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Connecting nutrition to the science of brain connectivity

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Key messages

- Brain structural processes such as myelination support the establishment of neural functional networks and are critical for brain connectivity
- Recent *in vitro* data showed addition of a specific nutrient blend with docosahexaenoic acid (DHA), arachidonic acid (AA), vitamin B_{12}, folic acid, iron and sphingomyelin (SM) resulted in an increased number of cells that are responsible for myelination, as well as their myelinating properties
- The coordination of executive functions (EFs) is dependent on brain maturation and connectivity, therefore early dietary intake of key nutrients supporting myelination may be important

Brain structural processes such as myelination, the formation of the myelin sheath around axons, support the establishment of neural functional networks and brain connectivity[1,2]. This is important as several structurally connected brain regions may work in conjunction to carry out cognitive tasks[1]. There is evidence to show distinct functional connectivity patterns are present during visual, motor and language skills development, where increased skill complexity is coupled with the amount of functional network being recruited[1]. While there are marked changes in functional network organization across developmental stages, inter-individual differences are also present[1,3].

Now a question to ask is, can nutrition help to set up a better brain connectivity foundation in early life? SM may be one of the nutrients to look at as it is known to support the myelination process[4]. An exploratory observational study with 88 infants showed a higher dietary intake of SM (in the range of 28-71 mg/L from infant nutrition products) in the first three months of life was significantly associated with myelin content in specific brain regions and cognitive development, such as higher myelin content in bilateral cerebellum at 12 to 24 months ($r = 0.56$, $p = 0.001$), and better verbal development in the first two years ($r = 0.65$, $p < 0.001$)[4]. The authors suggested these effects may be mediated through oligodendrocytes (OLs) proliferation and differentiation as demonstrated in the *in vitro* models in the study[4].

OLs are specialized glial cells in the central nervous system responsible for carrying out the myelination process[2]. Recent *in vitro* data employing primary cell cultures that contained neurons and OLs showed the addition of a specific nutrient blend with DHA, AA, vitamin B_{12}, folic acid, iron and sphingomyelin resulted in an increased number of oligodendrocyte precursor cells (OPCs), while also promoting their differentiation and maturation into OLs, with improved myelinating properties[2]. As individual nutrients did not exhibit the same positive results, the nutrient blend may have driven synergistic effects, to be verified in an *in vivo* follow-up experiment[2].

EFs refer to a set of higher-order cognitive processes and have been shown to be predictive of academic achievement[5]. The coordination of EFs is dependent on brain maturation and connectivity[5]. Consequently, early dietary intake of key nutrients supporting myelination has been brought into focus in regard to EF development. A review by Costello *et al.* (2020) explored this area by diving into the emerging clinical evidence of key nutrients on myelination and synaptogenesis, including iron, omega-3 polyunsaturated fatty acids such as DHA, zinc, iodine, vitamin B_{12} and folate[5].

The authors also highlighted the potential of supplementation and/or fortification with multiple micronutrients in school-aged children[5]. Continued research in this area is crucial, allowing us to probe into the potential nutritional interventions to promote EFs in children.

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CONFERENCE VIDEOS...

Expert sharing

- **Dr. Fanny Wai Fan Lam:**
  The development of executive functioning skills in preschool children: Research and clinical landscape in Hong Kong
- **Prof. Sean Deoni:**
  Mapping nutrition to child cognitive development and Learning

SCAN OR CLICK TO READ

Revealing risk of preterm birth

Emily Tai PhD, Mphil, MSc, BSc (Hons)

Key messages

- Preterm birth is a global public health priority influencing neonatal morbidity and mortality
- 11% of all livebirths worldwide occur preterm (birth < 37 weeks) while the rate in Hong Kong was reported to be 6.5% and early preterm birth (< 34 weeks) was a major contributor of perinatal mortality[1,2]
- Emerging science may predict preterm birth

VAGINAL DELIVERY VS. CAESAREAN SECTION

In a meta-analysis including 10 cohort studies (*n* = 10,333,501)[3],

- A significantly higher risk of preterm birth in subsequent birth was noted in women with previous caesarean section delivery compared with those with vaginal delivery (RR 1.10, 95% CI 1.01-1.20)

Gugusheff *et al.* (2021) investigated the risk of subsequent preterm birth following either vaginal, instrumental, intrapartum or prelabour caesarean full-term first birth in Australian populations (*n* = 242,438)[4],

