementation in Pregnancy Increases Gestational Age, Size for Gestational Age, and Birth Weight in Infants: A Randomized Controlled

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Fish Oil Supplementation in Pregnancy Increases Gestational Age, Size for Gestational Age, and Birth Weight in Infants: A Randomized Controlled Trial

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ABSTRACT

Background: Randomized trials have reported that supplementation with n–3 long-chain polyunsaturated fatty acids (LCPUFAs) in pregnancy can prolong pregnancy and thereby increase birth weight.

Objective: We aimed to examine the relations of n–3 LCPUFA supplementation in pregnancy with duration of pregnancy, birth weight, and size for gestational age (GA).

Methods: This was a double-blind randomized controlled trial conducted in 736 pregnant women and their offspring, from the Copenhagen Prospective Studies on Asthma in Childhood$_{2010}$ cohort. They were recruited between weeks 22 and 26 in pregnancy and randomly assigned to either of 2.4 g n–3 LCPUFA or control (olive oil) daily until 1 wk after birth. Exclusion criteria were endocrine, cardiovascular, or nephrologic disorders and vitamin D supplementation intake >600 IU/d. In this study we analyzed secondary outcomes, and further excluded twin pregnancies and extrauterine death. The primary outcome for the trial was persistent wheeze or asthma.

Results: The random assignment ran between 2008 and 2010. Six hundred and ninety-nine mother-infant pairs were included in the analysis. n–3 LCPUFA compared with control was associated with a 2-d prolongation of pregnancy [median (IQR): 282 (275–288) d compared with 280 (273–286) d, $P = 0.02$], a 97-g higher birth weight (mean ± SD: 3601 ± 534 g compared with 3504 ± 528 g, $P = 0.02$), and an increased size for GA according to the Norwegian population-based growth curves-Skjærven (mean ± SD: 49.9 ± 28.3 percentiles compared with 44.5 ± 27.6 percentiles, $P = 0.01$).

Conclusion: Supplementing pregnant women with n–3 LCPUFAs during the third trimester is associated with prolonged gestation and increased size for GA, leading to a higher birth weight in this randomized controlled trial. This trial was registered at clinicaltrials.gov as NCT00798226. *J Nutr* 2018;149:628–634.

Keywords: n–3 LCPUFA, fish oil, gestational age, birth weight, size for gestational age, micro nutrition supplementation, fatty acids, ω-3 fatty acids, cohort studies

Introduction

Poor maternal nutrition during pregnancy can influence the course of pregnancy and fetal growth (1), leading to poor intrauterine growth and decreased gestational age (GA). This is important because both of these have been associated with increased morbidity and impaired development in children (1). Observational studies have shown prolonged duration of pregnancy and increased birth weight in communities with high fish intake (2, 3), which represents a diet especially rich in important nutrients such as selenium, proteins, iodine, vitamin D, and n–3 long-chain PUFAs (n–3 LCPUFAs). The beneficial effects of a high fish intake on pregnancy outcomes have mainly been attributed to the n–3 LCPUFAs, and a number of randomized controlled trials

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(RCTs) have been performed to evaluate the efficacy of n–3 LCPUFA supplementation in pregnancy. A meta-analysis of 21 RCTs of pregnancy supplementation of fish oil showed increased GA and reduced risk of preterm delivery (4). However, another recent large meta-analysis of 34 RCTs concluded that there was not enough evidence to support the routine use of ω-3 fatty acid supplementation during pregnancy to improve mother and child health (5). It has been speculated that the increased birth weight is caused only by the prolonged duration of pregnancy (6, 7), but another explanation could be that n–3 LCPUFA supplementation also increases intrauterine growth.

In the population-based Danish Copenhagen Prospective Studies on Asthma in Childhood$_{2010}$ mother-child cohort, the women participated in a double-blind RCT of daily supplementation with n–3 LCPUFA (fish oil) or control (olive oil) from week 24 of pregnancy to 1 wk postpartum (8). We aimed to investigate the effect of fish oil supplementation compared with control on the secondary outcomes: duration of pregnancy, size for GA, and birth weight of the children.

