Long term effects of prenatal nutrition on brain development

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NUTRIMENTHE OPEN FORUM
“Feeding the Future Generation”
“Stimulus or insult operating at a critical or sensitive period of development could result in a long-standing or life-long effect on the structure or function of the organism”
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Time Course of Neurodevelopment

- competitive elimination
- synaptogenesis
- differentiation and myelination
- migration from ventricular zone
- neuronal selection
- neurogenesis

AA > DHA

DHA > AA
Critical Stages of Mental Development

- Binocular vision
- Emotional Control
- Habituation
- Social Ability
- Language
- Knows symbols
- Knows quantity

Age in years

Critical Stage
Critical Stage receding

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STEPS OF BRAIN MATURATION

1st brain regions:
Visual motor
Balance
Motor performance

2nd brain regions:
Learning
Memory
Language mature

3rd Region (the frontal lobes)
Executive functions (slow maturation process from 6 months to 15-16 year old with a critical period between 1 to 3 years and between 7 to 10 years old)
THE BRAIN AND ITS DEVELOPMENT

KEY NUTRIENTS

n-3 PUFAs  
Folate  
Vitamin B12  
Iron  
Vitamins C & A  
Zinc  
Selenium  
Iodine  
Choline  
Protein intake

Independently
In combination

COGNITIVE PERFORMANCE
BEHAVIOUR OF CHILDREN (ADHD, Dyslexia, Dyspraxia and Autism)

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DHA and brain

- Lipids bound DHA in the membrane bilayer
  - Membrane physicochemical properties
  - Interaction with membrane proteins
  - Membrane biogenesis

- Unesterified DHA
  - Gene expression
  - Ion channel activity
  - Neuroprotective metabolites

35% PUFA

3,000 nmol/g

25 w

Delivery

10,000 nmol/g

2 y

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DHA Deficiency

Deficits in behavioural tasks of learning
Increased stereotyped behaviour

Changes in the embryonic and fetal brain, brain synaptic membranes and retina: “structure function role”

FUNCTIONAL CONSEQUENCES

Altered metabolism of some neurotransmitters:
- DOPAMINE
- SEROTONIN
- MEMBRANE-ASSOCIATED ENZYMES
- RECEPTOR ACTIVITIES
Decrease of the mean cell body size of neurons (hippocampus, hypothalamus and parietal cortex)

Decrease the complexity of cortical dendritic arborization

Stage of development
Duration
Severity

Neurogenesis
Dendritic arborization
Synaptogenesis
Selective Pruning
Myelination
(Georgieff, 2005)
Increased risk of poor visual and neural development
(Bouwstra, 2003; Dunstan, 2006; Uauy, 2006; Hibbeln, 2007; Innis 2008)

Increased risk of dementia and cognitive decline in older individuals
(Dullemeijer, 2007; Nurk, 2007; Van Gelder, 2007; Schaefer, 2006; Kalmijn, 2004)

Low dietary fatty acids + Genetic variation in fatty acid metabolism

Poor central nervous system functioning in infants & children
Long-lasting sequelae
DHA accretion by the developmental brain

Fatty acids transplacental transport

Mother-fetal plasma fatty acids gradient

Fatty acids net flux through the placenta (Elphick 1997)

Fatty Acids Chain Lenght

Placental transfer (Godfrey KM 2002)

Placental Fatty acids transport protein (p-FATP)

Placental membrane


Order of preference
DHA>AA>ALA>LA


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N-3 LCPUFAs Interventional studies

**Differences**

- **Helland 2003**
  - K-ABC at 4 y

- **Judge 2007**
  - Problem solving at 9m

- **Dunstan 2008**
  - Eye hand coordination at 2½ y

**No differences**

- **Helland 2001/2008**
  - EEG at 2 d and 3 m
  - FTII at 6 m and 9 m
  - K-ABC at 7 y

- **Malcolm 2003**
  - Electroretinogram at 15 w

- **Tofail 2006**
  - BSID at 10 m

- **Judge 2007**
  - FTII at 9 m

- **Dunstan 2008**
  - PPTV at 2½ y
  - CBCL at 2½ y

**Dziechciarz, 2010.** Systematic review

RCTs – n-3 LCPUFA supplementation (pregnant and/or lactating women) - No differences in Neurodevelopment, nor in Visual function
LCPUFA supplementation of formula during the first 2 postnatal months in healthy term infants does not promote neurological condition at school age.

