Effect of long-chain polyunsaturated fatty acid supplementation during pregnancy or lactation on infant and child body composition: a systematic review

Beverly S Muhlhausler, Robert A Gibson, and Maria Makrides

ABSTRACT

Background: n–3 (omega-3) Long-chain polyunsaturated fatty acids (LC-PUFAs) inhibit fat cell differentiation and fat storage in adults, and this has led to the hypothesis that maternal n–3 LC-PUFA supplementation may reduce fat mass in children.

Objective: The objective of this systematic review was to evaluate the effect of n–3 LC-PUFA supplementation in pregnancy or lactation on infant and child body composition in randomized controlled trials.

Design: MEDLINE and EMBASE databases were searched for relevant articles. Human trials that supplemented the maternal diet with n–3 LC-PUFAs during pregnancy or lactation and assessed either body fat mass or body mass index in children were included. Trials had to be randomized in design. The quality of all included studies was assessed against set criteria, and results of eligible trials were compared.

Results: There were only 3 human trials (4 publications) that met our inclusion criteria. There was considerable disparity in study design and trial quality. The results were variable and showed positive, negative, or neutral effects of maternal n–3 LC-PUFA supplementation on body fat mass in children.

Conclusions: This systematic review highlights the paucity of robust data from human studies to evaluate the effect of increased n–3 LC-PUFA exposure during the perinatal period on body fat mass in offspring. Further studies are required in which the intervention is confined to the perinatal period and that are sufficiently powered, have appropriate controls, have adequate blinding of participants and investigators, and have high retention rates.

INTRODUCTION

Childhood obesity is now recognized as a global epidemic and represents a major public health issue in both industrialized and semi-industrialized countries (1, 2). Although multiple factors are likely to contribute to the development of obesity, there is now evidence that an individual’s susceptibility to becoming overweight or obese is influenced by the nutritional environment they experience during fetal and early postnatal life (3–5). In animal studies, offspring exposed to a high-fat or high-glucose environment before birth are heavier and have a higher percentage of body fat throughout the life course (4). Similarly, in humans, children born to mothers who are obese (6) or diabetic (7, 8) during their pregnancy have an increased incidence of obesity and type 2 diabetes in childhood and adult life.

In addition to increases in total energy intake, there is also evidence that the fatty acid composition of the maternal diet during pregnancy and/or lactation may play a role in determining body composition of the offspring (9, 10). Much of this evidence is based on adult studies, in which the dietary long-chain polyunsaturated fatty acids (LC-PUFAs), particularly those of the n–6 and n–3 classes, have been varied. These studies have shown that n–3 LC-PUFAs suppress, whereas n–6 PUFAs promote, both the differentiation of fat cells and subsequent fat accumulation (10, 11).

This evidence, coupled with the trend of increased n–6 PUFAs to n–3 PUFA ratio in the diets of pregnant and lactating women over the past 2 decades (12), has led to the proposal that an excess of n–6 PUFAs relative to n–3 PUFAs in the maternal diet during critical windows in the development of fat cells, may be one of the factors contributing to the upward trend in childhood obesity over this period (12). Following this suggestion, there has been growing interest in determining whether there is a causal relation between the balance of n–6 to n–3 PUFA to which individuals are exposed during critical periods of fat cell development—ie, in utero and during early infancy—and fat deposition and susceptibility to becoming overweight or obese in postnatal life. This article reports a systematic review of studies investigating the effect of maternal n–3 LC-PUFA supplementation in pregnancy or lactation on infant and child body composition in randomized controlled trials, because these

1 From the School of Agriculture, Food, and Wine, The University of Adelaide, Adelaide, Australia (BSM and RAG); the Sansom Institute for Health Research, School of Pharmacy and Medical Sciences, University of South Australia, Adelaide, Australia (BSM); the Women’s and Children’s Health Research Institute, Women’s and Children’s Hospital, North Adelaide, Australia (BSM, RAG, and MM); and the School of Pediatrics and Reproductive Health, the University of Adelaide, Adelaide, Australia (MM).

2 Supported by Senior Research Fellowships from the National Health and Medical Research Council of Australia (NHMRC) (MM and RG) and by a Peter Doherty Postdoctoral Fellowship from the NHMRC (BM).

