


MÆLKEMATRICENS KOMPONENTER OG DERES INDFLYDELSE PÅ HJERNESUNDHED

Marie Stampe Ostenfeld
Senior R&D Manager, Nutrition & Health

Arla Foods Ingredients
Discovering the wonders of whey 



AGENDA

1. Introduction

1. Trends in Brain Health among consumers and markets
2. Nutritional components linked to Brain Health

2. Vitamin B12

1. Dairy as a unique delivery matrix
2. B12 deficiency and bioavailability

3. Brain development and dairy phospholipid components

1. Differences between breastfed and IF formula fed infants- cognition
2. Milk fat globular membrane (MFGM) for infant brain development

4. Brain 'decay' and potential effects of dairy phospholipid components

1. Global demographic shift and cognitive decline
2. Finding nutritional solutions to support elderly brain health

5. Conclusions & Perspectives

THE RIGHT FUEL FOR THE BRAIN



Your Brain!

- Takes care of thoughts, movements, breathing and heartbeat, your senses
- It works hard 24/7 (awake and asleep)
- Constant supply of fuel



Vitamins
Minerals
Antioxidants
Fatty acids



Premium fuel for premium performance!



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BRAIN HEALTH PRODUCTS

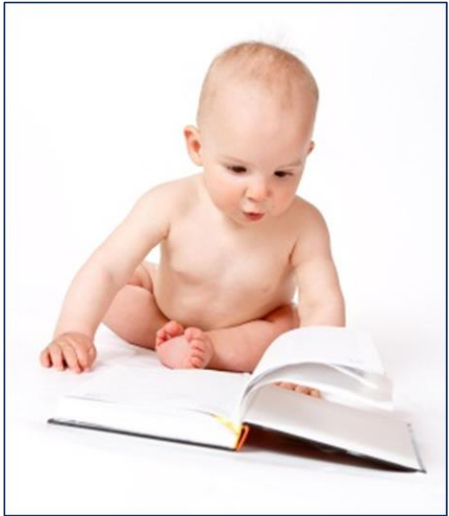
Global market trends

- Global market products with a **"brain health and memory"** claim was valued in 2017 at **US\$ 5.1 billions**.
 - 94 % driven by milk infant formula
- 6.2% compound annual growth rate (CAGR) from 2013 to 2017
 - **Second fastest growing positioning within health and wellness packaged food.**
- Brain health and memory products are often associated to other claims (heart, immune system, gut)
- From January 2008 to July 2018, **12,996 products** with the functional claim "brain health and nervous system" were launched around the world



Source: Euromonitor International

CONSUMERS CARE ABOUT BRAIN HEALTH



Infant nutrition

How to maximize brain development for the future benefit of our children



Trends

Boost brain performance

Manage stress and anxiety



Elderly nutrition

how to prevent cognitive decline

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WHAT IS COGNITION?



A mental action or process:

Acquiring knowledge and understanding through thoughts, experience, and the senses

Brain-boosting functional foods are set to go mainstream

By Nick Hughes

23-Aug-2017 - Last updated on 23-Aug-2017 at 16:28 GMT



MIND Diet: Best Foods to Eat to Keep Your Brain Young

...s on the MIND diet can help reduce your risk of Alzheimer's

Morris MC et al. Alzheimers Dementia . 2015

Dairy Consumption Linked to Better Brain Health

by Sandeep Ravindran in SPLASH! milk science update: May 2015

- Oxidative stress has been implicated in aging and several neurodegenerative diseases, including Alzheimer's disease and Parkinson's disease.
- A new study finds that higher dairy consumption is associated with higher brain concentration of glutathione, a potent antioxidant that can help protect the brain from oxidative stress.
- A follow-up intervention trial could confirm whether increasing dairy intake could enhance the brain's antioxidant defenses and protect against aging and various neurodegenerative diseases.

Lancet Psychiatry, 2015

Nutritional me

Sarris J¹, Logan AC²,
D¹¹, Ramsey D¹², Ruc

[+ Author informa](#)

Abstract

Psychiatry is at an i
burden of poor men
nutrition as a crucia
cardiology, endocrinology, and gastroenterology. Evidence is steadily growing for the relation between dietary quality (and potential nutritional deficiencies) and mental health, and for the select use of nutrient-based supplements to address deficiencies, or as monotherapies or augmentation therapies. We present a viewpoint from an international collaboration of academics (members of the International Society for Nutritional Psychiatry Research), in which we provide a context and overview of the current evidence in this emerging field of research, and discuss the future direction. We advocate recognition of diet and nutrition as central determinants of both physical and mental health.

It's well known that milk and calcium are good for your bones, but it turns out that they might also be good for your brain. A new study suggests that dairy consumption could potentially play a role in protecting the brain from oxidative stress, a process that has been implicated both in normal aging and in many neurodegenerative conditions such as Alzheimer's disease or Parkinson's disease [1,2].

oulon D⁹, Mizoue T¹⁰, Nanri A¹⁰, Nishi
ational Psychiatry Research.

modest benefits in addressing the
gging and compelling evidence for
s important to psychiatry as it is to
diary quality (and potential nutritional
deficiencies) and mental health, and for the select use of nutrient-based supplements to address deficiencies, or as monotherapies or augmentation therapies. We present a viewpoint from an international collaboration of academics (members of the International Society for Nutritional Psychiatry Research), in which we provide a context and overview of the current evidence in this emerging field of research, and discuss the future direction. We advocate recognition of diet and nutrition as central determinants of both physical and mental health.



one glass per day)

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NUTRIENTS IN 'BRAIN HEALTH'-PROMOTED PRODUCTS

Top nutrients (Product launches Jan 2016- June 2018)

Vitamin B	# products	Polyunsat. fatty acid	# products	Antioxidant	# products	Choline	# products
Folic Acid	1315	Docosahexaenoic acid (food)	380	Vitamin C	1307	Choline chloride	264
Riboflavin	1170	Arachidonic acid (food)	289	Vitamin E	663	Choline Bitartrate	248
Vitamin B6	1009	Docosahexaenoic acid (animal origin)	90	Ascorbyl Palmitate (Food)	350	Choline	104
Niacin	969	Docosahexaenoic acid (non-animal origin)	79	Sodium Ascorbate (Food)	331	Citicoline	12
Vitamin B1	967	Omega 3 fatty acids	43	Tocopherol concentrate mixed	200		
Vitamin B12	954	Omega 6 fatty acids	25	Tocopherol (Food)	182		

Source: Euromonitor International

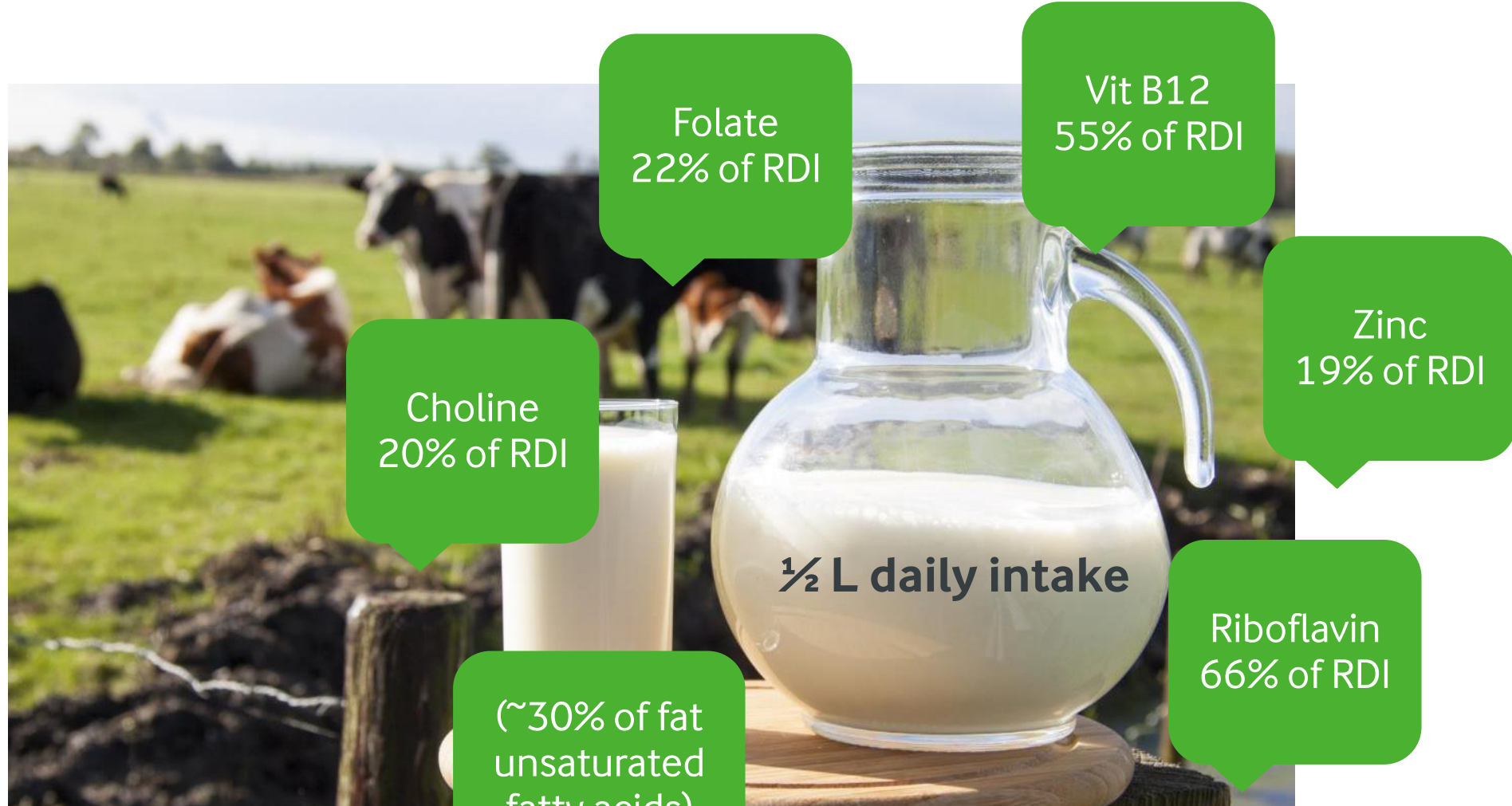


BRAIN FOOD SUPPLEMENTS
 ★★★★★
 ✓ BRAIN HEALTH
 ✓ CLEARER THINKING
 ✓ CONCENTRATION
 UK'S LEADING BRAIN SUPPLEMENT SPECIALIST



