DHA and ARA in early life -
What we know and what we need to know

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University of Dundee, Scotland, UK
Brain Growth, DHA and ARA

Human brain at 25 and 40 weeks gestation

Martinez M 1992

The n-3 fatty acids in the forebrains of 34 infants
(including both preterm and postnatal normally-fed infants up to age 2)

The n-6 fatty acids in the forebrains of 34 infants
(including both preterm and postnatal normally-fed infants up to age 2)
# LCP Dietary Sources

## Omega-6 FAs

- **Maize (corn) oil**
- **Cottonseed oil**
- **Safflower oil**
- **Soybean oil**
- **Eggs**
- **Meat**
- **Milk**
- **Fungal Oil from Mortierella Alpina**

### LA (18:2)
- Linoleic acid

### ARA (20:4)
- Arachidonic Acid

**Poor levels of conversion in infants**

## Omega-3 FAs

- **Linseed (flax) oil**
- **Rape seed oil**
- **Fish**
- **Fish oil**
- **Fish/Fish Oil Fortified foods**
- **Algal oil**

### ALA (18:3)
- Alpha-linolenic acid

### EPA (20:5)
- Eicosapentaenoic Acid

**Poor levels of conversion in humans**

### DHA (22:6)
- Docosahexaenoic Acid

**Negligible levels of conversion in humans**

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* Brenna et al 2009, ISSFAL Position Statement No. 5
**Carnielli et al 2007; Pawlosky et al., 2006
Maternal and Infant LCPUFA status

Inequality in supply
Inequality in infant feeding

Long Chain Fatty Acid Composition of Human Milk and Formulae

<table>
<thead>
<tr>
<th>Fatty Acid</th>
<th>Breast Milk</th>
<th>Formulae</th>
</tr>
</thead>
<tbody>
<tr>
<td>C18:2n-6  (Linoleic)</td>
<td>7.2</td>
<td>10 - 16</td>
</tr>
<tr>
<td>C20:4n-6  (Arachidonic)</td>
<td>0.7</td>
<td>ND</td>
</tr>
<tr>
<td>C18:3n-3  (α-Linolenic)</td>
<td>0.8</td>
<td>0.4 - 1.5</td>
</tr>
<tr>
<td>C22:6n-3  (DHA)</td>
<td>0.4</td>
<td>ND</td>
</tr>
</tbody>
</table>

Data: Mean weight percentage of total fatty acid present in milks (1992)

DHA and cerebral cortex

Farquharson et al, 1995
Inequality in maternal diet and breast milk

- 10 fold variation in dietary DHA intake
- 10 fold variation in breast milk DHA levels

Reference list available

Yuhas, et al. Lipids 2006;41:851-858
## Fatty Acid Composition of Breast Milk from Five Regions in China

(Chulei et al, Journal of Nutrition, 1995)

<table>
<thead>
<tr>
<th></th>
<th>Marine</th>
<th>Urban</th>
<th>Rural</th>
<th>Pastoral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fish intake g/d</td>
<td>136 (29)</td>
<td>49 (27)</td>
<td>11(6)</td>
<td>None</td>
</tr>
<tr>
<td>Breast Milk DHA (%FA)</td>
<td>2.78 (1.2)</td>
<td>0.88 (0.34)</td>
<td>0.68 (0.29)</td>
<td>0.44 (0.29)</td>
</tr>
</tbody>
</table>

**Marine** – Zhangzi Island

**Urban** – Dalian, Shenyang

**Rural** – Outskirts of Dalian

**Pastoral** – Balinyouqi county
Inequality in Maternal – Fetal Transfer

- Maternal DHA status
- Placental fatty acid transfer protein
- FADS gene cluster and ELOVL gene family

Erythrocyte Membrane DHA Concentration

Maternal venous

Infant cord

p<0.001
Inequality in infant formula

DHA status of infants fed a Formula supplemented with DHA or a formula not supplemented with DHA

Weaning foods and LCPUFAs

“Weaning foods cannot replace breast milk as sources of long-chain polyunsaturated fatty acids ...”