Methods

Study design

This was a single-center, double-blind, placebo-controlled, parallel-group study (NCT00798226) (9). The recruitment procedure is detailed in the **Supplemental Methods**. The primary outcome of the n–3 LCPUFA RCT was persistent wheeze or asthma (8, 9). In this study we analyzed the predefined secondary endpoints of GA, birth weight, and size for GA as outcomes.

Exclusion criteria were GA above week 26, any endocrine, cardiovascular, or nephrologic disorders, and vitamin D supplementation intake >600 IU/d. For this analysis, we further excluded women with twin pregnancies and women who did not attend both of the 2 pregnancy visits, with the exception of women who gave birth before pregnancy week 36 to ensure their participation in the trial.

Study intervention

The women were randomly assigned 1:1 in a double-blind design at 24 wk of pregnancy to daily supplementation with either four 1-g fish oil capsules containing a total amount of 2.4 g n–3 LCPUFAs [55% EPA (20:5n–3) and 37% DHA (22:6n–3)—Incromega TG33/22; Croda Health Care, see **Supplemental Table 1** for production specification] in triacylglycerol form or 4 identical-looking control capsules of 1 g olive oil (72% n–9 oleic acid and 12% n–6 linoleic acid; Pharmatech A/S).

A subgroup from this pregnancy cohort ($n = 623$) also participated in a 1:1 RCT of 2400 IU cholecalciferol supplementation/d, in a factorial design complementing the n–3 LCPUFA intervention (10); and a smaller subgroup participated in a phase IV, randomized, participant-blinded comparison of influenza A/California/2009 vaccines ($n = 142$) (9, 10).

Study allocation and adherence to the trial are detailed in the supplemental Methods.

Ethics

The study was conducted in accordance with the guiding principles of the Declaration of Helsinki and was approved by the Local Ethics Committee (H-B-2008-093) and the Danish Data Protection Agency (2015-41-3696). Both parents gave oral and written informed consent before enrollment.

Endpoints

GA.

GA was calculated based on expected due date, determined by the scheduled ultrasound scan, which is performed in all pregnant Danish women around pregnancy week 12. In women with no ultrasound scan, due date was calculated from their last menstrual period with the use of Naegele's rule. The due date was collected by interviews at the pregnancy week 24 visit and was compared against the mothers' pregnancy record and subsequently against the national Danish foetodatabase (11). In the few occasions of discrepancy, we used the data from the foetodatabase, because these data were from the ultrasound clinics. Preterm delivery was defined as birth before week 37.

Birth anthropometrics.

Birth length and weight were obtained at the first clinical visit 1 wk after birth by personal interview and thereafter compared with the national Danish Birth Registry. Furthermore, if there was a difference >10 g and >5 cm, data were compared against the length and weight measures at 1 wk from the research clinic, where weight was measured without clothes with the use of calibrated digital weight scales and length was measured with the use of an infantometer (Kiddimeter; Raven Equipment Ltd.).

Fetal anthropometrics.

The fetal weight at midpregnancy was estimated from the scheduled ultrasound scans around pregnancy week 20 by the Hadlock equation (12, 13) with the use of the fetal biometrics for head, abdomen, and femur.

Size for GA and intrauterine growth.

We used size for GA according to 2 standards based on Northern European populations: ultrasound-based fetal growth curves according to Marsál et al. (14) and population-based fetal growth curves according to Skjærven et al. (15). These standardized fetal growth curves were used to find the difference between each child's birth weight and expected birth weight given their GA and afterwards to calculate each child's birth weight as a percentage of their expected birth weight. Percentage for GA is a sensitive measure for all age groups. Small for GA and large for GA were defined as below and above 2 SD on the fetal growth curve of Marsál et al. (14).

In addition, we calculated a proxy for the intrauterine growth rate from week 20 to birth by subtracting the Hadlock weight estimate from the birth weight and dividing this weight gain by the number of days from the week 20 ultrasound scan to birth [birth weight (g) – Hadlock estimated weight (g)]/[GA at birth (d) – GA at scanning (d)] (13, 16).

Pregnancy complications.