- Compared with women who birthed vaginally, higher risks of subsequent preterm birth (any birth < 37 weeks) were observed in women having:
  - Intrapartum caesarean first birth (RR 1.26, 95% CI 1.19-1.32), or
  - Prelabour caesarean first birth (RR 1.26, 95% CI 1.18-1.35)
- Reduced risk of subsequent spontaneous preterm birth was recorded in women having:
  - Previous instrumental birth (RR 0.85, 95% CI 0.79-0.91), or
  - Prelabour caesarean section birth (RR 0.74, 95% CI 0.67-0.82)

BABY BOY VS. BABY GIRL

Analysis of four datasets explored the relationship between fetal gender and preterm birth risks in 24 populations of singleton births showed that[5]:

- More males were born preterm and early preterm in most populations including those underwent IVF (OR 1.09-1.24)
- i.e. 0.5-1.0% higher preterm rate for males versus females

A national cohort in Netherland further implicated male fetal gender is a relative risk factor of preterm birth (*n* = 1,736,615)[6],

- Higher risk of spontaneous preterm birth with intact membranes was reported in males compared with females (RR 1.5, 95% CI 1.4-1.6)
- Males were also at a higher risk of preterm premature rupture of membranes between 27 and 37 weeks (RR 1.2, 95% CI 1.16-1.23)

FAMILY HISTORY

Among 23,816 deliveries with 2,345 born preterm (< 37 weeks)[7],

- There was a significant association between preterm birth and maternal family history of preterm birth (adjusted RR 1.44, $p < 0.001$)
  - All sub-components of family history (i.e. history in more distant relatives like aunts or grandmothers) were individually significant
- Nulliparous women with a sister who experienced preterm birth was associated with the greatest risk (adjusted RR 2.25, $p = 0.003$)

CAN NUTRITION HELP?

Protein status

- A Chinese prospective study (*n* = 3,478) revealed that the third-trimester maternal plasma total protein level was inversely related to risk of preterm birth[8]
  - Each standard deviation increment was associated with an increase of 0.13 week in gestation

Omega-3 fatty acids and DHA

- Low total omega-3 fatty acid status during early pregnancy was related to an elevated risk of early preterm birth[9]
- Omega-3 fatty acid supplementation could reduce the risk of early preterm among women who had a total omega-3 status ≤ 4.1% of total fatty acids versus control group (0.73% versus 3.16%, RR 0.23, 95% CI 0.07-0.79)[9]
- 600 mg DHA supplementation resulted in fewer infants born early preterm ($p = 0.025$) and shorter hospital stays for infant born preterm (40.8 versus 8.9 days, $p = 0.026$) when compared with controls[10]

Calcium intake

- In a cross-sectional study in Northwest China (*n* = 7,159)[11],
  - Daily dietary calcium intake was not associated with preterm birth
  - But, calcium supplementation during pregnancy was significantly linked with lower risk of preterm birth (OR 0.72, 95% CI 0.60, 0.87, $p = 0.001$)
  - Increased daily calcium intake from supplement was associated with lower risk of preterm birth (every 100 mg increase: OR 0.87, 95% CI 0.79, 0.96, $p = 0.004$)

(Continued on the next page)

EXPERT INTERVIEW...

Higher DHA Intake on Birth & Maternal Outcomes: Practical Pearls from Dr Susan Carlson

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EXPERT RECOMMENDATIONS

"Advise pregnant women that supplementation with omega-3 long-chain polyunsaturated fatty acids (800 mg DHA and 100 mg EPA per day) may reduce their risk of preterm birth, if they are low in omega-3 intake."
– Australian Government Department of Health, 2020[12]

"Long-chain polyunsaturated fatty acids during pregnancy reduces the risk of preterm birth before 34 weeks of gestation… Higher intake (600-800 mg DHA/day) may provide greater protection against early preterm birth."
– European Experts, 2014[13]

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Host genetics, HMO diversity and gastrointestinal health

Kelly Ching Full Member (HKDA), Registered Dietitian (USA), BSc

Quick facts on fatty acid desaturases[1,2]

- Secretor (*FUT2*) gene influences the diversity of human milk oligosaccharides in human milk, gut microbiota composition as well as gastrointestinal infections in young infants and children
- Understanding the connection between these elements of early life development is key to optimizing HMO supplementation in products designed for those who cannot be breastfed

The formation of human milk oligosaccharides (HMOs) in the mammary gland involves innumerable biosynthetic steps governed by glycosyltransferases[1]. The resulting heterogeneity in oligosaccharide profiles is highly dependent on maternal secretor gene status[2-6].