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BRAIN HEALTH-SUPPORTIVE NUTRIENTS IN COWS MILK



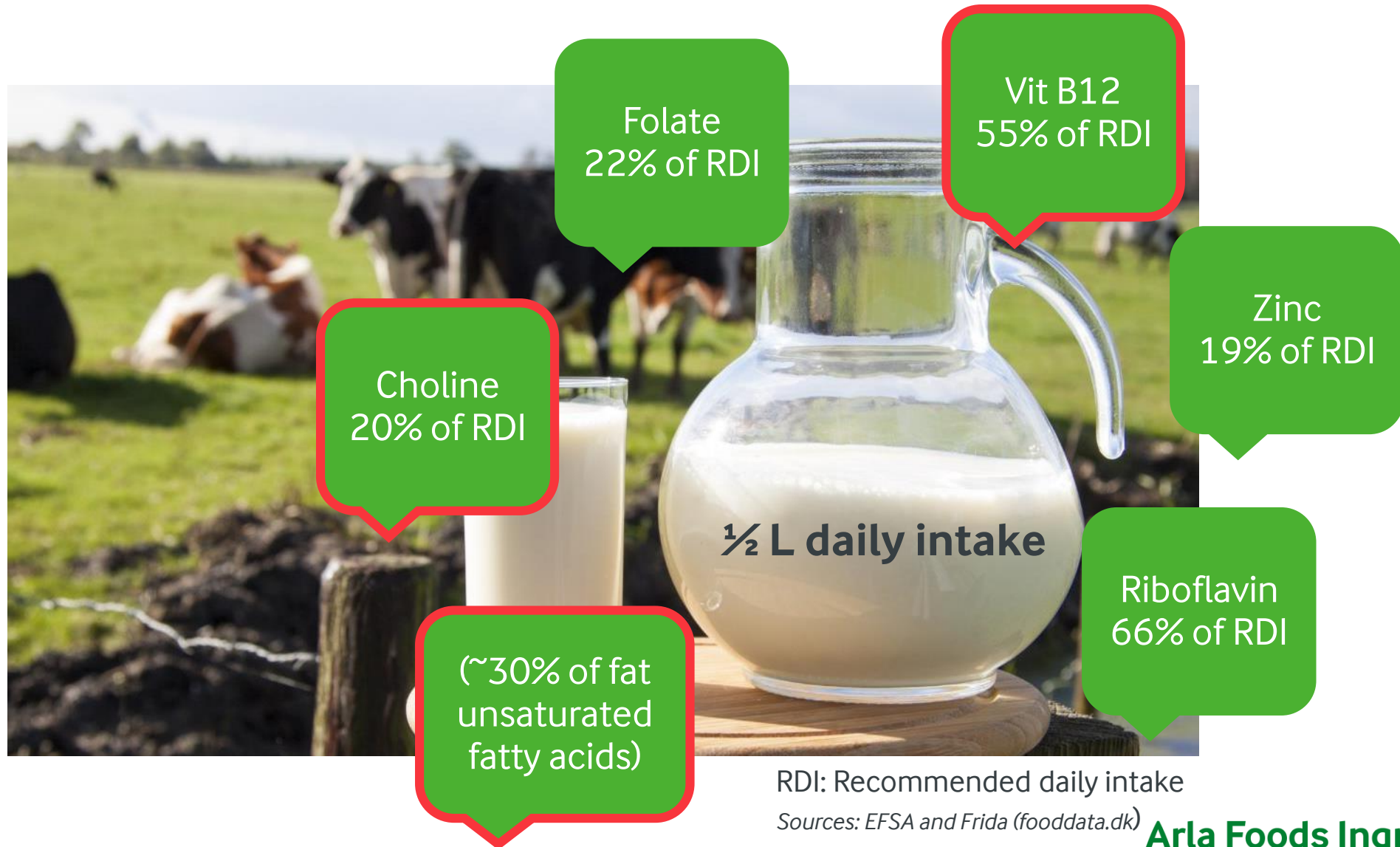
RDI: Recommended daily intake

Sources: EFSA and Frida (fooddata.dk)

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BRAIN HEALTH-SUPPORTIVE NUTRIENTS IN COWS MILK



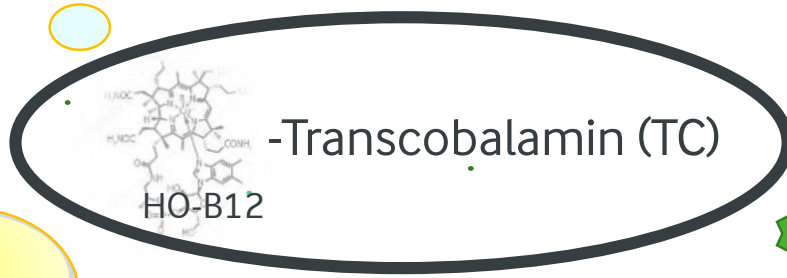
RDI: Recommended daily intake

Sources: EFSA and Frida (fooddata.dk)

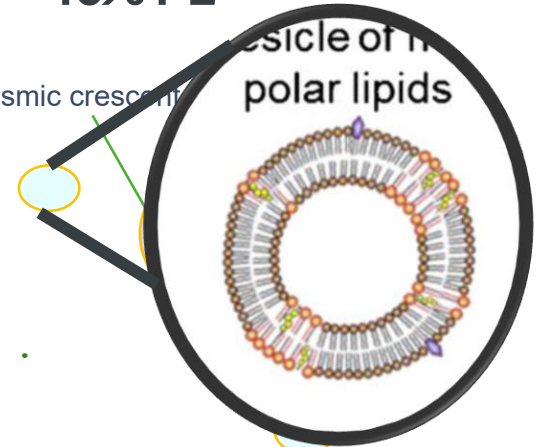
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THE MILK MATRIX



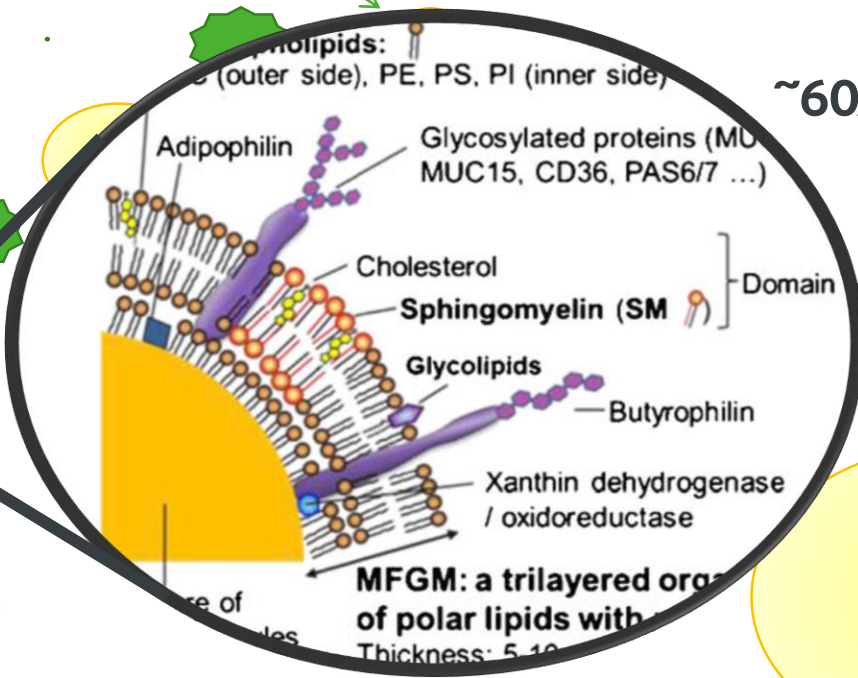
~40% PL



Whey (milk serum)

Membrane vesicles/particles

~60% PL



Casein micelles
~200 nm in diameter

Fat globules

0.1-15 µm in diameter
Triglyceride core
Phospholipid membrane

Milk cells
White blood cells
Sloughing epithelial cells

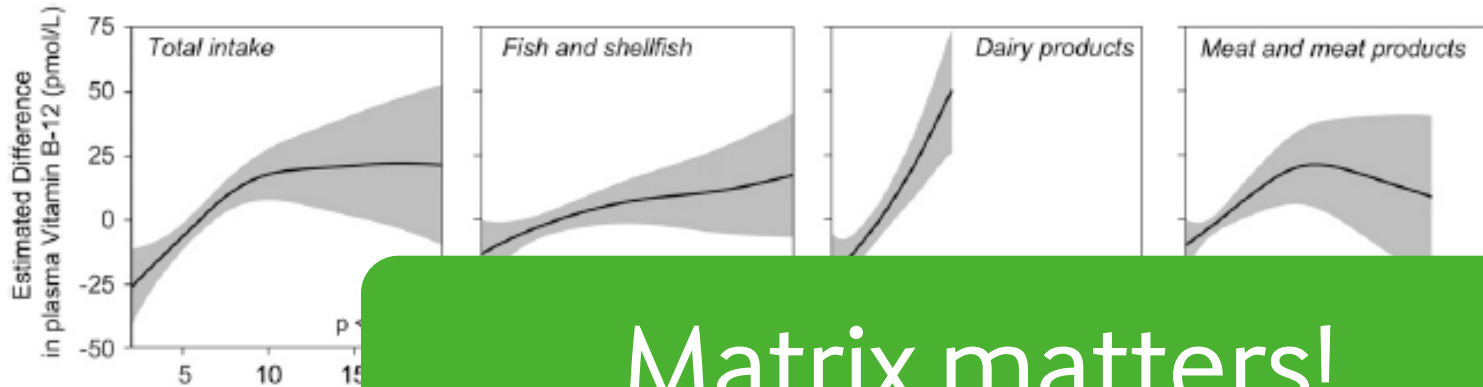


DAIRY GIVES SUPERIOR B12 BIOAVAILABILITY



Dietary sources of vitamin B-12 and their association with plasma vitamin B-12 concentrations in the general population: the Hordaland Homocysteine Study.

Conclusion: Vitamin B-12 appears to be more bioavailable from dairy products



7 subjects in 2 age groups
(60-70 and 71-74 y).

Vogiatzoglou A et al. Am J Clin Nutr. 2009

Brouwer-Brolsma et al, Nutrients. 2015

Association study (>65 yrs): Dietary Sources of Vitamin B-12 and Their Association with Vitamin B-12, B-PROOF Study.

Results: Higher intakes of dairy, meat, and fish and shellfish were significantly associated with higher serum vitamin B-12 concentrations, where meat and dairy-predominantly milk were the most potent sources

VITAMIN B12 DEFICIENCY

A global micronutrient challenge



LATIN AMERICA

40% (GEN POP)

Finkelstein et al. 2015

SOUTH AMERICA

VENEZUELA: 60%

Garcia-Casal et al. 2005

ITALY

48% (PREGNANT)

Scolamiero et al. 2014

DENMARK

43% (PREGNANT)

Milman et al. 2006

SOUTH-EAST ASIA

70-80% (GEN POP)

Finkelstein et al. 2015

INDIA

51% (PREGNANT)
36% (BF)
9% (NON-BF)
50-66% (ADULTS)