3 Address correspondence to M Makrides, Child Nutrition Research Centre, Women’s and Children’s Health Research Institute, 72 King William Road, North Adelaide SA 5006, Australia. E-mail: maria.makrides@health.sa.gov.au.

Received March 10, 2010. Accepted for publication July 8, 2010.

First published online August 4, 2010; doi: 10.3945/ajcn.2010.29495.
would provide information about the cause-and-effect relation between increased exposure to \( n-3 \) LC-PUFAs during the perinatal period and childhood fat mass.

METHODS

Search strategy

MEDLINE (www.ncbi.nlm.nih.gov/pubmed) and EMBASE (www.embase.com) databases were searched for relevant articles by using the search terms “omega-3 fatty acid OR omega-3 OR \( n-3 \) OR \( n-3 \) fatty acid OR fish oil or PUFA” AND “pregnancy OR lactation OR fetus” AND “BMI OR fat mass OR adipocyte.” The search was restricted to human studies. The reference lists of eligible articles identified by the search were also checked to reveal other potentially relevant articles. The last literature search was completed in March 2010. A total of 7 human trials (8 articles) were evaluated for inclusion (Figure 1).

Selection of articles

Trials were eligible for inclusion if they involved maternal \( n-3 \) LC-PUFA supplementation for \( \geq 2 \) wk during pregnancy or lactation or both pregnancy and lactation. The trials also had to report a measure of adiposity in children such as body mass index (BMI), BMI \( z \) score, or percentage body fat mass. We did not include studies that assessed weight and length if they did not also report weight-for-length or BMI, because it was important that the outcome target was a clinical indicator of body composition and not only overall growth.

Studies identified by search strategy

Of the 8 articles identified by our search strategy, 1 was excluded without reviewing the full manuscript, because the \( n-3 \) LC-PUFA supplement was given to the infant and not the mother (13). Three further studies were excluded because they did not report any of the outcomes of interest (14–16); these studies included a study that presented a protocol only (14), a study that presented a scientific hypothesis but no results (16), and a study that assessed the effect of maternal \( n-3 \) LC-PUFA supplementation on cognitive development but did not include any measure of BMI or body composition (15). Of the trials that were included, 2 of the articles assessed body composition of children from a single trial at 2 different ages (17, 18). Therefore, data from 3 trials and 4 publications are included in this review (17–20). The 8 human studies evaluated for inclusion and the reasons for their inclusion or exclusion are summarized in Table 1. Further details of the included studies are summarized in Table 2.

Few studies that met the inclusion criteria had comparable study designs. There was considerable variation in the type and timing of intervention, the outcomes assessed, and the timing of assessments. Therefore, the approach of combining results in a meta-analysis was deemed inappropriate.