Breast-fed infants have a slightly better neurodevelopmental outcome than formula-fed infants – reflected by a reduced prevalence of fine manipulative dysfunction.
Linoleic acid (18:2\textsubscript{ω-6})

- \(\Delta-6\)-Desaturase
- \(FADS2\)

\(\gamma\)-linolenic acid (18:3\textsubscript{ω-6})

- \(\Delta-5\)-Desaturase
- \(FASD1\)

DGLA (20:3 \textsubscript{ω-6})

- Elongase
- \(ELOVL5\)

AA (20:4 \textsubscript{ω-6})

- Elongase
- \(ELOVL5, ELOVL2\)

Eicosanoids

Eicosanoids

Membranes

\(\Delta-6\)-Desaturase

- \(FADS2\)

\(\Delta-7\)

\(\Delta-9\)

Fish, eggs, poultry

- Elongase
- \(ELOVL5, ELOVL2\)

\(\Delta-9\)

\(\Delta-7\)

\(\Delta-6\)

\(\beta\)-oxidation

DHA (22:6\textsubscript{ω-3})

- \(FADS2\)
- \(CS\)

\(\Delta-6\)

\(\beta\)-oxidation

\(\Delta-6\)

\(\Delta-9\)

\(\Delta-7\)


Innis S, Brain Research 2008
DIFFERENT RESULTS →
→Different potentiality of endogenous synthesis on a genetic basis!

Common genetic variants of the FADS1 FADS2 gene cluster and their reconstructed haplotypes are associated with the fatty acid composition in phospholipids

Linda Schaeffer¹, Henning Gohlke¹, Martina Müller¹,², Iris M. Heid¹,², Lyle J. Palmer³, Iris Kompauer¹, Hans Demmelmaier⁴, Thomas Illig¹, Berthold Koletzko⁴ and Joachim Heinrich¹,*
NUHEAL STUDY

LC-PUFAS and/or 5-MTHF SUPPLEMENTATION DURING PREGNANCY and NEURODEVELOPMENT IN THE OFFSPRING

Campoy C¹, Escolano V¹, Ramos R², Haile G³, Csábi Gy⁴, Pérez-García M⁵, Décsi T⁴ and Koletzko B³

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²CIBER de Epidemiología y Salud Pública (CIBERESP), Spain.
³Dept. of Paediatrics. Ludwig-Maximilians University of Münich. Germany.
⁴Department of Paediatrics. University of Pécs. Hungary.
⁵Department of Neuropsychology. University of Granada. Spain

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Randomized and double blinded

311 healthy pregnant women recruited
270 healthy pregnant women

Recruitment

DHA (n:69)
(500 mg/day)

5-MTHF (n:65)
(400 µµ µµ/day)

Placebo (n:72)

DHA+5-MTHF (n:64)

Bayley’s Test

Hempel Test
Touwen Test
Kaufmann Test

Recruitment

25 35

Delivery

20 30

Wks gestation

2 mon 6 mon 20 mon 4 yrs 5.5 yrs 6.5 yrs

cVEP

cVEP
Significant increase of DHA plasma phospholipids during the last weeks of pregnancy in the mothers & their offspring

Campoy C, et al. JPGN, 2004
General linear model of repeated measures

Significant increase of DHA plasma phospholipids during the last weeks of pregnancy in the mothers & their offspring

Campoy C, et al. JPN, 2004
Correlation between DHA in plasma Phospholipids and the % of DHA in Phosphatidil Etanolamina during pregnancy

Evolution of folic acid concentrations through gestation and in the neonate, depending on the mother’s supplement received.
• 4 years
  HEMPEL Test
• 5.5 years
  TOUWEN Test
• 6.5 years
  KAUFMAN Test