Duggan et al. 2014
Taneja et al. 2007

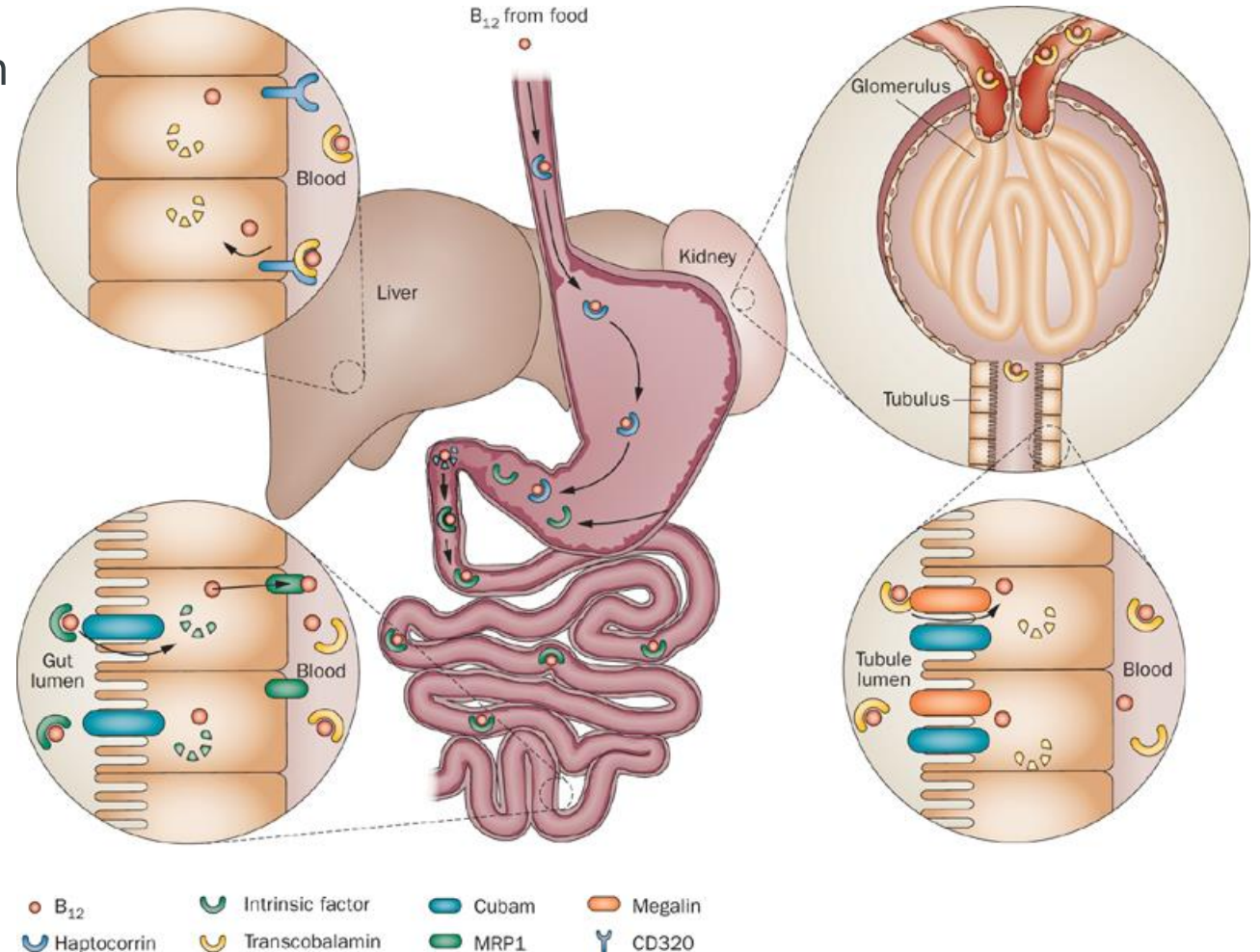
AFRICA

70% (GEN POP)

Finkelstein et al. 2015

B12 UPTAKE AND BIOAVAILIBILITY

- Vit-B12 is synthesized by ruminal microflora in cows (not present in plants)
- Food matrice dependency
- Protein binding partner exchange
 - Haptocorrin (HC)
 - Intrinsic Factor (IF)
 - Transcobalamin (TC)
- Type of B12 (CN, HO, Me, 5-DeoxyAd)



CAUSES TO B12 DEFICIENCY

1. Inadequate intake
2. Raised gastric pH
3. Reduced Intrinsic factor
4. Intestinal malabsorption

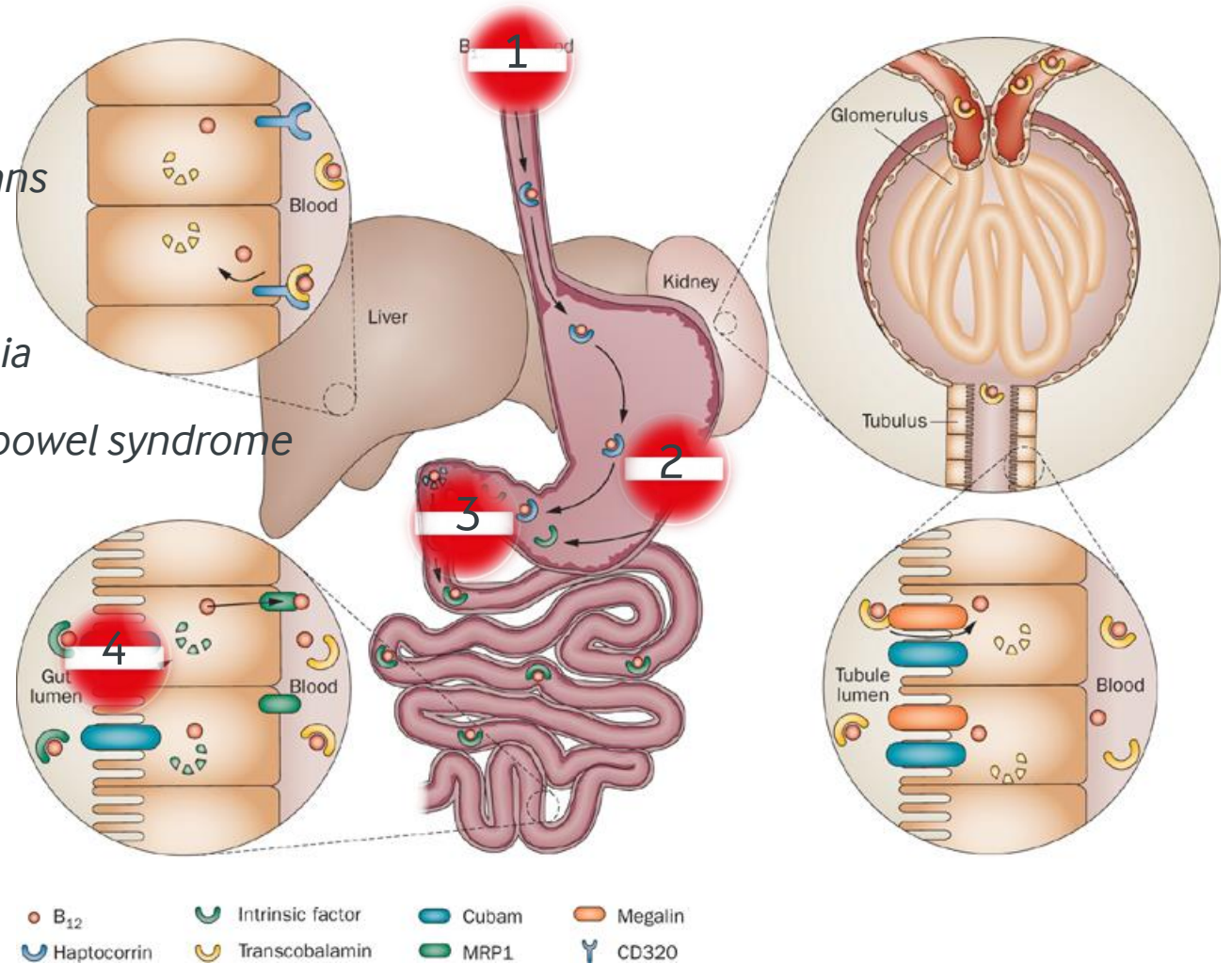
At risk:

Vegetarians, Vegans

Elderly, PPI use

Pernicious anemia

Metformin, short bowel syndrome



CONSEQUENCES OF B12 DEFICIENCY



Fetal and infants

Complications

Mothers with <250 ng/L B12 had >2.5-fold higher risk of bearing a child with an NTD¹.

In India (low B12) the rate of NTD is 0.5-11/1000 births².

Maternal B12 deficiency (<180 pg/L) was associated with a 9-fold greater risk of recurrent pregnant loss³.

Cognitive

Children of mothers with low B12 had mental scores 1.6 points lower than children with adequate intake-mothers¹.

Maternal B12 during pregnancy significantly predicted children's B12 status at age 6².

B12 status in infancy correlates positively with cognitive performance at age 5³.

Elderly

General

Weakness, tiredness, or lightheadedness.

Heart palpitations and shortness of breath.

Pale skin.

Constipation, diarrhea, loss of appetite.

Nerve problems like numbness or tingling, muscle weakness, and problems walking.

Vision loss.

Cognitive

Low B12 status in Mild cognitive impairment correlates to poorer learning ability¹.

Low B12 correlates to cognitive impairment in early Parkinson Disease².

B12 supplementation improves nerve conductivity³.

¹Molloy et al, 2009. ²Rush et al, 2014. ³Reznikoff-Etievant et al, 2002.

¹Del Rio et al, 2009. ²Bhate et al, 2008. ³Kvestad I 2017.

¹Langan RC, 2017

¹Köbe T 2016. ²Cristine CW 2018. ³ Brito A 2016

BIOAVAILABILITY AND RELEVANCE OF DIFFERENT B12 FORMS

Research collaboration

Aarhus University Hospital

Prof. Em. Ebba Nexø
PhD Eva Greibe

Aarhus University

Sen. Sct Christian Heegaard
Sen. Sct Sergey Fedosov

UC Davis Health

Prof. Ralph Green

Deenanath Mangeshkar Hospital, India

Dr Sadanand Naik

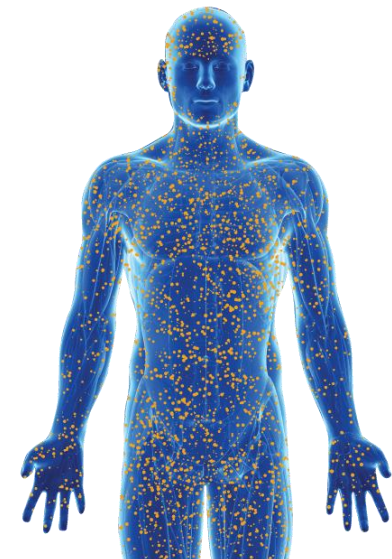
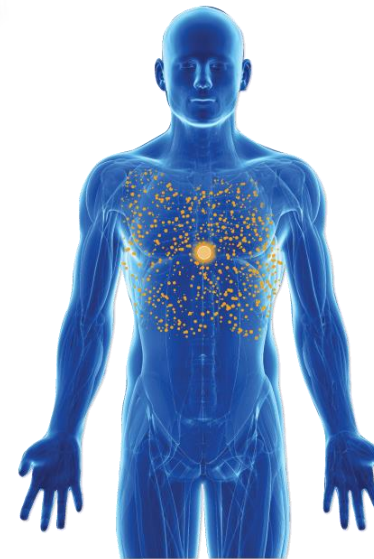
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Cyanocobalamin
(CN-B12)

Hydroxycobalamin
(OH-B12)

Adenosyldeoxy-
cobalamin (Ado-B12)

