Metabolische Programmierung durch die perinatale Zufuhr essentieller mehrfach ungesättigter Fettsäuren (G. Hornstra)

Inzwischen wird weithin akzeptiert, dass eine unzulängliche Ernährung in entscheidenden Phasen des perinatalen Lebens sozusagen Ereignisse «vorprogrammieren» kann, die den späteren Gesundheitszustand, Funktionen oder Leistung beeinflussen. Die essentiellen mehrfach ungesättigten Fettsäuren (ePUFA) erfüllen lebenswichtige Funktionen im menschlichen Körper. Diese Fettsäuren können nicht oder kaum vom Menschen synthetisiert werden, daher ist ihre ausreichende Zufuhr von hoher funktioneller Bedeutung. Bei der Zusammenstellung der Maastricht Essential Fatty Acid Birth Cohort (MEFAB-Kohorte) zeigte sich, dass der ePUFA-Status der Neugeborenen (der vom mütterlichen ePUFA-Konsum, Stoffwechsel und Placentatransfer abhängt) ziemlich unterschiedlich und für einen Teil der Neugeborenenpopulation möglicherweise nicht optimal ist.
Spätere Beobachtungsstudien bestätigten im Allgemeinen den positiven Zusammenhang zwischen der frühzeitigen Versorgung mit Omega-3-PUFA und der späteren geistigen Entwicklung.
Adipositas und Insulinresistenz sind grosse und noch immer zunehmende Gesundheitsprobleme, die nachweislich früh im Leben vorprogrammiert werden. Untersuchungen an der MEFAB-Kohorte haben gezeigt, dass die Konzentrationen von gamma-Linolensäure (GLA) und/oder Dihomo-gamma-Linolensäure (DGLA), Vorstufen der wichtigen funktionellen Omega-6-PUFA Arachidonsäure, im Nabelschnurplasma im Alter von 7 Jahren umgekehrt mit diesen Komponenten des metabolischen Syndroms sowie den Triacylglycerol-(TAG)-Plasmakonzentrationen bei Follow-up assoziiert sind. Diese Beobachtungen könnten bedeuten, dass eine höhere mütterliche (D)GLA-Zufuhr während der Schwangerschaft möglicherweise zur Prävention des metabolischen Syndroms und seiner Komplikationen wie ischämische Herzkrankheit und Diabetes mellitus Typ 2 beitragen könnte.
Interessanterweise waren Insulinresistenz und TAG-Plasmakonzentration im Alter von 7 Jahren positiv mit den (D)GLA-Konzentrationen bei Follow-up assoziiert. In der Tat wurden die niedrigste Insulinresistenz und die niedrigsten TAG-Plasmakonzentrationen bei den Kindern mit einer hohen perinatalen (D)GLA-Zufuhr und einem niedrigen (D)GLA-Status bei Follow-up beobachtet. Diese Beobachtung weist darauf hin, wie wichtig es ist, die frühe Geschichte der Studienteilnehmer in Design und Interpretation zukünftiger Studien einzubeziehen.

La représentation de l‘alimentation dans les médias et son influence potentielle sur les consommateurs (G. Hornstra)