Although some fresh foods such as brains, liver, and eggs are rich in long-chain PUFA, large amounts of food are necessary to achieve the desired level of supplementation because of the low fat content (Jackson and Gibson, 1989)

The diets in most low-income countries consist mainly of basic staple foods—cereals, legumes, and roots and generally, the content of PUFA in these foods is low (Michaelsen et al, 2009)
Inequality in Maternal and Infant LCPUFA Status

- Low maternal DHA intake
- Genetic Effects
- Low supply of DHA to fetus
- Infant formulas devoid of DHA
- Low levels of DHA and ARA in infant blood and brain
- Low supply of DHA to breast milk

But, is there health inequality?
Biological Evidence

Potential neural effects of LCPUFA at cellular level

- Promotes the synthesis of synaptic membranes
- Increases the numbers of dendritic spines
- Increases the “fluidity” of neuronal membranes
- Is transformed to active neuroprotective metabolites
- Promotes neurogenesis by stimulating the differentiation of neuronal stem cells
Arachidonic acid metabolism

Abbreviations: AA, arachidonic acid; PLA₂, phospholipase A₂; PLC, phospholipase C; COX, cyclooxygenase; NSAIDS, non-steroidal anti-inflammatory drugs; +, vasoconstriction; −, vasodilation.
Clinical Evidence

- A slow rising learning curve
- Recurring design and methodological issues
- Many RCTs reporting positive effects, several reporting no difference between intervention and control, and reports of negative effects extremely rare
Authors’ conclusions:

• Majority of the RCTS have not shown beneficial effects of LCPUFA supplementation on visual or neuro-developmental outcomes of term infants.

• The results were same irrespective of the type, concentration and duration of LCPUFA supplementation.

• Implications for practice
  Routine supplementation of term infant milk formula with LCPUFA can not be recommended.

20 July 2011
Supplementation studies need to ensure relative deficiency in the target population.

Cochrane Review:
15 studies of postnatal supplementation
2 Studies with baseline fatty acid levels

But, need to define relative deficiency

<table>
<thead>
<tr>
<th></th>
<th>DHA (RBC%FA)</th>
<th>ARA (RBC%FA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perth, Australia</td>
<td>7.36</td>
<td>7.44</td>
</tr>
<tr>
<td></td>
<td>15.76</td>
<td>15.54</td>
</tr>
<tr>
<td>West Kiang, Gambia</td>
<td>3.75</td>
<td>4.00</td>
</tr>
<tr>
<td></td>
<td>6.66</td>
<td>6.90</td>
</tr>
<tr>
<td>Dundee, Scotland</td>
<td>4.05</td>
<td>3.95</td>
</tr>
<tr>
<td></td>
<td>15.18</td>
<td>15.29</td>
</tr>
</tbody>
</table>
SCIENTIFIC OPINION

Scientific Opinion on the essential composition of infant and follow-on formulae

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)2,3
European Food Safety Authority (EFSA), Parma, Italy

“The Panel notes that even though studies have shown that feeding an IF containing DHA alone, (without addition of ARA) leads to lower concentrations of ARA in erythrocytes compared with the consumption of control formula without DHA, no direct functional consequences have been observed…..”

“Therefore, the Panel considers that there is no necessity to add ARA to IF even in the presence of DHA.”
We know, there are known knowns; there are things we know we know. We also know there are known unknowns; that is to say we know there are some things we do not know. But there are also unknown unknowns -- the ones we don't know we don't know.