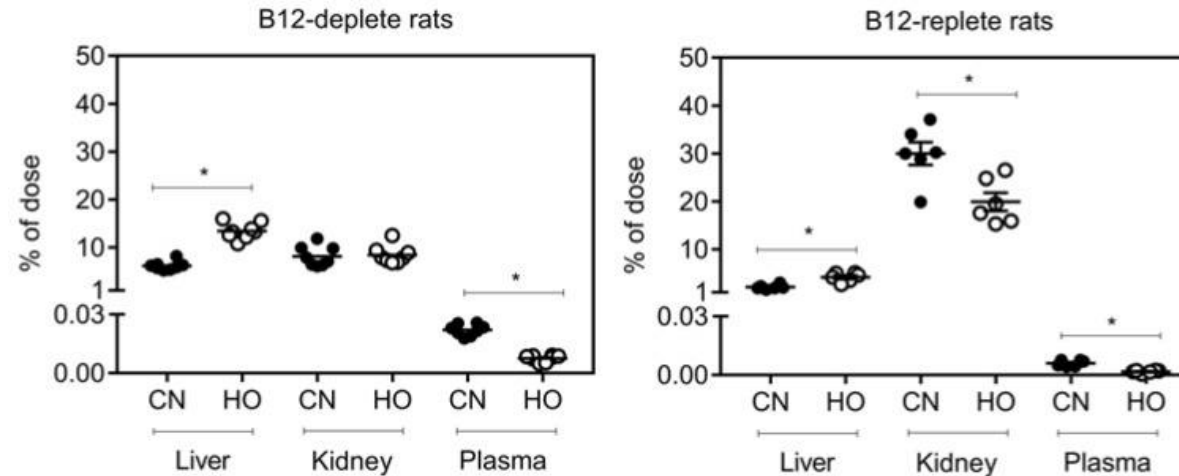
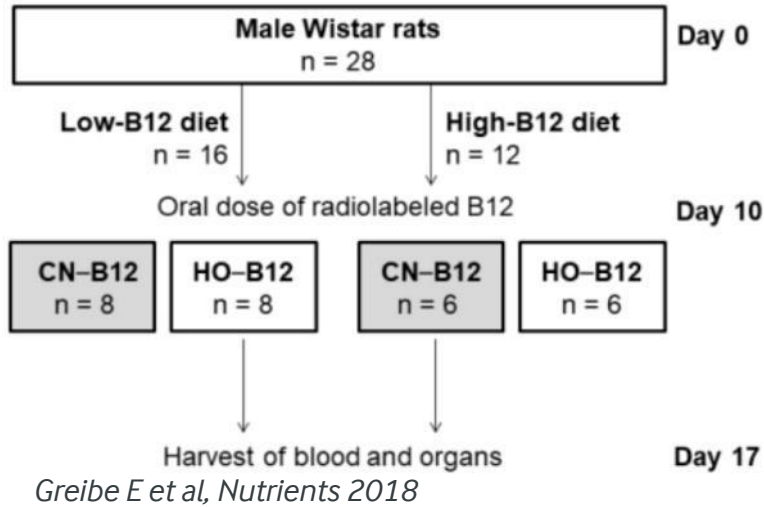
Methylcobalamin
(CH3-B12)



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RAT MODEL- BIOAVAILABILITY OF B12 FORMS



“Data suggests long-term differences in tissue utilization of the two B12 forms and warrant further studies concerning the possible benefits of consuming HO⁻B12 (food) instead of CN⁻B12 (vitamin pill).”

Article

Dietary Intake of Vitamin B12 is Better for Restoring a Low B12 Status Than a Daily High-Dose Vitamin Pill: An Experimental Study in Rats

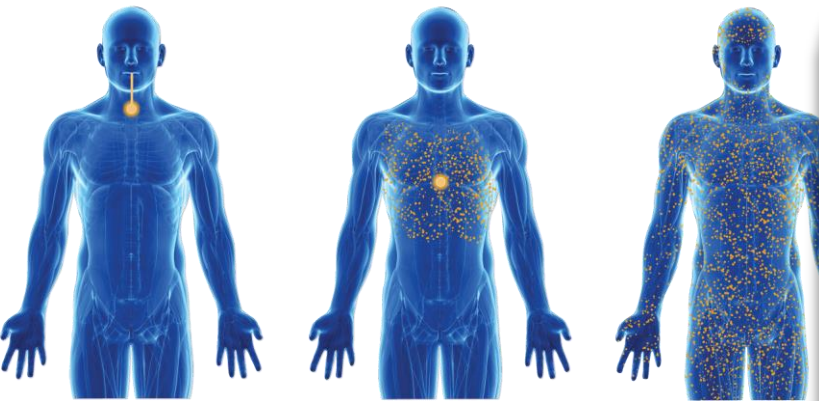
Eva Greibe 1*

Food matrix matters for Vitamin B12 bioavailability!

Ebba Nexo 1

ard 99,

00 Aarhus C,



Article

Cyano-B12 or Whey Powder with Endogenous Hydroxo-B12 for Supplementation in B12 Deficient Lactovegetarians

Sadanand Naik 1*, Namita Mahalle 1, Eva Greibe 2, Marie S. Ostenfeld 3, Christian W. Heegaard 4, Ebba Nexo 2 and Sergey N. Fedosov 4*

¹ Department of Pathology, Deenanath Mangeshkar Hospital and Research Center, Pune 411004, India; pnmahalle@gmail.com

² Department of Clinical Biochemistry and Institute of Clinical Medicine, Aarhus University Hospital, DK

THE MILK MATRIX

Whey (milk serum)

Casein micelles
~200 nm in diameter

Milk cells
White blood cells
Sloughing epithelial cells

HO-B12

-Transcobalamin (TC)



Membrane vesicles/particles

Phospholipids: PE (outer side), PE, PS, PI (inner side)

Adipophilin

Glycosylated proteins (MUC15, CD36, PAS6/7 ...)

Cholesterol

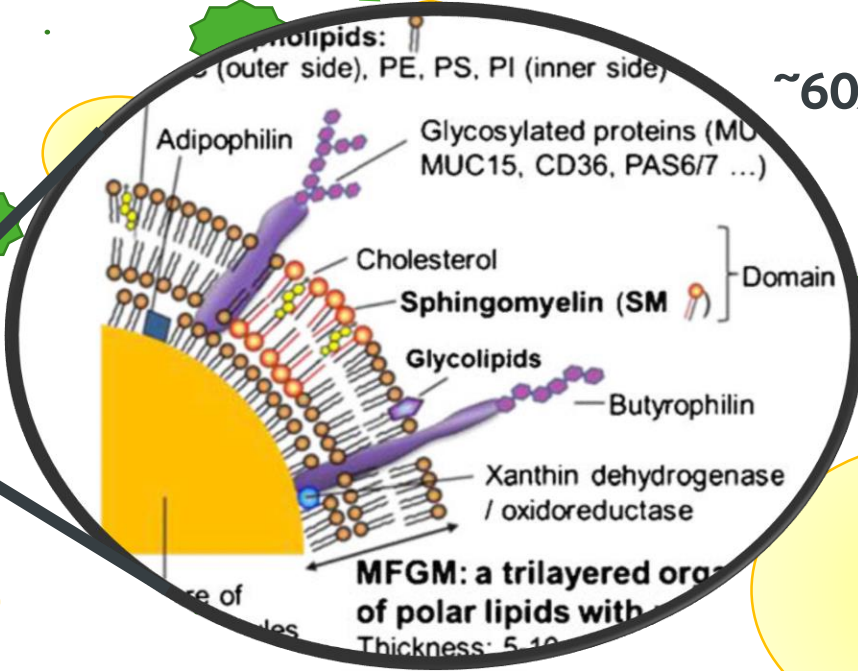
Spingomyelin (SM)

Glycolipids

Butyrophilin

Xanthin dehydrogenase / oxidoreductase

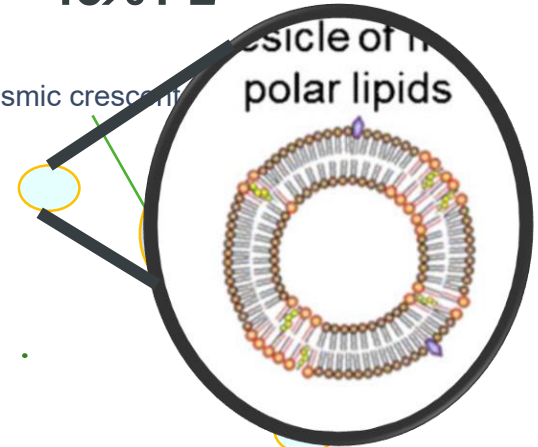
MFGM: a trilayered org of polar lipids with
Thickness: 5-10



~40% PL

Cytoplasmic crescent

Vesicle of non-polar lipids



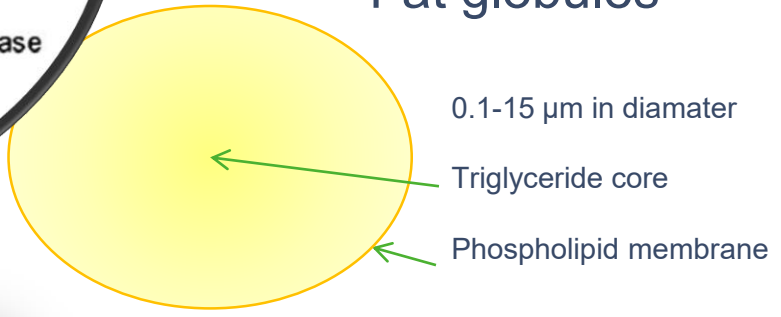
~60% PL

Fat globules

0.1-15 µm in diameter

Triglyceride core

Phospholipid membrane



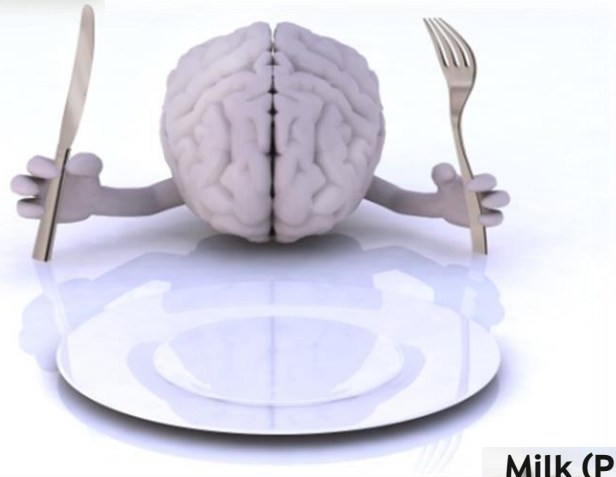
DIETARY PHOSPHOLIPIDS

Liver (chicken, veal, beef)



Egg yolk (PL ~10% of weight)

Peanuts (PL 1-2% of total lipid)



Krill (PL >50% of total lipid)