Il est désormais communément admis qu’une nutrition inappropriée à des stades essentiels de la vie périnatale peut déclencher des événements de «programmation» influençant à long terme la santé, les fonctions ou les performances des individus.
Les acides gras polyinsaturés essentiels (AGPIe) remplissent plusieurs fonctions de première importance dans l’organisme humain. Ces acides gras ne peuvent être synthétisés par l’homme, ou difficilement ; un apport approprié est donc indispensable au bon fonctionnement de l’organisme. Lors de la constitution de la cohorte Maastricht Essential Fatty Acid Birth (cohorte MEFAB), il est apparu que le statut en AGPIe néonatal (qui dépend des apports en AGPIe de la mère, du métabolisme et du transfert placentaire) est relativement variable, et peut ne pas être optimal pour une partie de la population néonatale. Par conséquent, l’impact potentiel des différences d’exposition périnatale aux AGPIe sur le développement du fœtus et du nourrisson constitue un axe de recherche important.
L’obésité et l’insulino-résistance sont des problèmes de santé publique majeurs, de plus en plus fréquents, dont la programmation intervient aux premiers stades de la vie. Les études menées auprès de la cohorte MEFAB ont démontré que les concentrations plasmatiques ombilicales d’acide gamma-linolénique (GLA) et/ou d’acide dihomo-gamma-linolénique (DGLA), précurseurs d’un AGPIe oméga-6 jouant un rôle fonctionnel majeur, l’acide arachidonique, sont inversement corrélées à ces composants du syndrome métabolique à l’âge de 7 ans, ainsi qu’aux concentrations plasmatiques de triglycéride (TG) lors du suivi (6). Ces observations nous permettent de supposer qu’un apport en (D)GLA accru pendant la grossesse pourrait contribuer à prévenir le syndrome métabolique et ses complications, telles que les cardiopathies ischémiques et le diabète de type 2.
Il est intéressant de noter que l’insulino-résistance et la concentration plasmatique de TG à l’âge de 7 ans ont été positivement associées aux concentrations de (D)GLA lors du suivi. De fait, l’insulino-résistance la moins marquée et les concentrations plasmatiques de TAG les plus faibles ont été observées chez les enfants qui associaient une exposition périnatale au (D)GLA importante et un faible statut de (D)GLA lors du suivi. Il sera donc important de tenir compte des antécédents infantiles des sujets de l’étude pour élaborer le plan des futures études et interpréter leurs résultats.

Prof. Gerard Hornstra, Universität Maastricht und NUTRI-SEARCH, Gronsveld, Niederlande

Gerard Hornstra (*1938) studierte Medizin an der Erasmus-Universität in Rotterdam und an der Staatsuniversität Leiden, wo er seinen Abschluss mit ‚cum laude' machte. Seine berufliche Ausbildung auf dem Gebiet der Experimentellen Ernährung absolvierte er in den Unilever Research Laboratories in Vlaardingen. Im Jahr 1981 promovierte er an der Universität Maastricht mit einer Dissertation mit dem Titel ‚Diätetische Fette und Arterienthrombose' zum Dr. med.
1980 ging Prof. Hornstra an die Universität Maastricht und richtete dort eine Forschungsreihe zur Untersuchung der Relevanz der essentiellen Fettsäuren für die Gesundheit mit dem besonderen Schwerpunkt kardiovaskuläre Erkrankung und frühe menschliche Entwicklung ein. 1995 wurde er an der gleichen Universität zum Professor für Experimentelle Ernährung berufen. Aber auch nach seiner Pensionierung Anfang 2003 betreut und berät Prof. Hornstra weiterhin PhD-Studenten und befasst sich mit der Untersuchung der potenziellen Bedeutung essenzieller mehrfach ungesättigter Fettsäuren für die Programmierung der menschlichen Entwicklung. Ausserdem ist er als privater Berater auf dem Gebiet ‚Nahrungsfette in Gesundheit und Krankheit' tätig. Prof. Hornstra ist Vorsitzender des niederländischen Arbeitskreises 'Choose Healthy Fats / Wähle gesunde Fette' und Mitglied des Lenkungsausschusses des International Expert Movement on Health Significance of Fat Quality of the Diet.

Prof. Gerard Hornstra, Université de Maastricht et NUTRI-SEARCH, Gronsveld, Pays-Bas

Gerard Hornstra (*1938) a poursuivi ses études de médecine à l'université Erasmus de Rotterdam, ainsi qu'à l'université d'État de Leiden, où il obtient son diplôme avec distinction. C'est ensuite dans le domaine de la nutrition expérimentale qu'il acquiert son expérience professionnelle, dans les laboratoires de recherche Unilever à Vlaardingen. En 1981, Gerard Hornstra obtient son doctorat de médecine à l'université de Maastricht, après avoir soutenu avec succès une thèse intitulée Dietary fats and arterial thrombosis.
En 1980, le Prof. Hornstra rejoint l'université de Maastricht, où il initie des travaux de recherche sur les effets sur la santé des acides gras essentiels, spécifiquement axés sur les maladies cardiovasculaires et les premières années de la vie. En 1995, il est nommé professeur de nutrition expérimentale dans cette même université. Depuis son départ à la retraite, début 2003, le Prof. Hornstra continue de superviser et conseiller les doctorants, et d'étudier l'importance potentielle des acides gras polyinsaturés essentiels dans la programmation du développement de l'être humain. Il exerce par ailleurs en tant que consultant dans le domaine des lipides alimentaires et leur effet sur la santé et la morbidité. Le Prof. Hornstra préside le groupe de travail néerlandais Kies Gezond Vet (Choisir les bonnes matières grasses), et siège au comité directeur de l'International Expert Movement on Health Significance of Fat Quality of the Diet.