Now is the time to give your child the gift of reading.
Hempel Neurologic Examination

5 clusters:
1. Fine motor function
2. Gross motor function
3. Posture and muscle tone
4. Reflexes
5. Visuomotor

Clinical conclusion: Neurologically normal (no clusters of dysfunction)
Simple MND (1 cluster of dysfunction)
Complex MND (≥ 2 clusters of dysfunction)
Definitely neurological abnormality
Touwen neurological examination

- Evaluation of spontaneous motor behavior into the neurological assessment
- Neurological examination of children with MND
- Evaluation of school age children from 4 years onwards

Touwen, 1979
Hadders-Algra, 2002
NUHEAL FOLLOW-UP

Optimal:
- 4 y → NOS=56
- 5½ y → NOS=64

Suboptimal:
- 4 y → NOS<56
- 5½ y → NOS<64

T-Student

- 5½ y

P=0.015

P<0.001

P=0.002
# NUHEAL FOLLOW-UP

<table>
<thead>
<tr>
<th></th>
<th>Exp (B) (95% CI)</th>
<th>P</th>
<th>% correct classification</th>
<th>Naegelkerker R Square</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cord DHA in plasma PLs</strong>&lt;br&gt;Maternal age</td>
<td>1.094-2.262</td>
<td><strong>0.014</strong></td>
<td>89.8%</td>
<td>14.5%</td>
</tr>
<tr>
<td><strong>Cord DHA in RBC PE</strong></td>
<td>1.091-2.417</td>
<td><strong>0.017</strong></td>
<td>94.2%</td>
<td>19%</td>
</tr>
<tr>
<td><strong>Cord DHA in RBC PC</strong></td>
<td>1.003-2.643</td>
<td><strong>0.049</strong></td>
<td>91.7%</td>
<td>10.8%</td>
</tr>
<tr>
<td><strong>Maternal DHA in RBC PE at delivery</strong>&lt;br&gt;Maternal age</td>
<td>1.235-2.603</td>
<td><strong>0.002</strong></td>
<td>92.4%</td>
<td>38.1%</td>
</tr>
<tr>
<td><strong>Maternal DHA in RBC PC at delivery</strong>&lt;br&gt;Maternal age</td>
<td>1.445-4.664</td>
<td><strong>0.001</strong></td>
<td>92.8%</td>
<td>37.1%</td>
</tr>
</tbody>
</table>

Adjusted for: residence area, maternal age, pregnancy risk factors, delivery risk factors, perinatal morbidity, length of gestation, maternal status at work, parental education, study center


**Logistic regression**

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NUHEAL FOLLOW-UP

6.5 years
# NUHEAL FOLLOW-UP

<table>
<thead>
<tr>
<th></th>
<th>Exp (B) (95% CI)*</th>
<th>P</th>
<th>% correct classification</th>
<th>Naegelkerker R Square</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythrocyte PE DHA at delivery</td>
<td>1.094-2.449</td>
<td><strong>0.017</strong></td>
<td>90</td>
<td>0.429</td>
</tr>
<tr>
<td>Erythrocyte PE AA/DHA at delivery</td>
<td>0.130-0.821</td>
<td><strong>0.017</strong></td>
<td>92.2</td>
<td>0.390</td>
</tr>
</tbody>
</table>

Confounders: parental cultural level, maternal status at work, length of gestation, perinatal morbidity, sex

![22:6n-3](image)

\[\text{MPC > 50th Percentile}\]

Supplementation effectively increases DHA levels in maternal and umbilical plasma and erythrocyte PL.

Plasma and erythrocyte fatty acids appear adequate to assess the fatty acid status. Type of study is a major consideration.

Higher maternal and foetal DHA status during related to better performance on neuropsychomotor tests at 5 ½ and cognitive examination at 6 ½ years of age.

LC-PUFA status prior to the 20th week of gestation might be relevant for children neurological development.
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ALL OBSTETRICIAN TEAMS IN THE THREE COUNTRIES

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