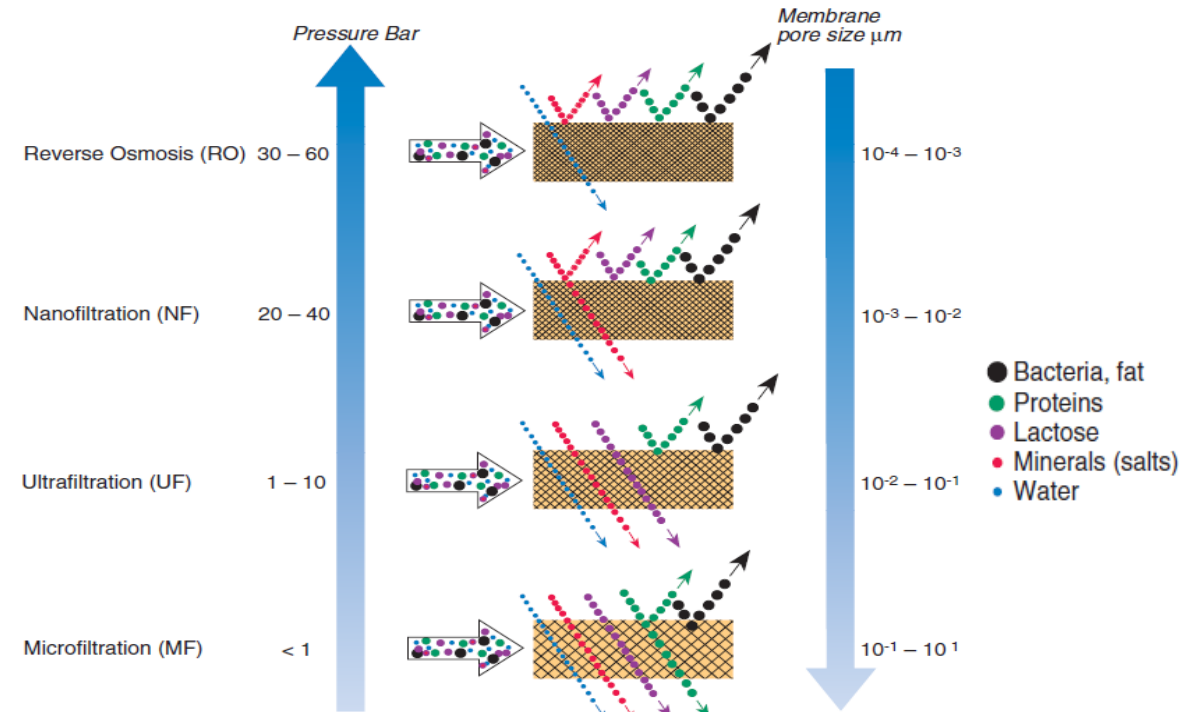
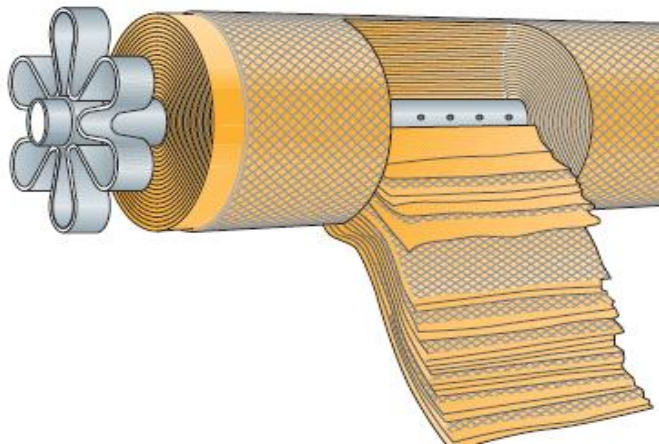
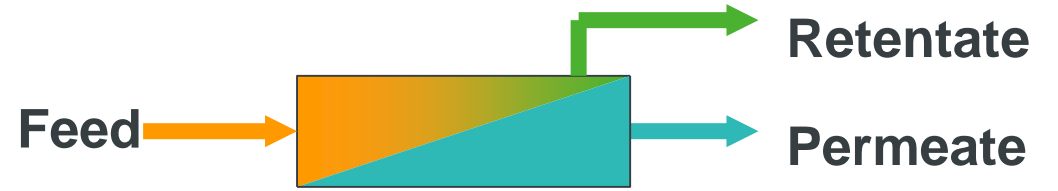
Soy (PL 4% of total lipid)



Milk (PL ~1% of total lipid)

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Dairy Processing- Separation



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A PHOSPHOLIPID-ENRICHED DAIRY INGREDIENT

Lacprodan® MFGM-10

Chemical specification

Protein (Nx6.38) as is		69-76 %
Lactose	max.	3 %
Total fat		16-22 %
Total PLs	min.	6-8 %
IgG	level	4 %

Typical phospholipid composition

Sphingomyelin	1.6 %
Phosphatidyl choline	1.8 %
Phosphatidyl ethanolamine	1.9 %
Phosphatidyl serine	0.8 %
Phosphatidyl inositol	0.5 %
Others	0.5 %

Table 2. Means and standard error of total polar lipid content (wt %) of some dairy samples (n = 4).¹

Sample	PL (% of sample)	PL (% of DM)	PL (% of fat)	GLUCER (% of PL)	LACCER (% of PL)	PE (% of PL)	PI (% of PL)	PS (% of PL)	PC (% of PL)	SM (% of PL)
Raw milk	0.029 ± 0.001	0.232 ± 0.001	0.708 ± 0.003	2.74 ± 0.05	6.66 ± 0.10	41.99 ± 0.28	4.83 ± 0.28	6.72 ± 0.35	19.15 ± 0.25	17.93 ± 0.16
Cream	0.139 ± 0.008	0.308 ± 0.017	0.354 ± 0.020	3.74 ± 0.58	5.25 ± 1.23	39.97 ± 2.07	8.16 ± 0.54	8.23 ± 0.18	20.72 ± 0.74	13.93 ± 0.93
Butter	0.181 ± 0.011	0.215 ± 0.013	0.223 ± 0.014	2.69 ± 0.99	5.84 ± 0.25	36.52 ± 1.31	6.48 ± 0.53	8.11 ± 0.19	20.15 ± 0.53	20.22 ± 1.61
Buttermilk	0.091 ± 0.003	1.146 ± 0.036	21.849 ± 0.695	1.60 ± 0.09	6.10 ± 0.58	42.90 ± 0.25	8.91 ± 0.27	8.55 ± 0.12	19.10 ± 0.11	12.83 ± 0.44
Whey (Cheddar)	0.018 ± 0.001	0.264 ± 0.004	5.321 ± 0.084	1.55 ± 0.23	8.90 ± 0.55	41.13 ± 0.24	3.69 ± 0.23	9.33 ± 0.34	19.04 ± 0.45	16.38 ± 0.50
Quarg	0.032 ± 0.001	0.246 ± 0.007	24.655 ± 0.727	2.60 ± 0.49	10.39 ± 1.56	39.07 ± 1.45	3.91 ± 0.16	5.93 ± 0.31	18.74 ± 0.26	19.36 ± 0.90
Cheddar	0.153 ± 0.012	0.248 ± 0.019	0.474 ± 0.036	2.37 ± 1.90	6.91 ± 0.41	37.96 ± 2.11	7.73 ± 1.16	8.50 ± 0.57	20.25 ± 1.32	16.29 ± 0.57

¹GLUCER = Glucosylceramide; LACCER = lactosylceramide; PA = phosphatidic acid; PE = phosphatidylethanolamine; PI = phosphatidylinositol; PS = phosphatidylserine; PC = phosphatidylcholine; SM = sphingomyelin.

Rombaut et al. J Dairy Sci. 2005



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Phospholipids - a BRAIN perspective

Phospholipids constitute more than 60% of total brain lipid, most of which are incorporated in the membrane system

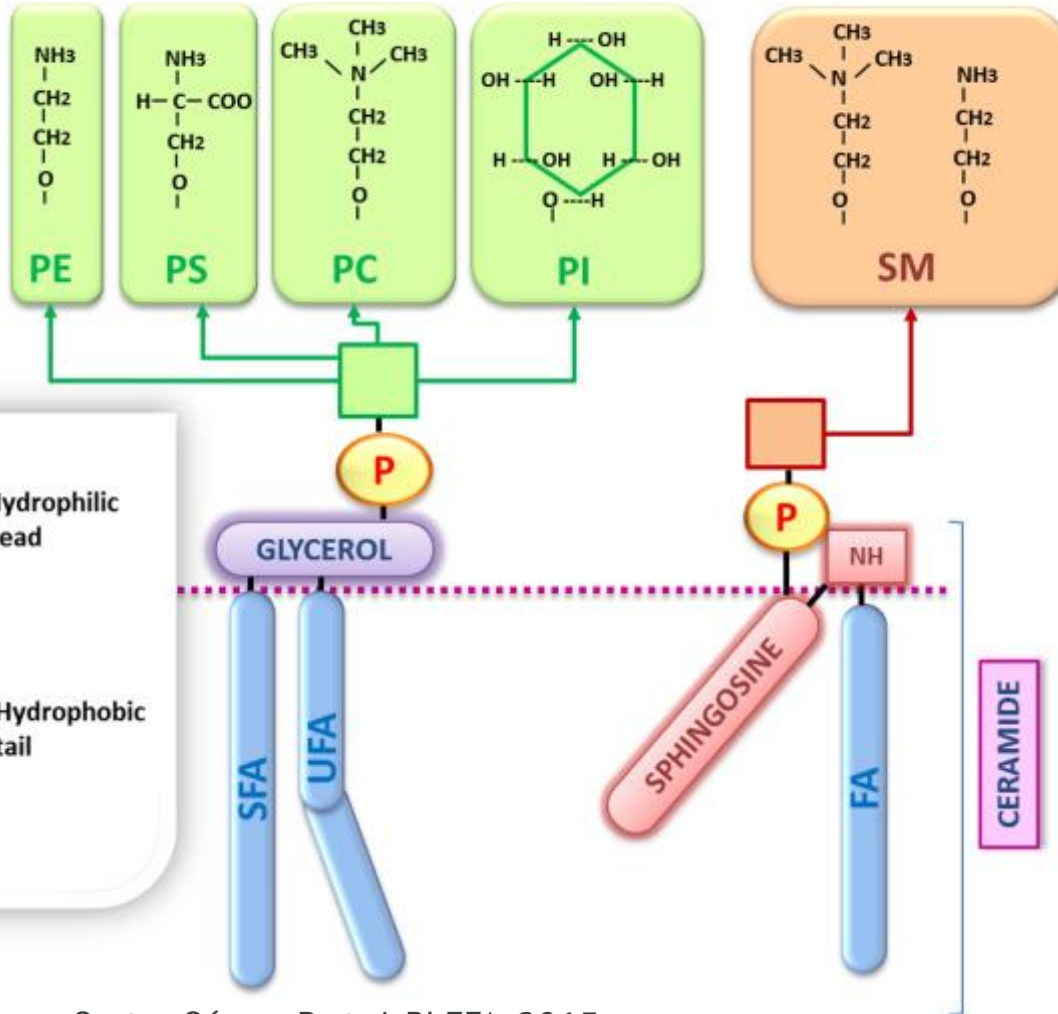
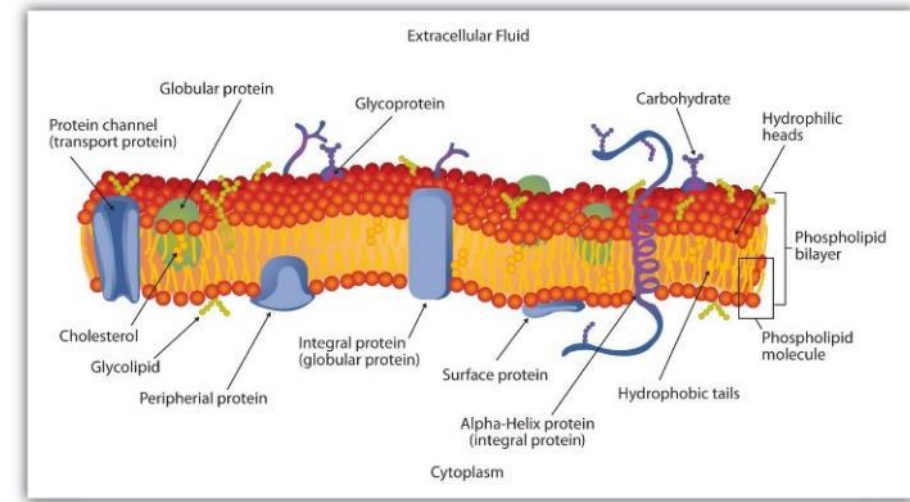


PC, PE, PS, PI, SM represent FIVE of the most abundant phospholipids of brain cell membrane

- **PC** Phosphatidyl choline (**PC**) [33-37% brain PL] key building block of membrane bilayers and provides choline for synthesis of neurotransmitter acetylcholine and de novo SM synthesis
- **PE** Phosphatidyl ethanolamine (**PE**) [36% brain PL] key building block of membrane bilayers
- **PS** Phosphatidyl serine (**PS**) [10-20% brain PL] - plays a key role in biosynthesis and release of neurotransmitters. PS is neurotrophic, increasing total number and size of neurons
- **PI** Phosphatidyl Inositol (**PI**) [2-5% brain PL] key membrane constituent and as a participant in essential metabolic processes
- **SM** Sphingomyelin (**SM**) [11% brain PL] contributes to myelination of neurons, is required for the activity of a number of membrane-bound proteins. SM not found in plants.