Nutritional programming by perinatal essential polyunsaturated fatty acids

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Programming by perinatal essential polyunsaturated fatty acids

- Introduction
- Birth weight
- Brain development
- Metabolic syndrome
- Summary and implications

Nutritional programming

- 'Programming' occurs when an early stimulus, operating at a critical or sensitive period, results in a permanent or long-term change in the structure or function of the organism (Lucas, 1991)
- Inadequate nutrition during fetal- or early life may act as a programming event and, thereby, may permanently affect later health, function, or achievement in man (Dobbing, 1981)

Essential polyunsaturated fatty acids (ePUFA)

- Essential fatty acids (EFA) and their longer-chain, more-unsaturated derivatives (LCPUFA) are collectively called essential polyunsaturated fatty acids (ePUFA)
- There are two ePUFA families, the omega-6 and omega-3 families
- These fatty acids serve vital functions in the human body, but cannot (EFA) or hardly (LCPUFA) be produced in the human body
- Therefore, their adequate dietary intake is essential for optimal health

Arachidonic acid (ARA) and docosahexaenoic acid (DHA) are the most important functional LCPUFA

ARA (omega-6)

- growth
- metabolic control
- gene expression
- inflammation
- thrombosis

DHA (omega-3)

- brain function
- neuro-motor control
- visual performance
- gene expression
- ARA modulation

Programming by breastfeeding

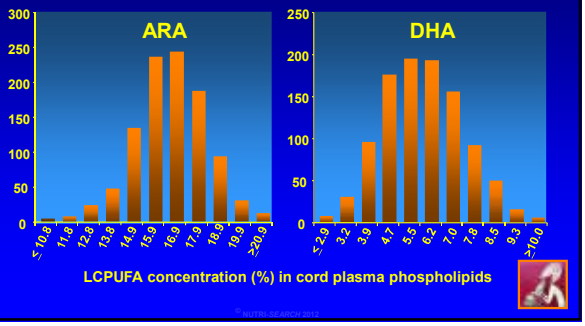
- Compared to formula feeding, breastfeeding has been shown to be associated with health benefits in later life (e.g. less obesity, improved mental development, lower cardiovascular risk, etc.)
- Multiple factors, genetic, psychological as well as compositional, are considered of importance in this association
- One of the compositional factors may be the difference in ePUFA concentrations: formula is rich in EFA, breast milk contains larger amounts of a variety of omega-6 and omega-3 LCPUFA

The Maastricht Essential Fatty Acid Birth (MEFAB) cohort

To investigate whether the early availability of LCPUFA (as indicated by their concentrations in maternal and cord PL) may be involved in programming pregnancy outcome and/or child development

The neonatal LCPUFA status is quite variable

(MEFAB database, n=1016)



LCPUFA concentration (%) in cord plasma phospholipids

Programming by perinatal essential polyunsaturated fatty acids

- Introduction
- **Birth weight**
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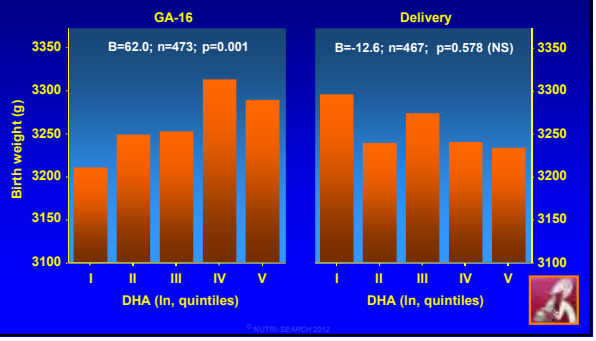
Programming of birth weight