![Figure 1](https://academic.oup.com/ajcn/article-abstract/92/4/857/4597561)
<table>
<thead>
<tr>
<th>Author and year of publication (reference)</th>
<th>Participants</th>
<th>Intervention</th>
<th>Methods</th>
<th>Outcome assessments</th>
<th>Excluded or included</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hauner et al, 2009 (14)</td>
<td>Pregnant women</td>
<td>Maternal n−3 LC-PUFA supplementation 15 wk pregnancy to term</td>
<td>Randomized double-blinded</td>
<td>BMI and body fat mass in children</td>
<td>Excluded</td>
<td>Presented study design for a planned RCT that has yet to be conducted (no results)</td>
</tr>
<tr>
<td>Helland et al, 2003 (15)</td>
<td>Pregnant women</td>
<td>10 mL cod liver oil or corn oil from wk 18 of pregnancy to 3 mo after delivery</td>
<td>Randomized double-blinded</td>
<td>Kaufman Assessment Battery for Children body weight</td>
<td>Excluded</td>
<td>No measure of body composition or BMI</td>
</tr>
<tr>
<td>Crawford et al, 2003 (16)</td>
<td>Preterm infants</td>
<td>None</td>
<td>Scientific hypothesis article</td>
<td>Tests of IQ/cognitive development</td>
<td>Excluded</td>
<td>Presented scientific hypothesis but no results</td>
</tr>
<tr>
<td>Groh-Wargo et al, 2005 (13)</td>
<td>Preterm infants</td>
<td>DHA + ARA supplementation until 1 y corrected age</td>
<td>Prospective, randomized, controlled trial</td>
<td>Body weight, lean mass, and fat mass</td>
<td>Excluded</td>
<td>n−3 Fatty acid supplement provided directly to infant and not to the mother</td>
</tr>
<tr>
<td>Lauritzen et al, 2005 (17)</td>
<td>Lactating women</td>
<td>1.5 g n−3 LC-PUFAs/d for the first 4 mo of lactation</td>
<td>RCT</td>
<td>Sum of skinfold thicknesses, BMI, BMI z score (based on Danish growth charts)</td>
<td>Included</td>
<td>Randomized design: maternal diet supplemented with n−3 LC-PUFAs during lactation and for &gt;2 wk Assessed at least one outcome of interest (BMI, BMI z score)</td>
</tr>
<tr>
<td>Asserhoj et al, 2009 (18)</td>
<td>Lactating women</td>
<td>1.5 g n−3 LC-PUFAs/d for the first 4 mo of lactation</td>
<td>RCT</td>
<td>Sum of skinfold thicknesses, BMI, BMI z score (based on Danish growth charts)</td>
<td>Included</td>
<td>Randomized design: maternal diet supplemented with n−3 LC-PUFAs during lactation and for &gt;2 wk Assessed at least one outcome of interest (BMI, BMI z score, skinfold thickness)</td>
</tr>
<tr>
<td>Helland et al, 2008 (20)</td>
<td>Pregnant/lactating women</td>
<td>10 mL cod liver oil or corn oil from wk 18 of pregnancy to 3 mo after delivery</td>
<td>RCT</td>
<td>BMI, BMI z score</td>
<td>Included</td>
<td>Randomized design: maternal diet supplemented with n−3 LC-PUFAs during pregnancy/lactation and for &gt;2 wk Assessed at least one outcome of interest (BMI, BMI z score)</td>
</tr>
<tr>
<td>Lucia Bergmann et al, 2007 (19)</td>
<td>Pregnant/lactating Women</td>
<td>200 mg DHA (included in vitamin and mineral capsule along with probiotic) from 21 wk of pregnancy to 3 mo after delivery</td>
<td>RCT</td>
<td>BMI z score</td>
<td>Included</td>
<td>Randomized design: maternal diet supplemented with n−3 LC-PUFAs during pregnancy/lactation and for &gt;2 wk Assessed at least one outcome of interest (BMI, BMI z score)</td>
</tr>
</tbody>
</table>

1 LC-PUFA, long-chain polyunsaturated fatty acid; RCT, randomized controlled trial; IQ, intelligence quotient; DHA, docosahexaenoic acid; ARA, arachidonic acid.
<table>
<thead>
<tr>
<th>Author and year of publication (reference)</th>
<th>Country</th>
<th>Participants</th>
<th>Intervention</th>
<th>Methods</th>
<th>Total enrolled</th>
<th>Available for analysis of body composition/BMI</th>
<th>Method used to assess body composition</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lauritzen et al, 2005 (17); Asserhoj et al, 2009 (18)</td>
<td>Denmark</td>
<td>Pregnant women with fish intake (&lt;0.40 g LC-PUFAs/d)</td>
<td>First 4 mo of lactation</td>
<td>Randomized: yes</td>
<td>174; n = 101; n = 29</td>
<td>At 2.5 y, BMI, BMI z score, and waist circumference increased in n = 3 LC-PUFA group compared with olive-oil and high-fish intake reference group</td>
<td>Sum of skinfold thicknesses, BMI, BMI z score (based on Danish growth charts)</td>
<td>At 2.5 y, BMI, BMI z score, and waist circumference increased in n = 3 LC-PUFA group compared with olive-oil and high-fish intake reference group</td>
</tr>
<tr>
<td>Helland et al, 2008 (20)</td>
<td>Norway</td>
<td>Pregnant women</td>
<td>18 wk pregnancy to 3 mo postpartum</td>
<td>Randomized: yes</td>
<td>341; n = 143; n = 82</td>
<td>At 7 y, no difference in BMI, BMI z score, or percentage body fat between treatments</td>
<td>ITT analysis: no</td>
<td>No difference in BMI between groups</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No relation between fatty acid status during perinatal period and BMI</td>
</tr>
</tbody>
</table>

(Continued)
TABLE 2 (Continued)