CHEMICAL STRUCTURE

Glycerophospholipids and sphingolipids



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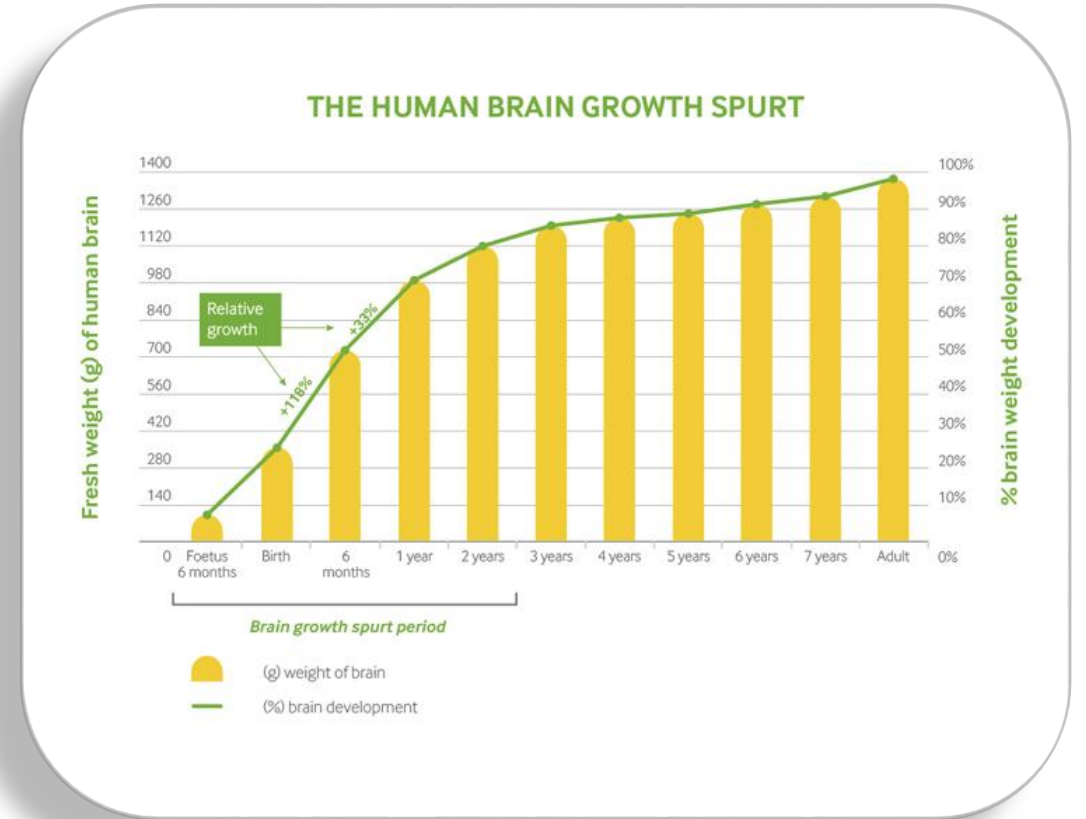
BRAIN DEVELOPMENT

Infant cognitive development



Prenatal and infancy is a very critical period for cognitive development due to rapid neuronal growth and maturation

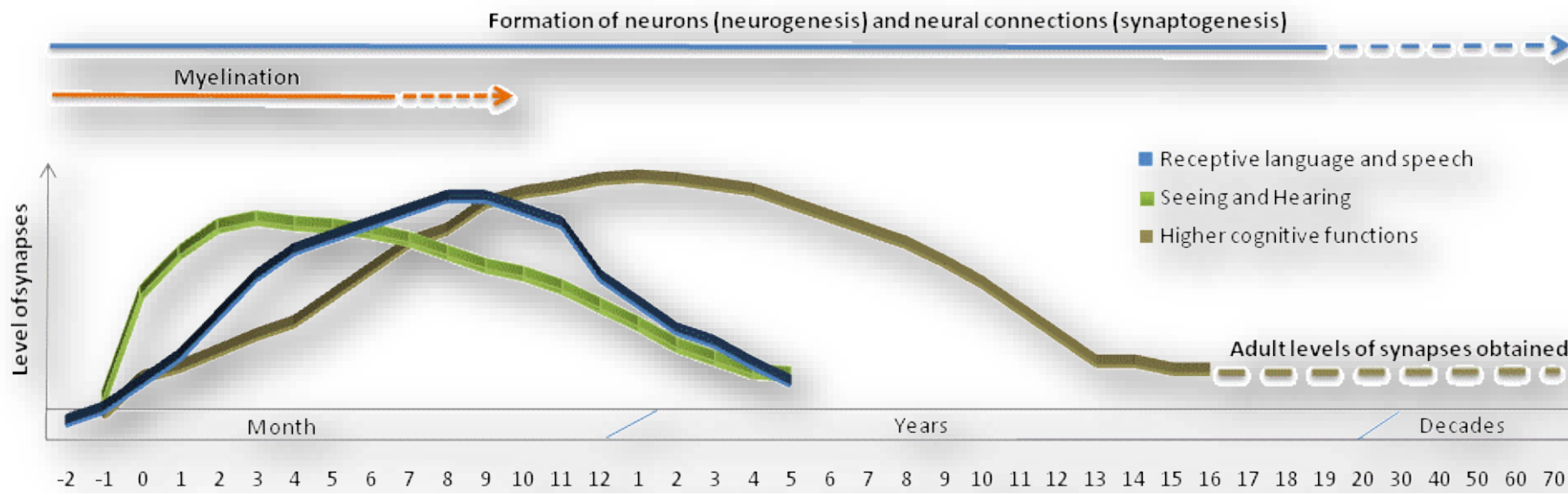
- The infant brain is at birth approx. 25% of its adult volume
- By the end of the first postnatal year it reaches 75% of its adult volume
- The remaining 25% of brain growth is achieved over the next few years



HUMAN BRAIN DEVELOPMENT- A LIFE-LONG PROCES



- The brain will keep its development and maturation into adulthood, but the first 2 years of life are the most critical
- Lipids needed for the very critical period are all present in milk
- **Reasonable to explore neurocognitive benefits of milk derived PL**



Time course of brain maturation events by age

Higher cognitive functions

- problem solving
- reasoning
- self-regulation
- Personality & strategic functioning

have a maturational course spanning the entire school age and extending into adulthood

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COGNITIVE DEVELOPMENT

Milk phospholipids

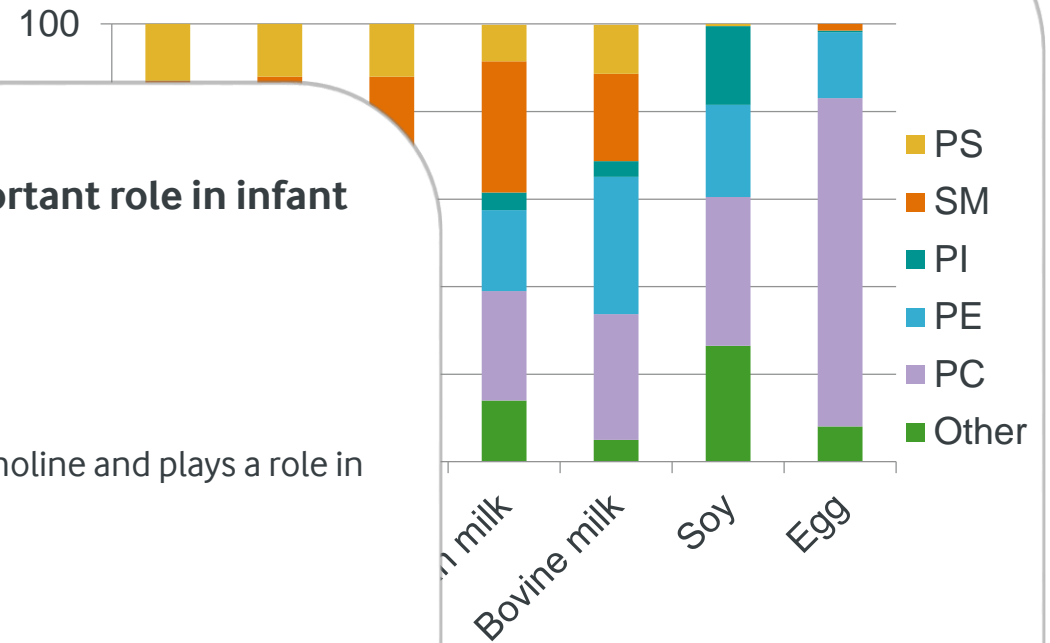
Bovine milk has a similar phospholipid profile compared to human milk

% distribution of milk lipids in different sources (% of total milk lipids)	Human milk ¹	Bovine Milk ¹
Phosphatidylcholines (PC)	24.5	28.7
Phosphatidylethanolamines (PE)	18.3	18.3
Phosphatidylserines (PS)	8.1	8.1
Sphingomyelins (SM)	29.7	29.7
Phosphatidylinositols (PI)	3.8	3.8
Others	13.9	13.9
Gangliosides		
GD3 (mg/L)	3.8 - 0.9 ²	
GM3 (mg/L)	4.3 - 9.8 ²	

GD3 and GM3: the two major gangliosides in human milk
 Human milk gangliosides measured at day: 0-11, 30, 60 and 120
 Bovine milk gangliosides measured at day: 2, 15 and 90. *15.2 mg/L at 90 days

¹Garcia et al 2012, ²Giuffrida et al. 2014, ³Lee et al. 2013

Average PL distribution



Lipid components play an important role in infant cognitive development

Phospholipids:

- support myelination of the CNS
- Phosphatidylcholine contains choline and plays a role in cell signalling

Sphingomyelin:

- is important for CNS myelination

Gangliosides:

- are essential for brain development and cognition
- high content in nervous tissue

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DIFFERENCES IN COGNITIVE ABILITIES



Breastfeeding (BF)



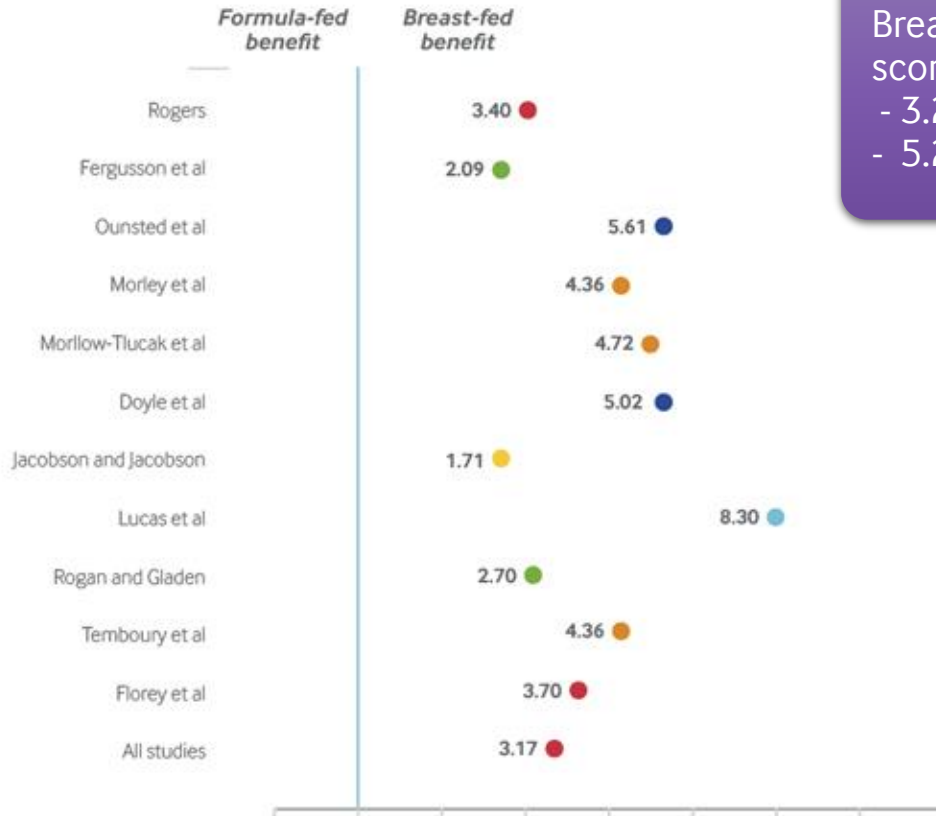
Infant formula feeding (FF)