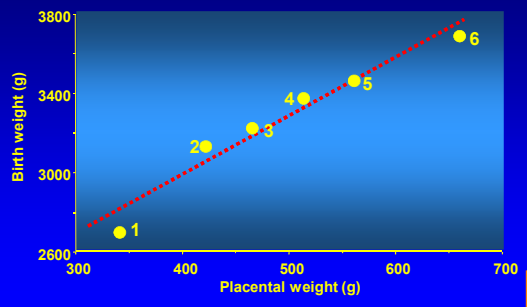
- Low birth weight is a reliable risk indicator for later health problems because it is associated with higher risks of chronic diseases, like cardiovascular disease and type 2 diabetes
- The underlying mechanism may include higher catch-up growth, resulting in unfavorable programming effects of metabolic stress
- Observational studies suggest that maternal fish intake during pregnancy promotes fetal growth, thereby reducing the stimulus for catch-up growth
- Further studies point to omega-3 LCPUFA as the active principle
- However, results of observational and intervention studies are not consistent

Birth weight is positively related to maternal plasma DHA concentrations *at early pregnancy only* (Dirix, 2008)

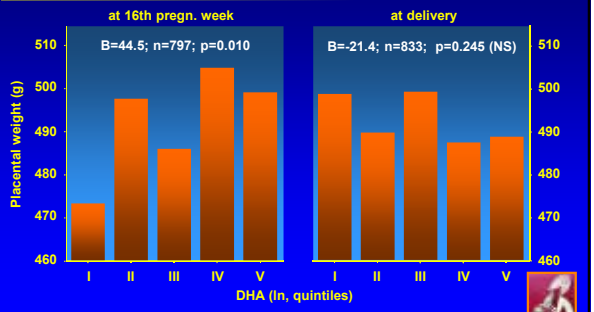


Birth weight is positively related to placental weight

(r=0.62; n=755; p<0.0001)



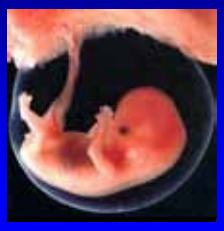
Placental weight is positively related to maternal plasma DHA concentrations *at early pregnancy only*



Programming of fetal growth by DHA

- Fetal growth, corrected for gestational age, is positively associated with the maternal DHA status *early in pregnancy only*
- This putative programming effect of DHA on fetal growth may be mediated by a stimulating influence of DHA on placental development
- Interestingly, in most intervention studies so far, maternal supplementation with DHA did not promote fetal growth corrected for gestational age
- However, supplementation usually started around mid-pregnancy, which may have been too late to initiate a placenta-mediated programming response

Programming by perinatal essential polyunsaturated fatty acids (ePUFA)



- Introduction
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- **Brain development**
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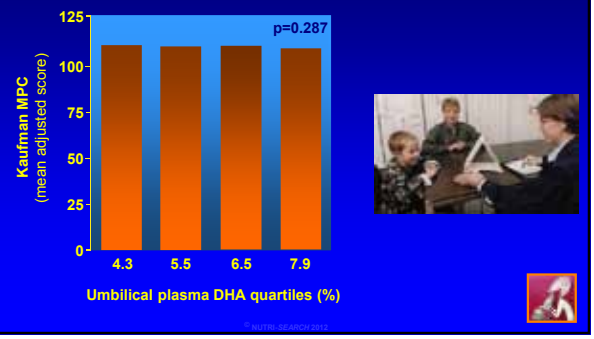
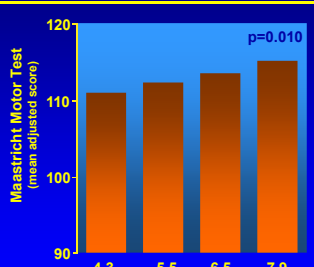
Programming of brain function by prenatal LCPUFA availability?