Donald Rumsfeld, the 21st United States Secretary of Defense

There's another way to phrase that and that is that the absence of evidence is not evidence of absence. Simply because you do not have evidence that something exists does not mean that you have evidence that it doesn't exist.
Studies of the effects of DHA and ARA in high-risk populations are few
### Limited ARA intake data and complementary foods

<table>
<thead>
<tr>
<th>Age</th>
<th>Method</th>
<th>Mean ARA intake (mg/d)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germany</td>
<td>6m 3 day weighed food record</td>
<td>72</td>
<td>Schwartz et al, 2010</td>
</tr>
<tr>
<td>Germany</td>
<td>9m 3 day weighed food record</td>
<td>24</td>
<td>Schwartz et al, 2010</td>
</tr>
<tr>
<td>Belgium</td>
<td>2.5-3y 3 day food diary</td>
<td>17</td>
<td>Sioen et al, 2007;</td>
</tr>
<tr>
<td>Belgium</td>
<td>4-6.5y 3 day food diary</td>
<td>18</td>
<td>Sioen et al, 2007;</td>
</tr>
<tr>
<td>Gambia</td>
<td>0-6m 1 day weighed food monthly</td>
<td>90</td>
<td>Prentice &amp; Paul, 2000</td>
</tr>
<tr>
<td></td>
<td>7-12m 1 day weighed food monthly</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td></td>
<td>13-17m 1 day weighed food monthly</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td></td>
<td>24m 1 day weighed food monthly</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

Limited ARA intake data and complementary foods.
Estimation of ARA and DHA dietary intakes in 6-36 month children living in 76 developing countries

<table>
<thead>
<tr>
<th>Gross National Income (GNI)</th>
<th>Mean daily intake of ARA from BM/Food mg (SD)</th>
<th>Mean daily intake of DHA from BM/Food mg(SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper middle</td>
<td>69.7 (21)</td>
<td>67.5 (81)</td>
</tr>
<tr>
<td>Lower middle</td>
<td>65.6 (10)</td>
<td>59.7 (29)</td>
</tr>
<tr>
<td>Low</td>
<td>64.1 (10)</td>
<td>53.9 (22)</td>
</tr>
<tr>
<td>Total</td>
<td>66.0 (13)</td>
<td>59.5 (44)</td>
</tr>
</tbody>
</table>

Forsyth et al, unpublished data
Relationship of breast feeding to daily ARA intake 6-36 months in developing countries

Correlation is significant at the 0.01 level (2-tailed).
Dietary intake of ARA from solid foods, no breast milk
Dietary ARA intakes in Developing Countries

• Key findings
  – 76 developing countries
  – Estimated daily intake of DHA and ARA in infants and young children between the ages of 6-36 months
  – Intake of ARA and DHA significantly lower than current global recommendations
  – The outcomes reflect diversity of dietary intake and related economic, demographic and geographic factors
  – Global recommendations on ARA and DHA in early life need to embrace the specific needs of infants and families living in low income countries
RCTs

- In relation to maternal and infant LCPUFA policy making, study design appears to take precedence over the value and quality of the data.

- RCT design (and therefore systematic reviews) tend to favour interventions where:
  - There is a medical rather than a societal focus.
  - The target for the intervention focuses on individuals rather than communities or populations.
  - The outcomes focus on early rather than late determinants of health.
Follow-up rates in selected RCTs and cohort studies, according to age at follow-up and type of investigations performed

WHO recommends mothers worldwide to exclusively breastfeed infants for the child's first six months to achieve optimal growth, development and health. Thereafter, they should be given nutritious complementary foods and continue breastfeeding up to the age of two years or beyond.
Breast Milk DHA and ARA remain relatively constant after the first 2 weeks of life

<table>
<thead>
<tr>
<th>DHA and ARA % FA Content</th>
<th>1 mo*</th>
<th>2 mo*</th>
<th>3 mo*</th>
<th>6 mo*</th>
<th>9 mo**</th>
<th>12mo**</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARA</td>
<td>0.51  (0.16 SD)</td>
<td>0.52  (0.13 SD)</td>
<td>0.52  (0.10 SD)</td>
<td>0.52  (0.15 SD)</td>
<td>0.51  (0.10 SD)</td>
<td>0.50  (0.10 SD)</td>
</tr>
<tr>
<td>DHA</td>
<td>0.25  (0.11 SD)</td>
<td>0.24  (0.11 SD)</td>
<td>0.26  (0.09 SD)</td>
<td>0.30  (0.15 SD)</td>
<td>0.25  (0.11 SD)</td>
<td>0.34  (0.18 SD)</td>
</tr>
</tbody>
</table>

Abbreviations  SD mean with standard deviation, %FA percentage fatty acid of milk total lipids; mo -age in months

Hind milk lipids used. Per Gibson & Kneebone 1980 and Koletzko 1986 the %FA does not change during a feed nor undergo diurnal variation.