BF infants have improved cognitive abilities compared to FF infants

COGNITIVE DEVELOPMENT

meta-analysis



Breastfeeding was associated with significantly higher scores for cognitive development than formula feeding

- 3.2 higher IQ score compared to formula feds
- 5.2 higher IQ score for low birth weight infants

The differences in cognitive development was manifested early in development and was sustained through childhood and adolescence

Small IQ impact at individual level
Large IQ impact at population level

Victora CG et al, The Lancet, 2015:

- Dose-response association with breastfeeding duration for IQ and educational attainment
- Confounder-adjusted analysis: ~3.7 point higher IQ score, ~1year longer education, higher income



ADDITION OF MFGM-10 TO INFANT FORMULA HUMANIZES THE PL PROFILE

Human
milk

Infant
formula

Claumarchirant et al, Int Dairy J 2016, J
& Food Chem 2016

“Only IFs with MFGM could supply the total and individual PL content present in all lactation periods”



Timby et al, Am J Clin Nutr, 2014

Breast
fed

IF
standard

IF
MFGM-10

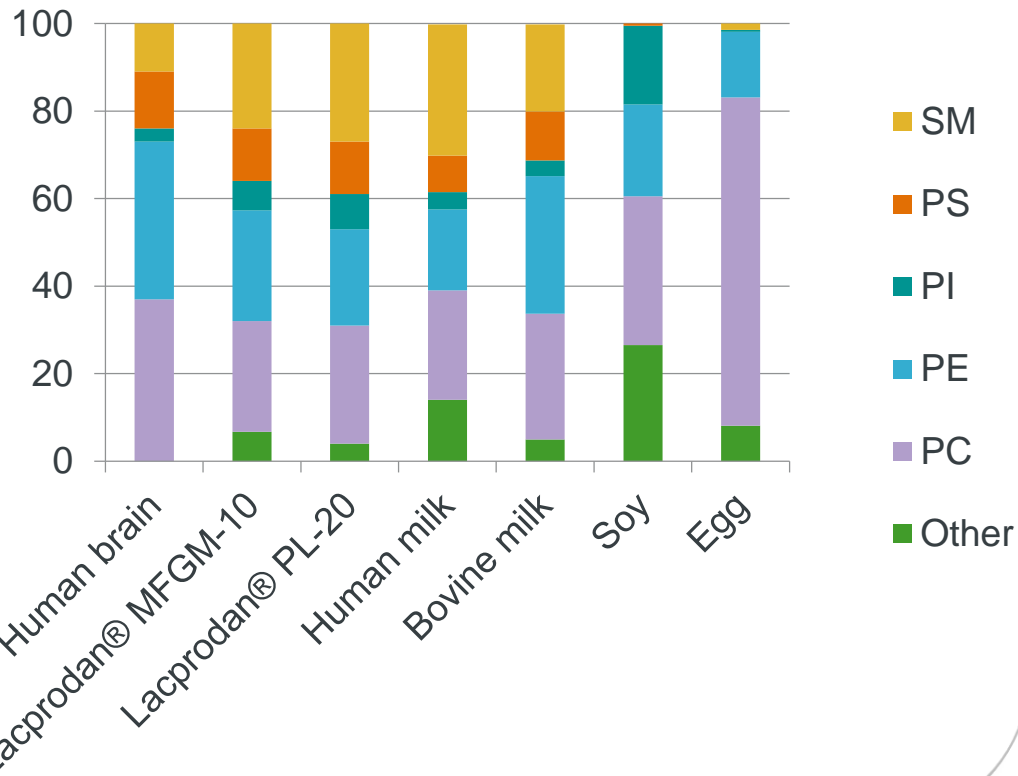
“MFGM-10 supplementation to infant formula narrows the gap in cognitive development between breastfed and formula-fed infants”

Conclusion: Enrichment for specific dairy matrix components (MFGM) into Infant formulas enhance brain development

AGENDA

1. Introduction
 1. Trends in Brain Health among consumers and markets
 2. Nutritional components linked to Brain Health
2. Vitamin B12
 1. Dairy as a unique delivery matrix
 2. B12 deficiency and bioavailability
3. Brain development and dairy phospholipid components
 1. Differences between breastfed and IF formula fed infants- cognition
 2. Milk fat globular membrane (MFGM) for infant brain development
4. **Brain ‘decay’ and potential effects of dairy phospholipid components**
 1. Global demographic shift and cognitive decline
 2. Finding nutritional solutions to support elderly brain health
5. **Conclusions & Perspectives**

DAIRY-DERIVED SPHINGOMYELIN (SM) AND COGNITIVE DECAY



Breastfed
(n=72)

Standard
formula
(n=68)

Formula +
MFGM-10
(n=73)

MFGM-10 supplementation to infant formula narrows the gap in cognitive development between breastfed and formula fed infants

Timby et al 2014

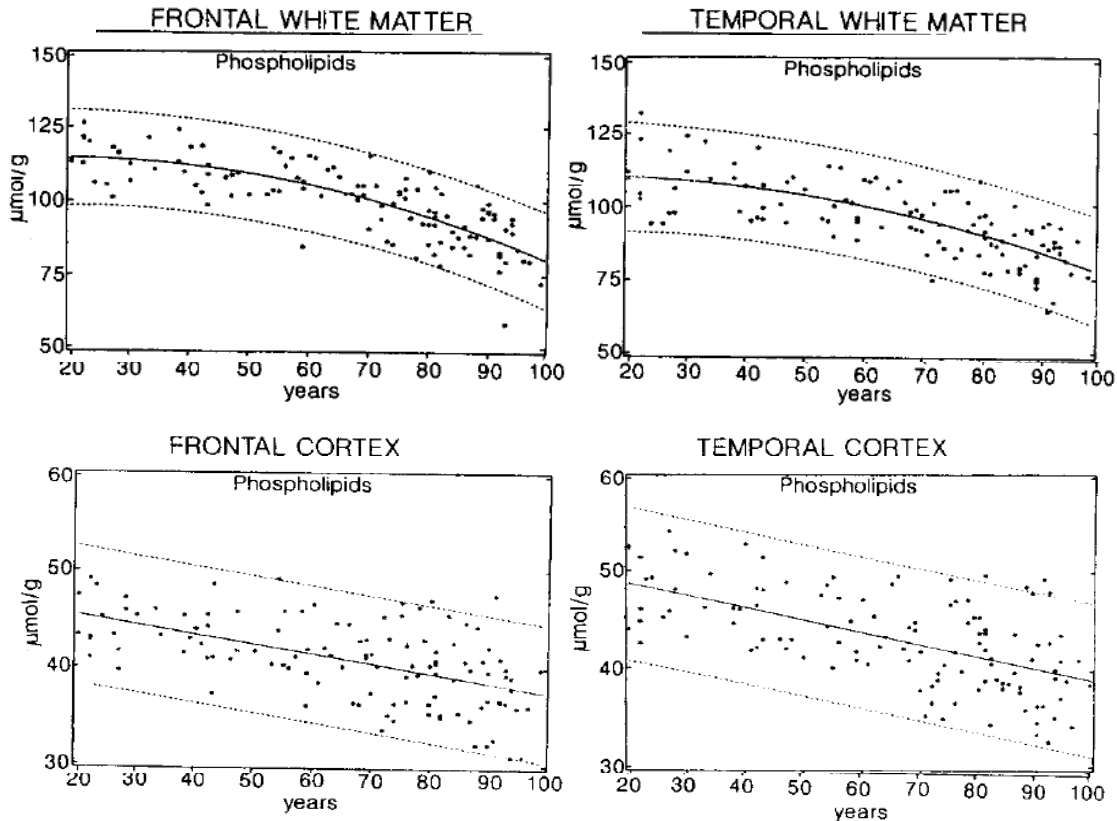
- ✓ Brain myelination in white matter occurs after birth
- ✓ Milk supplementing SM is believed essential
- ✓ White matter loss during age-related cognitive decline
- ✓ Prevention by dairy-derived SM?

Arla Foods Ingredients

Discovering the wonders of whey 

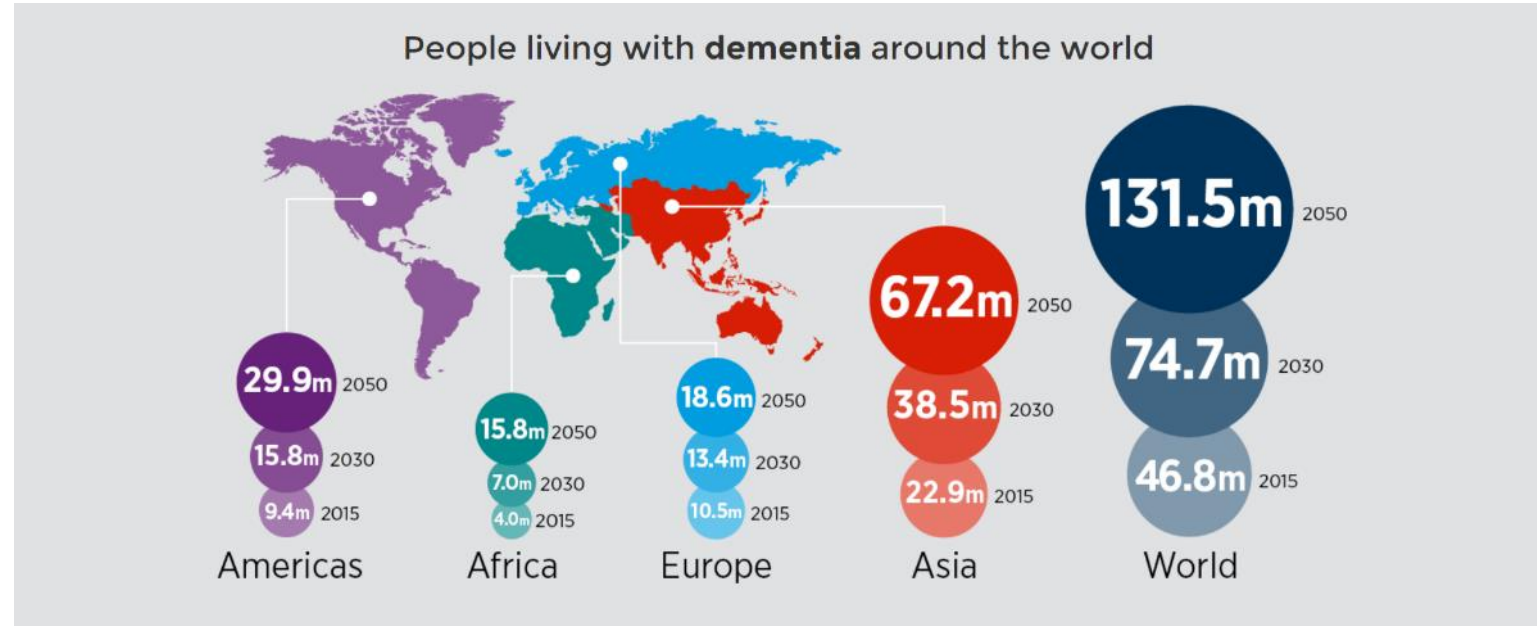
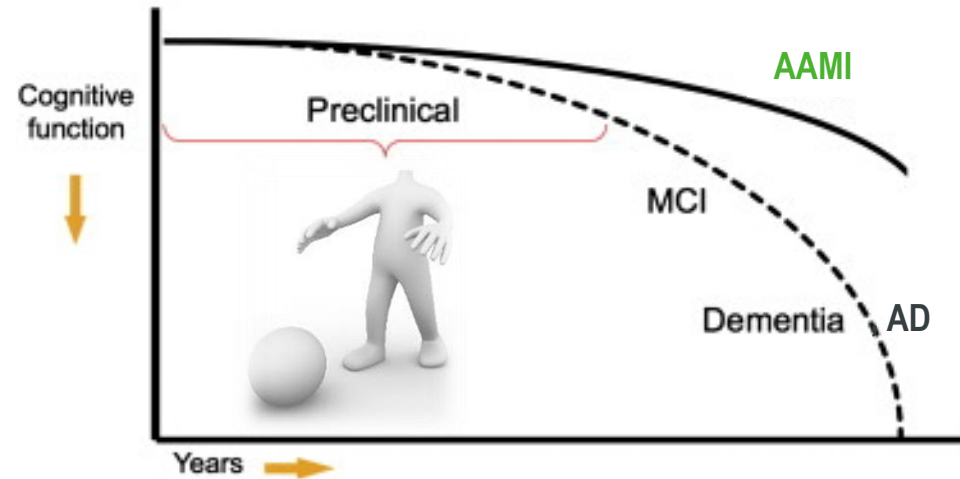
BRAIN COMPOSITION AND FUNCTIONING ALTERS AS WE AGE