- Breast feeding has been shown to be associated with later mental and visual benefits compared to formula feeding
- In contrast to the formula of that time, breast milk contains LCPUFA
- Certain LCPUFA are important 'building bricks' of the brain
- Brain development mainly takes place during late gestation and early extra-uterine life
- The perinatal LCPUFA is quite variable (ARA: 10-20%, DHA: 3-10%)
- Does this difference in perinatal LCPUFA availability affect later brain function, mental and visual development, and child behavior?

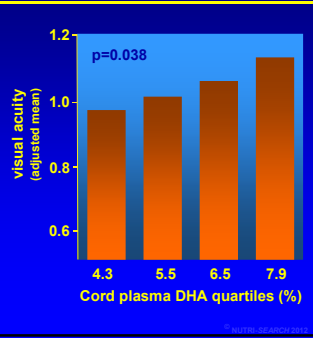
Cognitive performance at 7 years of age is not related to DHA status at birth (n=305; Bakker, 2003)



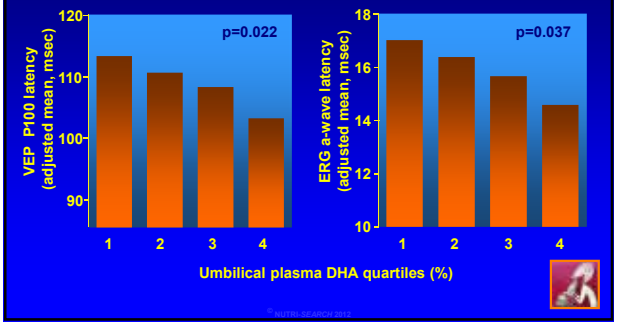
Brain development, as reflected by movement *quality* at 7 years of age, is positively related to DHA status at birth (n=290; Bakker, 2009)



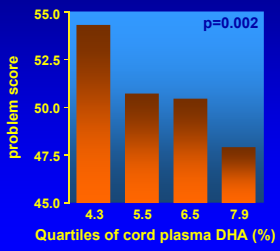
Brain maturation, as reflected by visual acuity at 8 years of age, is positively related to DHA status at birth (n=59)



Speed of visual information processing at 8 years of age is higher, the higher the DHA status at birth (n=33)



Internalizing behavior (CBCL) of formula-fed children at age 7 is less problematic, the higher their DHA status at birth (n = 215; Krabbendam 2007)



The Child Behavior Check List is a standardized parent-report instrument for the assessment of behavioral and emotional characteristics of children

Internalizing behavior

- somatic complaints
- anxious/depressed
- withdrawal

Programming of brain development by DHA-1

- In MEFAB, prenatal exposition to DHA is positively associated with various aspects of brain function later in life (e.g. visual functions, cognition, behavior, etc.)
- None of the outcome measures correlated significantly with the DHA status at 7 years of age
- This suggests that for certain aspects of brain development, programming by prenatal DHA availability is more important than the DHA availability in later life
- This may be the reason why supplementation of term infants with DHA hardly improves their mental and visual development

Programming of brain development by DHA-2

- A positive relationship between omega-3 LCPUFA consumption of mothers during pregnancy and later mental and visual development of their children has repeatedly been observed in large cohort studies
- However, maternal supplementation during pregnancy with DHA or fish oil did hardly benefit later selected brain functions of their infants
- Since supplementation usually started around mid-pregnancy, this may have been too late to initiate a successful programming response

Programming by perinatal essential polyunsaturated fatty acids

- Introduction
- Birth weight
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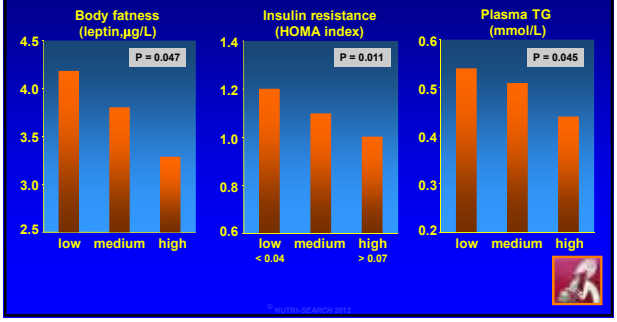
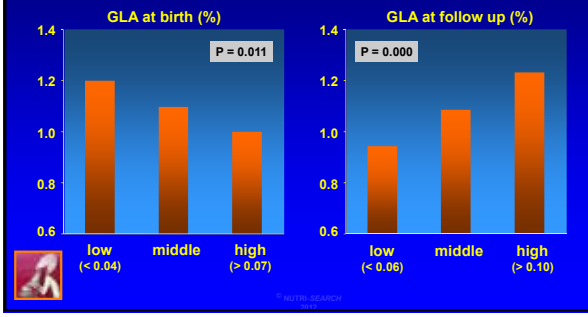
Programming of metabolic syndrome by LCPUFA?