Maternal milk DHA relates to cognitive performance at age 15 years

• Maternal milk DHA strongly related to student performance on standardized math test

Controlling for:

- National wealth
- Education spending
- Macronutrients

• Effect significant and substantial in cross national comparisons

Lassek & Gaulin 2013
Maternal and Child Nutrition
GDP and IQ

IQ and 1992 GDP per capita (Summers-Heston PPP$)

Source: Sala-i-Martin (1992) and Lynn and Vanhanen (2002)
Maternal DHA and Preterm Infants

1. Lower incidence of pre-term birth, low birth weight, fewer admissions to NICU, fewer children with delayed cognitive development with maternal supplementation of 800 mg DHA (+100 mg EPA) from 19 weeks to birth. Makrides et al JAMA 2009; 302:175-82

2. Fewer births less than 34 weeks, fewer births less than 1500g, fewer days in NICU with maternal supplementation with 600mg per day from <20 weeks gestation
Research and Policies

• General principles

  – It is important to maximise the research potential that is committed to LCPUFA research and in particular to effectively translate the rigorous laboratory data into the clinical setting.

  – **Clinical studies should be steadily building on our knowledge and understanding of the role of LCPUFAs in maternal and child health**

  – It is important that RCT’s and observational studies are both scientific and pragmatic, and carried out in real-world settings, in order to test effectiveness and not just efficacy.

  – **Need for a public health “safety net” for the most vulnerable mothers and infants**
Robust Research and Pragmatic Policies

If research is not robust, policies need to be pragmatic.

When managing a potential risk of LCPUFA deficiency or imbalance, the founding principle should be – what is in the best interest of the infant?

For regulatory support there is the Precautionary Principle, Regulation EC 178/2002 (Article 7)
Precautionary Principle

- Regulation EC 178/2002 (Article 7) formally establishes the Precautionary Principle as an option when decisions have to be made to protect health but scientific information concerning the risk is inconclusive or incomplete in some way.
- The principle implies that there is a social responsibility to protect the public from exposure to harm.
- These protections can be relaxed only if further scientific findings emerge that provide sound evidence that no harm will result.
**So, what do we know about LCPUFAs in early life?**

<p>| Improved understanding of role that DHA and ARA play at cellular level in brain development |
| Assessments measuring information processing, attention control and visual function are most likely to determine effects on cognition |
| Evidence that DHA supplementation has effects on visual function in early life |
| Premature infants may specifically benefit from LCPUFA supplementation |
| Formulas and weaning foods are not meeting infant and young child requirements |
| Global recommendations on LCPUFA intakes do not reflect the global diversity of the populations that they serve |</p>
<table>
<thead>
<tr>
<th>What do we need to know about LCPUFAs in early life?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clarity on the optimum DHA and ARA requirements for normal development in term and preterm infants</td>
</tr>
<tr>
<td>Clarity on the independent effects of ARA in early life and beyond</td>
</tr>
<tr>
<td>Information on the public health consequences of deficient LCPUFA weaning foods in both developed and developing countries</td>
</tr>
<tr>
<td>Consensus on the optimum supplementation dose and duration of LCPUFA supplementation in the at-risk mother, infant and child</td>
</tr>
<tr>
<td>Clarity on the relationship of LCPUFA status to learning, behavioural and mental health disorders in childhood</td>
</tr>
<tr>
<td>Clearer understanding of the relationship of LCPUFA status in early life to adult health and wellbeing</td>
</tr>
</tbody>
</table>
What do we need to know about LCPUFAs in early life?

And ultimately,

*We need to know the unknown unknowns of LCPUFAs in early life, a` la Rumsfeld.*