Information regarding preeclampsia, gestational diabetes mellitus, antibiotics usage in pregnancy, mode of delivery, birth induction, and the child's Apgar score were obtained during the scheduled visits and

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The funding agencies did not have any influence on study design, data collection and analysis, decision to publish, or preparation of the manuscript. No pharmaceutical company was involved in the study. No honorarium, grant, or other form of payment was given to anyone to produce the manuscript. We are aware of and comply with recognized codes of good research practice, including the Medical Research Council's Good Research Practice and the Guidelines for Good Scientific Practice by the Danish Committees on Scientific Dishonesty (UVVU). We comply with national and international rules on the safety and rights of patients and healthy subjects, including Good Clinical Practice (GCP) as defined in the EU's Directive on Good Clinical Practice, the International Conference on Harmonisation's (ICH) good clinical practice guidelines, and the Helsinki Declaration. We follow national and international rules on the processing of personal data, including the Danish Act on Processing of Personal Data and the practice of the Danish Data Inspectorate.
Supplemental Methods and Supplemental Table 1 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/jn/.
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Address correspondence to HB (e-mail: bisgaard@copsac.com).
Abbreviations used: GA, gestational age; LCPUFA, long-chain PUFA; RCT, randomized controlled trial.

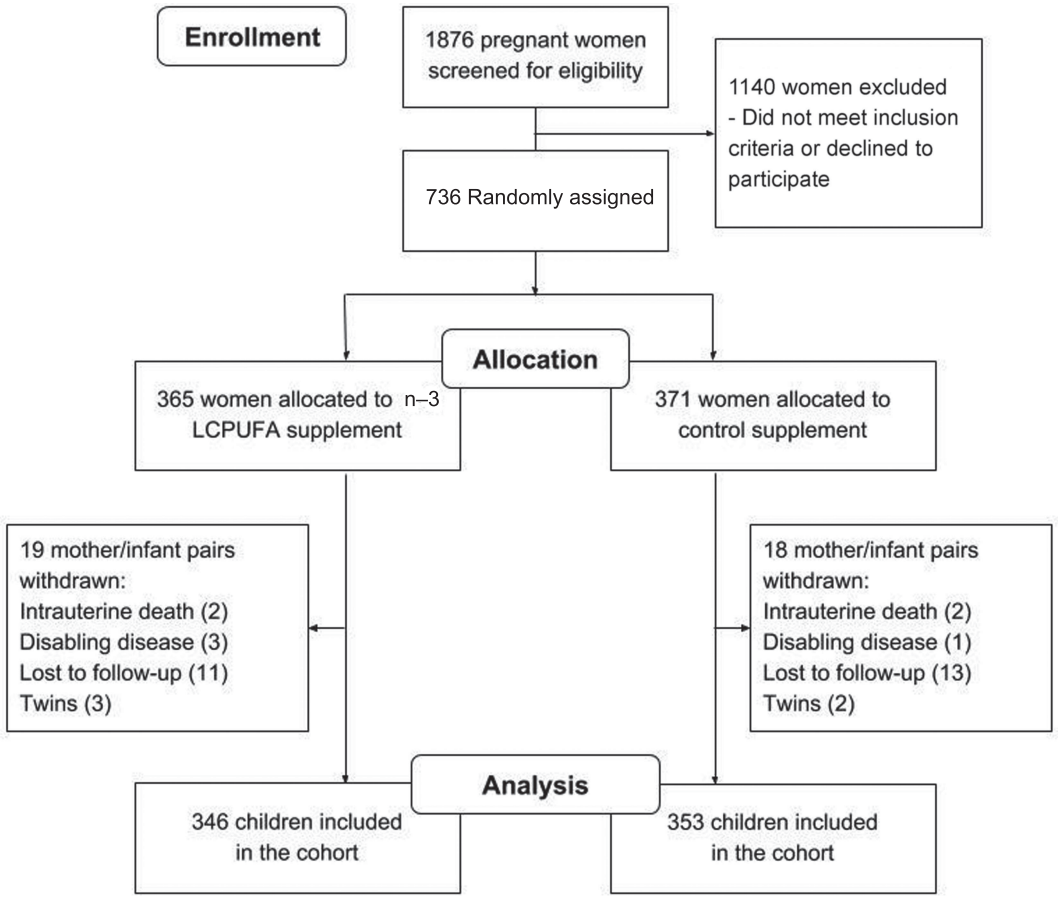

FIGURE 1 Flowchart of enrollment and allocation of the $COPSAC_{2010}$ pregnancy cohort and follow-up of the $COPSAC_{2010}$ birth cohort. $COPSAC_{2010}$, COpenhagen Prospective Studies on Asthma in Childhood$_{2010}$.

compared against register data. If there were discrepancies, the mother and child's medical record was checked to find the right value.