The *FUT2* gene, often referred as the "secretor" gene, encodes for the expression of fucosyltransferase 2 thus the presence or absence of 2'-Fucosyl-human milk oligosaccharides[2,3]. The milk of *FUT2*-positive mothers (i.e. "secretor milk") has been demonstrated to contain nearly twice the total HMO concentration of non-secretor milk (median, 9.67 vs 5.17 g/L, $p < 0.001$ for colostrum; 9.47 vs 5.61 g/L, $p < 0.001$ for transitional milk; and 8.67 vs 5.54 g/L, $p < 0.01$ for mature milk respectively)[4]. Together with the *FUT3* gene which dictates the Lewis blood type of an individual, the pair stratifies lactating mothers into distinct milk groups[4,5] each with a different set of HMOs dominating in the relative abundance in mature milk[4,5]. Notably, as opposed to fucosyllated and neutral HMOs listed below, acidic structures such as 3'-SL and 6'-SL were found to be independent of secretor and/or Lewis status[4] with 6'-SL being the most abundant representative across all milk groups[5].

Milk group 1 – Secretor with Lewis blood type Le(a-b+)

- 2'-FL, LNFP I and DFL (~50% of total HMO)[4]
- 2'-FL, LNFP I and LNDFH I[5]

Milk group 2 – Non-secretor with Lewis blood group Le(a+b-)

- LNT and LNFP II (~55% of total HMO)[4]
- 3-FL and LNFP II[5]

Milk group 3 – Secretor with Lewis blood type Le(a-b-)

- 2'-FL, LNT and LNFP I (~80% of total HMO)[4]
- 2'-FL, LNFP I[5]

2'-FL = 2'-Fucosyllactose; 3'-SL = 3'-Sialyllactose; 6'-SL = 6'-Sialyllactose; DFL = Difucosyllactose; LNDFH I = Lacto-N-difucohexaose I; LNFP I = Lacto-N-fucopentaose I; LNFP II = Lacto-N-fucopentaose II; LNT = Lacto-N-tetraose

Since histo-blood group antigen (HBGA) secretion and expression are also *FUT2*-dependent, secretor status also prognosticate the susceptibility to gastrointestinal infections caused by enteric pathogens[7,9]. A recent study in Taiwan reported 38 of 44 children (86.3%) with norovirus acute gastroenteritis being secretors while only six were non-secretors[8]. Similar observations were presented in a Brazilian study with only 1 out of 64 rotavirus infected children and 1 out of 35 norovirus infected children being non-secretors respectively[8]. Meanwhile, secretor milk and non-secretor milk also provide different degrees of immunological defense as evidenced by the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort[9]. By analyzing the morbidity reports and secretor status of 4971 infant subjects, the investigators found that higher magnitudes of protective effects against diarrhea were brought by breastfeeding in non-secretor infants (24%) versus their secretor counterparts (75%) at 0-6 months (67% vs. 59% reduction risk, $p = 0.18$) and at 6-18 months (32% vs. 14%, $p = 0.09$)[9].

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CONFERENCE VIDEO...

Understanding HMO diversity in human milk
By Miss Jodi Bettler (USA), MA, RD

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Nutrition News Column

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Clinical characteristics and transmission of COVID-19 in Hong Kong Children

This cross-sectional study looked into key clinical characteristics and the major sources of infections in 397 children and youths diagnosed with COVID-19 during the first three waves of outbreaks in Hong Kong. It was found that 38.8% of the subjects were asymptomatic and 99.2% had mild illness. The findings also suggested that households were the main route of transmission for this group, while the risk of being infected at school was small.

Read more from:

Chua GT et al. Clinical characteristics and transmission of COVID-19 in children and youths during 3 waves of outbreaks in Hong Kong. JAMA Netw Open. 2021;4 (5):e218824.

Free E-learning Module on 'Pediatric Nutrition in Practice'

THE PEDIATRIC NUTRITION IN PRACTICE E-LEARNING PROGRAM has been developed by field experts and aims to provide information to healthcare professionals who are looking for guidance on practically relevant issues to do with the nutrition of infants, children and adolescents. Some of the topics covered include childhood growth and nutritional assessment, breastfeeding, complementary feeding and nutritional challenges in special conditions and diseases. The Program is divided into 12 learning modules, which are combining different topics in pediatric nutrition. Each module takes between 60-90 minutes to complete and contains objectives, course material, a progress check to help prepare you for the exam, a list of key words and references.

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- MODULE 12: NUTRITION SUPPORT IN MALNUTRITION

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