- Compared to formula-feeding, breastfeeding reduces the risk of later obesity, hypertension, and diabetes type 2, all components of the metabolic syndrome
- Among the many factors possibly involved, the difference in fatty acid composition between human milk and formula may be of importance
- Formula are rich in linoleic- and alpha-linolenic acids, but only current formula contain ARA and DHA
- However, most formula are devoid of other omega-6 and omega-3 fatty LCPUFA, present in human milk

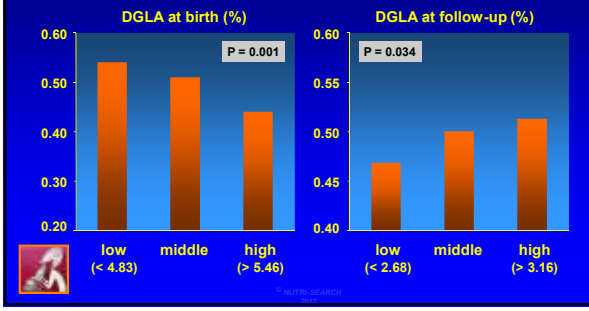
Plasma GLA content (%) at birth may predict later risk of metabolic syndrome (Rump, 2002)



Insulin resistance (HOMA) at follow-up (age 7) is *negatively* related to the GLA status at birth and *positively* to the GLA status at follow-up



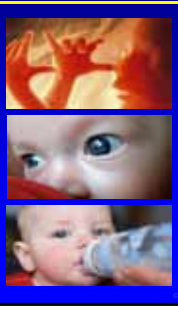
Plasma TG (mmol/L) at follow-up (age 7) is *negatively* related to the DGLA status at birth and *positively* to the DGLA status at follow-up



Programming of postnatal health aspects by prenatal GLA and DGLA status

- In MEFAB children, a higher prenatal availability of gamma-linolenic and/or dihomo-gamma-linolenic acid availability was associated with *reduced* levels of certain components of the metabolic syndrome (plasma TG, insulin resistance, body fatness) at 7 years of age
- This observation implies that prevention of the metabolic syndrome and its complications may be supported by a higher maternal intake of gamma-linolenic acid during pregnancy
- Postnatal (D)GLA supplementation, however, seems contra-indicated, but more research is needed

Programming by perinatal essential polyunsaturated fatty acids



- Introduction
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Programming by perinatal LCPUFA: Summary

- It is now widely accepted that nutrition during pre- and early post-natal life can program long-term health, and is involved in the risk of certain chronic diseases later in life
- Early exposition of the developing fetus to certain LCPUFA is positively associated with birth weight (DHA), and with certain aspects of brain development (DHA) and of the metabolic syndrome (DGLA) at childhood
- If causal, these associations imply that supplementation of pregnant women with these fatty acids could support the longer-term development and health of their offspring
- However, intervention studies with DHA during pregnancy mainly failed to confirm the promising results of observational studies

Programming by perinatal LCPUFA: methodological implications for further research

- Intervention studies, required to proof causality of associations, are of limited duration, whereas results of cohort studies relate to life-long dietary exposure
- In addition, most intervention studies may have started too late in pregnancy to initiate early programming effects
- Therefore, future intervention studies should start early in pregnancy or preferably before conception
- Whenever possible, design and interpretation of postnatal intervention studies should take into account potential programming-associated response differences
- Notwithstanding the problem of residual confounding, cohort studies remain of essential importance in nutrition research

Nutritional programming by perinatal essential polyunsaturated fatty acids