Baseline characteristics

Baseline characteristic data were collected at the research clinic (see the Supplemental Methods).

Statistics

Power analyses.

The trial was powered according to the primary outcome of persistent wheeze or asthma. Therefore, the detectable effect size of the RCT on GA, birth weight, and size for GA was calculated post hoc based on cohort data.

With 80% power, our sample size of 699 could detect a mean difference of 2 d in relation to GA, with an SD of 11 d, and a mean increase of 112 g in birth weight, with an SD of 530 g. With regards to difference in the growth curves of Marsál et al. (14), we could detect a mean increase of 6.0%, with an SD of 28%.

We used principal component analysis, which is a data-driven pattern recognition analysis, to assemble household income, maternal age, and maternal level of education at 2 y in 1 principal component called *social circumstances*. This component describes the main variation across all the 3 measures in 1 variable. We used Student's *t* test for normally distributed continuous variables and chi-square tests for categoric variables. Associations between n–3 LCPUFA supplementation and GA were analyzed via Wilcoxon's Signed Rank test, because GA was not normally distributed. Results with a P value <0.05 were considered significant. Missing data were treated as missing observations. The data processing was performed with the use of R version 3.1.0 (R Foundation for Statistical Computing, Vienna, Austria) and the package "ggplot2" for graphics. The power and sample size calculation and testing for the study hypotheses were based on a 2-sample, 2-tailed *t* test at the 0.05 level.

Results

Baseline characteristics

Enrollment began in November 2008, ended in November 2010, and the last child was born in April 2011. We randomly assigned 736 unselected women at pregnancy week 24 to either n–3 LCPUFA or control: 28 women were lost to follow-up before pregnancy week 36 (including 4 intrauterine deaths, 2 in each group), and 5 twin pregnancies and 4 children with disabling disease were excluded, leaving 699 mother-child pairs for the analyses with 346 in the n–3 LCPUFA group and 353 in the control group (see study group flowchart in Figure 1). The baseline characteristics are presented in Table 1, showing a successful randomization ($P > 0.05$ in all comparisons, data not shown). Adherence to the study supplementation, defined as an intake of >80% of the prescribed dose based upon capsule count, was estimated to be 69% ($n = 485$) of the included women with no differences between the n–3 LCPUFA and control groups.

GA, fetal growth, and birth weight

GA.

For the 699 included children, the median GA was 281 d.

Supplementation with n–3 LCPUFAs showed a significantly higher GA: median (IQR) 282 (274–288) compared with 280

TABLE 1 Baseline characteristics of the participants in the COpenhagen Prospective Studies on Asthma in Childhood$_{2010}$ mother-child cohort[1]