- DECLINE IN COGNITIVE AND MENTAL FUNCTIONING



- Concentration of most lipids in the human DECREASE after age of 20
- PL decreases 18-31% and the volume of the brain declines with age at a rate of around 5% per decade after the age of 40

AGEING AND COGNITIVE DECLINE



AAMI: Age-associated memory impairment
 MCI: Mild cognitive impairment
 AD: Alzheimers Disease (~70% dementia disease)
Increasing age is the most important risk factor for AD

Increased life expectancy and demographic shifts will >3 fold dementia increase
WHO 2015: Call for global health priority of AD and dementia

PROJECT DAIRY-SMART (2019-)

HEALTHY AGEING THROUGH NUTRITION

Research collaboration

University of Southern Denmark

Assoc Prof. Christer Ejsing

Copenhagen University

Prof. Trond Ulven

Rigshospitalet

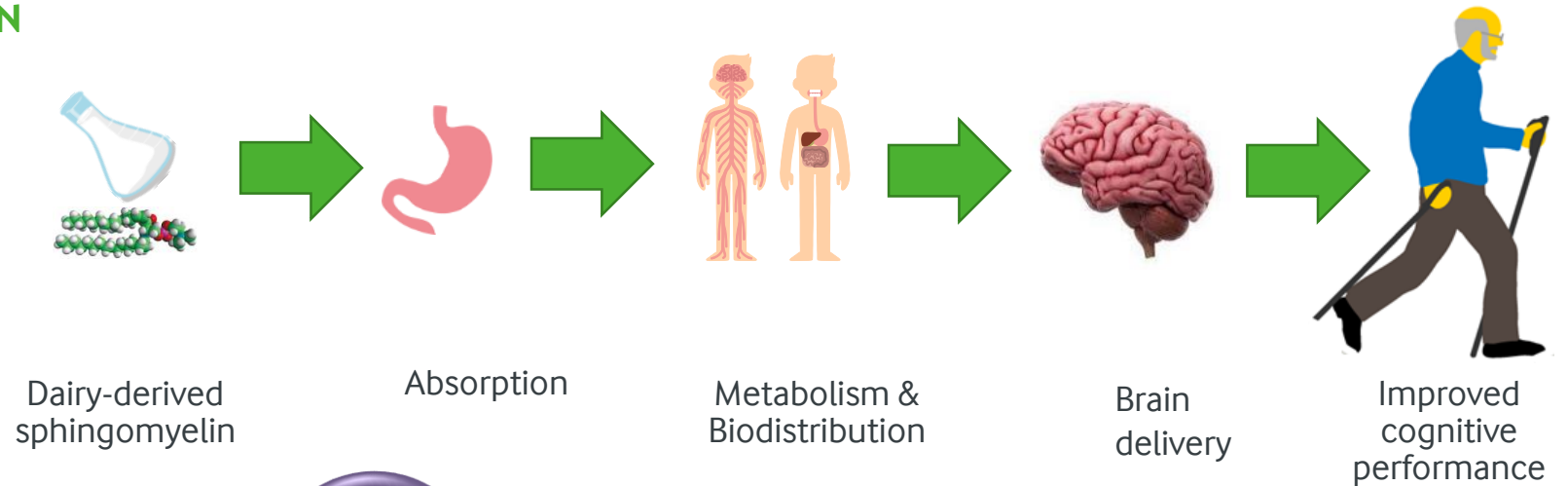
Prof Gitte Moos, Assoc Prof Hanne Demant

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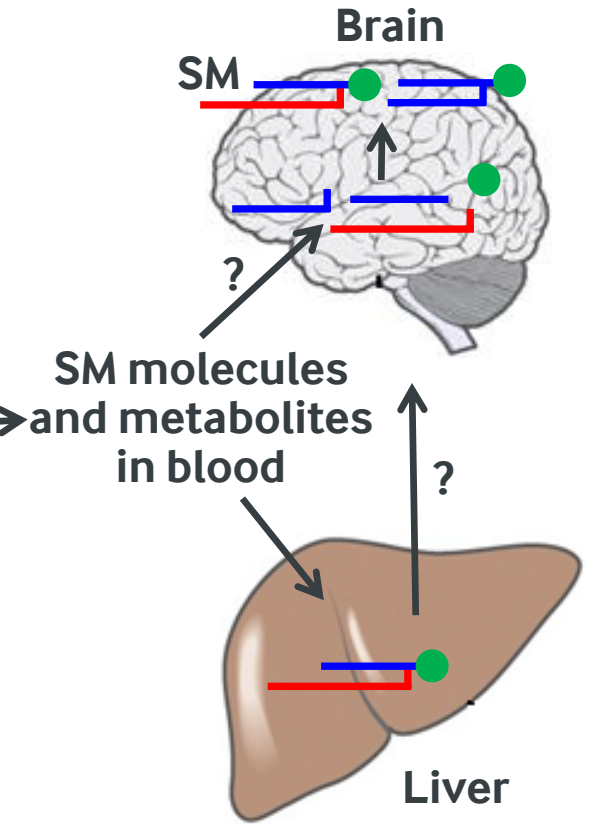
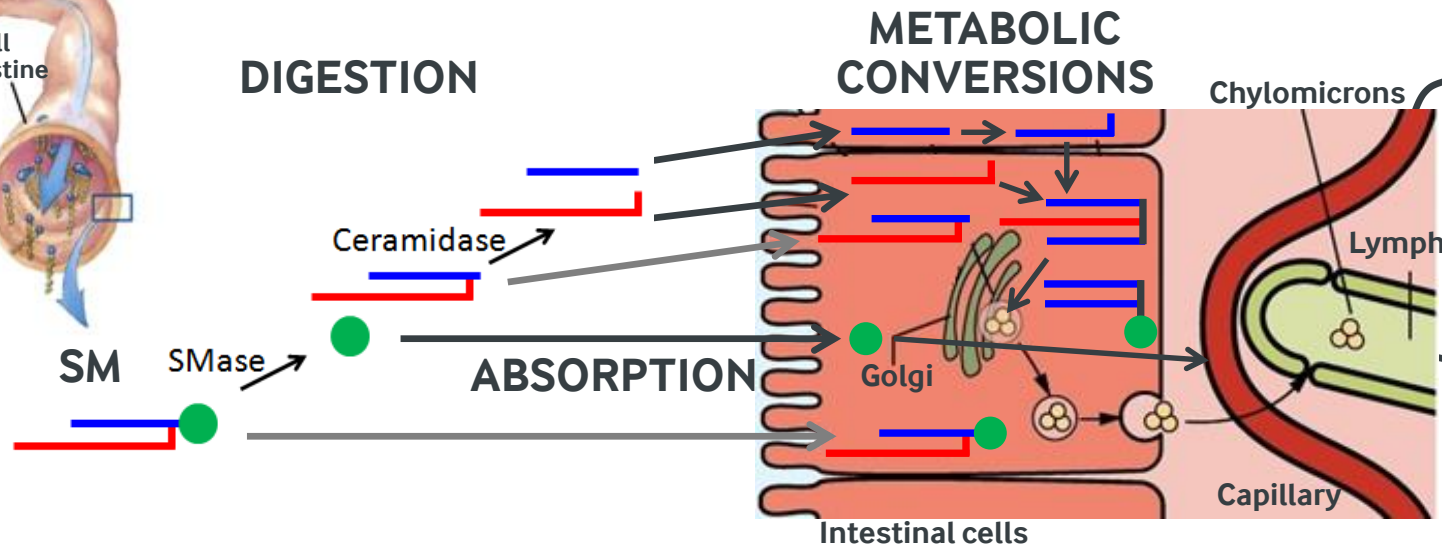
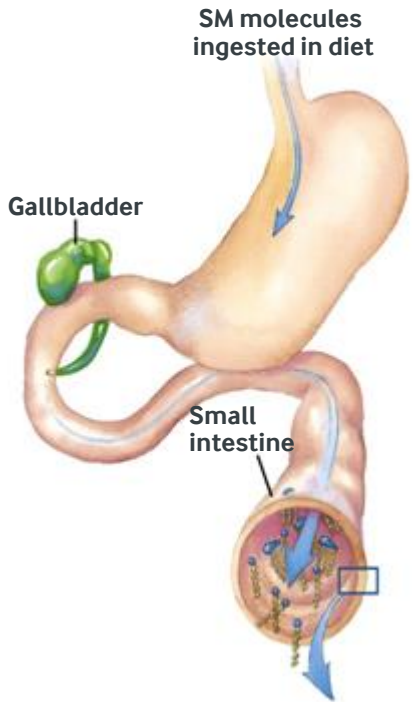
Nutr. Res. Sc. Ann Bjørnshave



THE SMART SOLUTION



Focus: Evidence for metabolism of dairy matrix components and brain delivery for brain structure support



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Discovering the wonders of whey 

Conclusions & Perspectives

Dairy and dairy ingredients contain nutrients that, due to their matrix, provide beneficial effects for brain health

- Vitamin B12
- Phospholipids in infant formula enrichment
- Potential for elderly nutrition

Still to be explored:

- Causality between intake and direct molecular action
- Gut-brain axis
- Link between obesity-low grade inflammation and brain health



ACKNOWLEDGEMENTS

External collaborators and funding



Aarhus University (AU)

Christian Heegaard
Sergey Fedosov
Jan Trige Rasmussen
Lars Wiking
Lotte Bach Larsen



Copenhagen University

Anette Mullertz
Per Torp Sangild
Thomas Thymann
Trond Ulven
Christine Heerup



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Mejeribrugets ForskningsFond

Innovation Fund Denmark



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