<table>
<thead>
<tr>
<th>Author and year of publication (reference)</th>
<th>Country</th>
<th>Participants</th>
<th>Intervention</th>
<th>Methods</th>
<th>Total enrolled</th>
<th>Available for analysis of body composition/BMI</th>
<th>Method used to assess body composition</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lucia Bergmann et al, 2007 (19)</td>
<td>Germany</td>
<td>Pregnant women</td>
<td>21 wk gestation to 3 mo postpartum</td>
<td>Randomized: yes</td>
<td>n = 144; n−3 LC-PUFA group: 47</td>
<td>BMI, BMI z score</td>
<td>At 21 mo of age body weight and BMI lower in n−3 LC-PUFA group</td>
<td>n−3 LC-PUFA group: 200 mg DHA (included in vitamin and mineral capsule along with probiotic), EPA not stated</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Concealed allocation: unclear</td>
<td>n = 69 (group allocation unclear)</td>
<td></td>
<td>BMI z score lower in n−3 LC-PUFA group throughout first 21 mo</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Blinded outcome assessment: yes</td>
<td></td>
<td></td>
<td>Infants: premature birth (&lt;37 wk), any major malformation or hospitalized for &gt;1 wk</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Attrition: 52% ITT analysis: no</td>
<td></td>
<td></td>
<td>Control group: same supplement without DHA, with or without probiotics (2 treatment groups combined)</td>
<td></td>
</tr>
</tbody>
</table>

1 LC-PUFA, long-chain polyunsaturated fatty acid; LA, linoleic acid; ALA, α-linoleic acid; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; ITT, intention-to-treat.
RESULTS

Summary of included studies

A total of 3 trials, all conducted in Europe, were included in this review. All trials reported a randomized design, but it was not always clear from the publications whether there was adequate concealment of allocation. All trials included a control group, although the nature of the control group varied. One trial used olive oil (17), another corn oil (20), and the study by Lucia Bergmann et al (19) commenced with 3 treatment groups: one receiving a probiotic supplement and vitamin tablet to which 200 mg docosahexaenoic acid (DHA) was added (n−3 LC-PUFA–supplemented group), one group receiving the probiotic supplement and an identical vitamin tablet that did not contain DHA, and one group receiving only the vitamin tablet without added DHA. The latter 2 “control” groups were reported not to be different in any of the outcome measures and were pooled for subsequent analysis.

Doses of n−3 LC-PUFAs in the supplemented groups ranged from 0.2 to 1.18 g DHA/d. The dose of eicosapentaenoic acid (EPA) was not reported in the study by Lucia Bergmann et al (19) and was 0.62 and 0.80 g/d in the Lauritzen and Helland trials, respectively (17, 18, 20). LC-PUFA supplements were derived from fish oils for all included trials. In 2 of the trials, the intervention period extended from 18 (20) or 21 (19) wk of pregnancy to 3 mo postpartum. In the third trial, maternal LC-PUFA supplementation was provided only during the first 4 mo of lactation (17, 18). All trials reported BMI as one of the outcomes; 2 also reported BMI z score (17–19), and 1 trial employed the sum of skinfold thicknesses to determine percentage body fat (17, 18). None of the studies included a direct measure of body composition—ie, dual-energy X-ray absorptiometry or bioelectrical impedance. The assessments occurred at 21 mo, 2.5 y, or 7 y of age. It was not clear from the publications whether the investigators were blinded at the outcomes assessments. All of the human trials suffered from high attrition rates, which ranged from 40% to 60% (Table 2).

The 2 trials in which n−3 LC-PUFAs were supplied in pregnancy and lactation reported contrasting results. The first reported a significant reduction in BMI z score in the infants of mothers in the n−3 LC-PUFA–supplemented group at 21 mo of age (19). Furthermore, longitudinal analysis in this study showed a significant time-dependent effect of DHA supplementation on reducing the rate of weight gain and decrease in BMI z score, but not length or head circumference, in this group of infants. However, Helland et al (20) found no effect of maternal n−3 LC-PUFAs on BMI in the children at 7 y of age. BMI z score was not reported in this study.