		Random assignment	
	All	n–3 LCPUFA	Control
n	699 (100)	346 (49)	353 (51)
Child, *n* (%)			
Male	353 (50.5)	166 (48.2)	187 (53.1)
Caucasian	667 (95.4)	335 (96.8)	332 (95.1)
Season of birth			
Winter	216 (30.9)	98 (28.3)	118 (33.4)
Spring	187 (26.8)	96 (27.7)	91 (25.8)
Summer	148 (21.1)	73 (21.1)	75 (21.2)
Fall	148 (21.1)	79 (22.8)	69 (19.5)
Pregnancy			
Primiparity, *n* (%)	317 (45.4)	152 (43.9)	165 (46.7)
Smoking in pregnancy, *n* (%)	55 (7.9)	20 (5.8)	35 (9.8)
Cat or dog in pregnancy, *n* (%)	244 (34.9)	124 (35.9)	120 (34.2)
Antibiotics in pregnancy, *n* (%)	245 (36.7)	121 (36.4)	124 (37.0)
GA at inclusion, wk	24.3 ± 0.7	24.3 ± 0.7	24.3 ± 0.7
Hadlock calculated in utero weight,[2] g	323.4 ± 54.0	321.7 ± 49.1	326.0 ± 58.5
Assisted reproduction, *n* (%)	66 (9.4)	30 (8.9)	36 (10.6)
Participation in the high-dose vitamin D intervention, *n* (%)	589 (84.3)	282 (40.3)	307 (43.7)
Daily fish intake before inclusion, g	27.9 ± 17.5	27.9 ± 16.7	27.8 ± 18.3
Maternal pretreatment blood concentrations of EPA + DHA,[3] %	4.9 ± 1.2	4.9 ± 1.2	4.9 ± 1.2
Parental factors			
Maternal age at birth, y	32.2 ± 4.5	32.3 ± 4.4	32.1 ± 4.5
Maternal prepregnancy BMI, kg/m^2	24.6 ± 4.4	24.7 ± 4.3	24.3 ± 4.5
Maternal asthma,[4] *n* (%)	182 (26.0)	84 (24.4)	98 (27.8)
Paternal height, cm	181.0 ± 6.7	181.1 ± 6.3	180.8 ± 7.1
Social circumstances[5]	0.0 ± 1.0	0.0 ± 1.0	0.0 ± 1.0

[1] Student's *t* test was used for normally distributed continuous variables and chi-square tests for categoric variables to analyze differences between the intervention and the control group. All comparisons were nonsignificant with $P > 0.05$. Values are means ± SDs or *n* (%). GA, gestational age; LCPUFA, long-chain PUFA.
[2] Calculated by the Hadlock equation with the use of the fetal biometrics for head, abdomen, and femur (13).
[3] Relative percentage of measured blood fatty acids.
[4] History of doctor-diagnosed asthma.
[5] Defined as the first component of a principal component analysis on household income, maternal age, and maternal level of education at 2 y with a mean value of 0 and SD of 1.

(273–286) d, $P = 0.02$, corresponding to a 2-d difference between the groups (Table 2). This prolongation of pregnancy duration did not lead to a reduction in the frequency of preterm delivery: 12 (4%) children in the n–3 LCPUFA group and 14 (4%) children in the control group, respectively. Figure 2A shows GA in the n–3 LCPUFA and control groups, indicating that the effect of n–3 LCPUFA supplementation is evenly distributed across the spectrum of GA in the population.

Birth weight.

For the 699 children included the mean ± SD birth weight was 3552 ± 533 g. Children born to mothers who were supplemented with n–3 LCPUFAs in pregnancy had a significantly higher birth weight compared with the control group: mean ± SD: 3601 ± 534 compared with 3504 ± 528 g, $P = 0.02$; corresponding to a mean increase of 97 g (95% CI: 17–176 g) (Figure 2B and Table 2).

Size for GA and intrauterine growth. The children were larger for GA in the n–3 LCPUFA group than in the control group when using standardized growth curves to estimate the size: by Marsál, mean ± SD: 51.6 ± 28.4 percentiles compared with 47.6 ± 28.3 percentiles, $P = 0.06$; and by Skjærven, mean ± SD: 49.9 ± 28.3 percentiles compared with 44.5 ± 27.6 percentiles, $P = 0.01$ (Figure 2C and Table 2).

We did not find any significant difference in children born small or large for GA according to the definition of Marsál et al. (14): 8 (2.3%) children in the n–3 LCPUFA group and 5 (1.4%) children in the control group were born small for GA, respectively, and 13 (3.8%) children in the n–3 LCPUFA group and 8 (2.3%) children in the control group were born large for GA, respectively.

Intrauterine growth rate, based on the difference between Hadlock calculated fetal weight (12) from pregnancy week 20 and weight at birth, was available for 691 (99%) of the children. The mean growth rate from this estimation was 23.19 ± 3.15 g/d in the n–3 LCPUFA group and 22.83 ± 3.17 g/d in the control group, corresponding to a mean difference of 0.36 g/d (95% CI: –0.11, 0.83 g/d) (Table 2).

Secondary analyses.

We found a trend toward an interaction between the intervention and sex for GA ($P = 0.06$). In females median (IQR) effect of n–3 LCPUFAs was 283.5 (276–289) compared with 280 (273–284) d, $P = 0.001$, and in males, it was 280 (273–287) d compared with 279 (273–288) d.

There were no interactions between sex and the intervention on birth weight and size for GA (data not shown), neither were there any interactions between smoking during pregnancy and

TABLE 2 Effects of fish oil supplementation in pregnancy on primary and secondary endpoints in children[1]

	n–3 LCPUFA ($n = 346$)	Control ($n = 353$)	*P* value
Primary endpoints			
GA, d	282 [274–288]	280 [273–286]	0.02
Birth weight, g	3601 ± 535	3504 ± 528	0.02
Birth length, cm	52.1 ± 2.4	51.8 ± 2.5	0.15
Birth head circumference, cm	35.1 ± 1.8	34.9 ± 1.6	0.27
Marsál percentage[2]	51.6 ± 28.4	47.6 ± 28.3	0.06
Skjærven percentage[2]	49.9 ± 28.3	44.5 ± 27.6	0.01
Secondary endpoints			
Preterm delivery (GA < week 37), *n* (%)	12 (3.5)	14 (4.0)	0.88
Born small for GA,[3] *n* (%)	8 (2.3)	5 (1.4)	0.55
Born large for GA,[4] *n* (%)	13 (3.8)	8 (2.3)	0.35
Fetal growth from week 20 to birth,[5] g/d	23.2 ± 3.2	22.8 ± 3.2	0.13
APGAR score 5 min <10, *n* (%)	17 (5.0)	15 (4.3)	0.82
Induced birth, *n* (%)	123 (36)	120 (35)	0.81
Emergency cesarean delivery, *n* (%)	48 (13.9)	37 (10.5)	0.22
Elective cesarean delivery, *n* (%)	31 (8.9)	35 (9.9)	0.90
Preeclampsia, *n* (%)	15 (4.4)	15 (4.3)	1.00
Gestational diabetes, *n* (%)	6 (1.8)	10 (2.9)	0.46

[1] Values are means ± SDs, medians [IQRs], or *n* (%). Student's *t* test was used for normally distributed continuous variables and chi-square tests for categoric variables to analyze differences between the intervention and the control groups. GA, gestational age; LCPUFA, long-chain PUFA.
[2] Calculated percentage of expected birth weight at a certain GA with the use of the 2 standardized growth curves (14, 15).
[3] Children with a Marsál percentage <–2 SD.
[4] Children with a Marsál percentage >2 SD.
[5] Calculated as (birth weight (g) – Hadlock estimated weight (g))/(GA at birth (d) – GA at scanning (d)).

the intervention on GA, birth weight, and size for GA (data not shown).

Stratifying the analyses on nulliparous and multiparous women yielded the same associations of the n–3 LCPUFA supplementation with GA, birth weight, and intrauterine growth measures (data not shown).

Because induction of birth is an external factor which interferes with the spontaneous progress of pregnancy, we performed a sensitivity analysis for timing of birth across the 2 trial arms, assuming induced birth to be a censoring event. We found an HR of 0.81 (95% CI: 0.6741, 0.9765), $P = 0.03$, for spontaneous delivery in the n–3 LCPUFA group compared with the control group.

No interactions existed between n–3 LCPUFA and vitamin D supplementation or between n–3 LCPUFA supplementation and the intervention with influenza-A vaccine with regards to our main study outcomes.

Adverse pregnancy and birth outcomes.

The n–3 LCPUFA supplementation had no significant effects on adverse pregnancy outcomes such as preeclampsia or gestational diabetes. Furthermore, there were no differences in delivery complications such as induced birth and emergency or elective cesarean delivery, and no difference in the Apgar score at 5 min (Table 2).