The study by Lauritzen et al (17), in which maternal DHA supplementation was confined to the lactation period, reported a significant increase in BMI and waist circumference at 2.5 y of age in the high-LC-PUFA group and found a direct relation between BMI and DHA concentrations in maternal erythrocytes at the end of the intervention. Interestingly, there was no effect of maternal n−3 LC-PUFA supplementation on BMI, BMI z score, or skinfold thicknesses when the infants in this trial were followed-up at 7 y of age (18).

DISCUSSION

This article reports a systematic review of the effect of maternal n−3 LC-PUFA supplementation on body composition in children and has highlighted the paucity of studies that have investigated this issue. There were only 3 human trials (and 4 articles) that met our inclusion criteria, and within these trials considerable disparity existed in study design and trial quality. Not surprisingly, the results were disparate; there was one positive, one negative, and one neutral result, making it impossible to draw robust conclusions. It is our view that there are several key issues that need to be addressed, including differences in timing and duration of the intervention, choice of control groups, the outcome assessments chosen, and study quality.

Dose of treatment and choice of control groups

The dose of n−3 LC-PUFAs provided to the treatment group varied between trials and, if the assumption is that higher doses would be associated with greater effects, then it is possible that this could account for some of the variation in the results of the respective studies. However, there was no clear relation between n−3 LC-PUFA dose and the study outcome, with the study with the lowest dose reporting a reduction in BMI (19), the study with the highest dose reporting no effect (20), and the study that used an intermediate dose reporting an increase in BMI at 2.5 y (17) and no effect at 7 y of age (18).

The choice of control groups for these studies was problematic, and 2 of the 3 trials used dietary treatments in their control groups that have been reported in previous studies to have effects on fatty acid metabolism and fatty acid profile. Olive oil and corn oil, which were used as control oils for 2 of the trials, have been shown to result in altered lipoprotein metabolism (21) and increased postprandial energy expenditure (22) in healthy adults. The choice of control groups that were not inert therefore raises the possibility that the effects seen in the trials were driven by the control group. To avoid this, it will be important in future studies to ensure that the control treatments do not induce a physiologic response or are at least representative of the standard diet.

Timing and duration of the intervention

The 2 periods during which the intervention was applied (late gestation compared with lactation) coincide with different stages in the development of fat cells in humans and times during which greater or lesser numbers of preadipocytes relative to mature adipocytes are present in maturing fat depots (9). As a result, it is possible that increased n−3 LC-PUFA exposure had different immediate and long-term effects on fat cell function in those studies that applied the intervention during pregnancy and lactation (19, 20) compared with those in which the intervention was applied during lactation only (17, 18).

Study quality

Although variations in the study design are likely to have contributed to the lack of consistency in results, perhaps of greater importance were issues related to trial quality. It was not clear in any of the publications whether there was adequate blinding of allocation and whether the investigators remained blinded to treatment group when outcomes were assessed at older ages (2.5 and 7 y). All trials suffered from high attrition rates (>40%). The inherent differences in sociodemographic...
characteristics as well as outcomes between participants who were followed-up successfully and those who are lost to follow-up are well documented (23). This selective loss may have introduced bias as well as the inevitable loss of statistical power, which would have led to an increased probability of random error. More importantly, high rates of attrition are likely to have affected the initial randomization and resulted in a loss of internal validity. The high rate of attrition also prevented researchers from carrying out an intention to treat analysis, which may have introduced further bias. It is our view that many of the issues in the human studies were driven by the fact that only one of these trials (19) was initially designed to examine the effects of maternal n–3 supplementation on body composition in the children, whereas in the 2 other trials, assessment of body composition was added as an outcome after the trial was already established and participants enrolled. Differences in the outcomes assessed and the time of assessment may also have contributed to variability in the results. In addition, BMI was not always corrected for age and sex (BMI z score), leading to greater variability within groups and reduced statistical power.

Conclusions

This systematic review highlights the paucity of robust data from human studies to evaluate the effect of increased n–3 PUFA exposure during the perinatal period on body fat mass in the offspring. Future clinical trials should be sufficiently powered and have appropriate controls, adequate blinding of participants and investigators, and high retention rates to address this knowledge gap.

The authors’ responsibilities were as follows—BM: conducted the systematic review of the literature; and all authors: contributed to the conception and design of this systematic review, contributed to the drafting and editing of the manuscript, and approved the final submitted version. None of the authors had a conflict of interest.

REFERENCES