Discussion

Primary findings

Daily supplementation with n–3 LCPUFAs compared with control from pregnancy wk 24 until 1 wk after birth resulted in a 2-d prolongation of pregnancy and a 97-g higher birth weight among mother-child pairs of the population-based Danish COpenhagen Prospective Studies on Asthma in Childhood$_{2010}$ cohort. The increase in birth weight was not only explained by a longer duration of pregnancy, because we also saw an increase in size for GA.

Strengths and limitations

Our study is among the largest RCTs on n–3 LCPUFA supplementation in pregnancy, investigating pregnancy length and fetal growth. Still, the number of participating mothers ($n = 699$) limited the opportunities to investigate if the increased size for GA also led to a reduction in children born small for GA, because we only had 13 children in that category (14). A major advantage of our trial is that it is nested in a population-based cohort, which increases the external validity of our findings.

Another advantage of our design is the quality of the endpoints with 99.8% of the due dates determined by early ultrasound scans and the birth weight captured by parental interviews and subsequently compared against register data. In addition, we acquired a broad range of data on adverse pregnancy and delivery endpoints, which were compared against register data. The study design precluded investigation of the effect of n–3 LCPUFA supplementation on very preterm delivery (GA < 24) because the supplementation was initiated after this point in pregnancy.

It is an important strength of our study that we found consistent results for different measurements of fetal size for GA, i.e., the Marsál percentage and Skjærven percentage, and a nonsignificant effect on fetal growth estimated as growth rate from week 20 of pregnancy based on ultrasound scans.

It could be a limitation that 35% of the births were induced; however, in a sensitivity analysis in which birth induction was a censoring factor, we still found a significantly increased risk of prolonged gestation in the n–3 LCPUFA group.

Another limitation is that only 69% of the mothers had a supplementation adherence >80%; however, when limiting the primary analyses to include only these mothers, it did not change the findings. Finally, it is a limitation that our outcomes

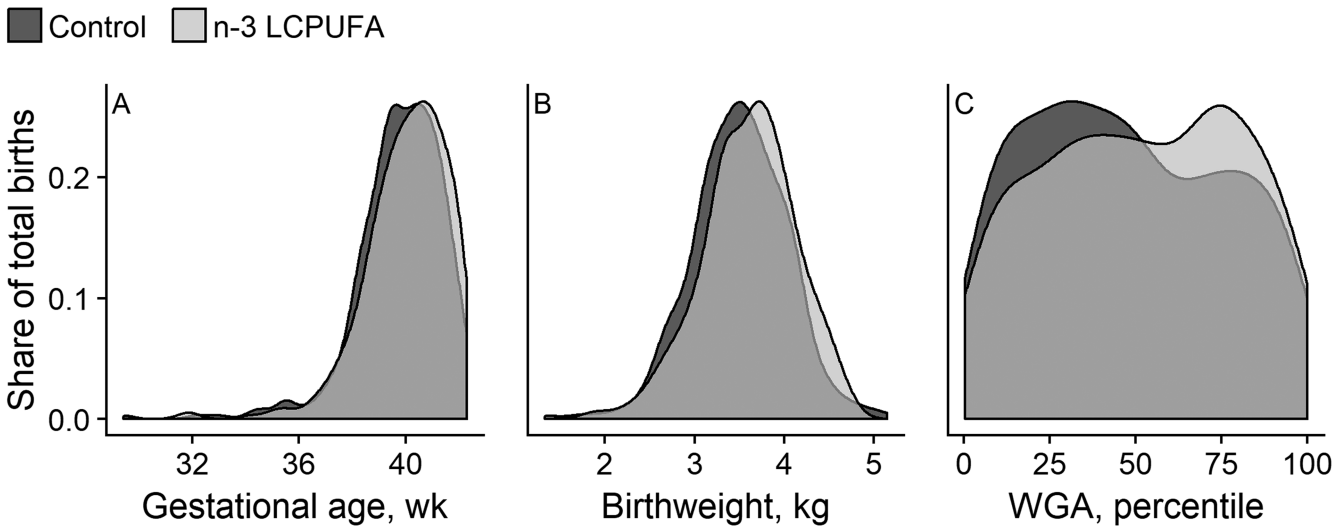

FIGURE 2 Density plot showing gestational age (A), birth weight (B), and the percentile of WGA (C) according to Marsál et al. (14). Standard growth curves stratified by supplementation group: n–3 LCPUFA and control. LCPUFA, long-chain PUFA; WGA, weight for gestational age.

were secondary outcomes in our RCT, but this also ensures that the population was not biased toward these endpoints.

Interpretation

In this RCT, we have confirmed earlier findings showing that fish-oil supplementation during pregnancy leads to a prolongation of pregnancy and an increase in birth weight (4). Furthermore, we demonstrate a significantly larger size for GA in the n–3 LCPUFA–supplemented group. This suggests that the increase in birth weight is not solely explained by the prolonged duration of pregnancy, but is also a consequence of increased intrauterine growth. To our knowledge this has not been shown before.

Our findings are in line with the results from the majority of other studies, demonstrating a prolongation of pregnancy of between 2 and 4 d and an increase in birth weight of between 70 and 170 g after fish oil supplementation (4, 5). An explanation for the slightly different effects observed in the previous studies could be differences in the time at which the supplementation was initiated during pregnancy and the amount of fish oil supplied. A recent study with 500 participants, which did not observe similar effects, supplemented from week 18 of pregnancy with less than one-fifth of the fish oil dose used in the present study (17) and another study with 1200 participants that used one-third of our dose from week 21 of pregnancy found a prolongation of pregnancy of 1 d and the birth weight was only increased by 70 g (7). This could imply that there is a dose-response relation between the amount of n–3 LCPUFA supplement and the effect on pregnancy duration and fetal growth and that a minimum threshold might exist (18).

The biological mechanism by which n–3 LCPUFAs can prolong pregnancy remains unclear, but many studies have suggested that eicosanoids regulate initiation of labor (19) and a proposed explanation has been that fish oil supplementation alters the balance of prostaglandins derived from the n–3 LCPUFAs and the n–6 LCPUFAs involved in parturition (20).

It has previously been suggested that the fish oil–induced increase in birth weight is only caused by the prolongation of pregnancy (6). However, our data show that n–3 LCPUFA supplementation also has an impact on the intrauterine growth, leading to an increased size for GA. A possible mechanism for the increased fetal growth could be that n–3 LCPUFAs increase the ratio of prostacyclin to thromboxane, thereby reducing blood viscosity and facilitating increased placental blood flow, which benefits fetal growth (21).

It is a relevant concern that prolongation of pregnancy and higher birth weight could cause unwanted complications during pregnancy and birth. We found no association between n–3 LCPUFA supplementation and any of our adverse pregnancy outcomes; furthermore, a broader evaluation of the safety profile has been published elsewhere (9), showing no differences between the groups. However, for most of these outcomes our numbers were low and larger studies are needed to confirm these findings.

We found a borderline significant interaction between n–3 LCPUFA and sex in relation to GA. This possible sex difference should be taken into account in future studies.

Unfortunately, our study was not sufficiently powered to demonstrate a reduction in preterm delivery or children born small for GA after n–3 LCPUFA supplementation in pregnancy, which has been suggested in epidemiologic observational studies (9). Larger studies are therefore needed to establish if it would be of clinical relevance for the health of the mother and child to recommend the routine use of n–3 LCPUFA supplementation during pregnancy (22).

However, in the n–3 LCPUFA–supplemented group we have further demonstrated a reduction in asthma and lower respiratory infections at 5 y of age (9) and the n–3 LCPUFA supplementation has affected BMI at 6 y of age and, in unpublished data, early neurologic outcomes with earlier achievement of motor milestones and higher cognitive scores in boys (23).

This impact on 3 different organ systems indicates that n–3 LCPUFA concentrations in pregnancy have an important role for these children's development and this potential should be further explored.

Conclusions

Fish oil supplementation during the third trimester of pregnancy led to a prolongation of gestation and a higher birth weight. The increase in birth weight was due to an increase in pregnancy duration and likely an increased intrauterine growth, because we found an increase in size for GA. Future studies should focus on dose-response relations and the composition of

n–3 LCPUFAs in fish oil supplementation as well as the overall potential for improving fetal and infant health.

Acknowledgments

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