Cholestérol, phytostérols et composés phytochimiques
intérêt/risque pour la santé de l'enfant allaité

jean-charles.martin@univ-amu.fr

Le Cholestérol
Ami ou ennemi?

L'enfant allaité reçoit l'équivalent de 5 à 10 fois la quantité de cholestérol d'un adulte

Oddy WH. Breastfeeding protects against illness and infection in infants and children: a review of the evidence. *Breastfeed Rev 2001;**9:11-18.***

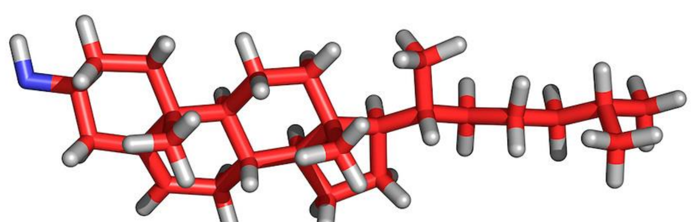


Table 4

Range of linoleic acid (LA) levels, range of LA to α-linolenic (LNA) ratios and fat sources used in term infant formulas marketed in Western countries during the last two decades[a]

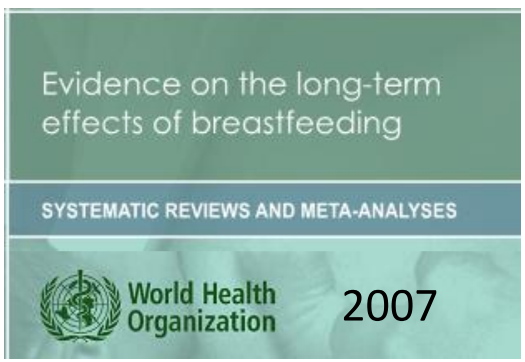
	Linoleic acid	LA/LNA ratio	Fat sources
Infant formulas marketed between 1980 and 1995	9.0–22.0	6.3–61.0	Cow milk fat, corn; cow milk fat, soybean, rapeseed, coconut
	(up to 57.0)	(up to 120)	Corn oil

[a] LA content is expressed as % of total fatty acids. Total lipid content was in the range of 2.5–3.6 g/100 mL of prepared milk. Adapted from Refs. [68,73,76,80,82,111,151–159,234–251] and from Guesnet (unpublished results).

D'après Ailhaud et Guesnet, Prog Lipid Res, 2006

breast milk: 150 mg/l of cholesterol (2.59–3.88 mM) vs Cow's milk : 0.28 to 0.85 mM cholesterol—3 to 14 times less than human milk
Exclusively breast-fed infants receive 15 to 20 mg cholesterol per kilogram body weight daily, whereas formula-fed infants receive 2 to 5 mg/kg

Berger A, et al. Nutritional implications of replacing bovine milk fat with vegetable oil in infant formulas. J Pediatr Gastroenterol Nutr 30: 115-130, 2000.



2007

Long-term effects of breastfeeding

...

A SYSTEMATIC REVIEW

...

World Health Organization

2013

Symposium II: Infant and childhood nutrition and disease
Breast-feeding and cardiovascular risk factors and outcomes in later life: evidence from epidemiological studies

Christopher G. Owen*, Peter H. Whincup and Derek G. Cook
Division of Population Health Sciences and Education, St George's, University of London, Cranmer Terrace, London SW17 ORE, UK

While **strong observational evidence suggests nutritional programming of adult cholesterol levels,** associations with other markers of cardiometabolic risk and their consequences in later life need to be confirmed in well-conducted observational and experimental studies.

« Exposition précoce au cholestérol module le risque cardiovasculaire de l'adulte (?) »

Les arguments

Table 5
Range of the linoleic acid (LA) levels, range of LA to α-linolenic (LNA) ratios and fat sources used in term infant formulas marketed in 2005[a]

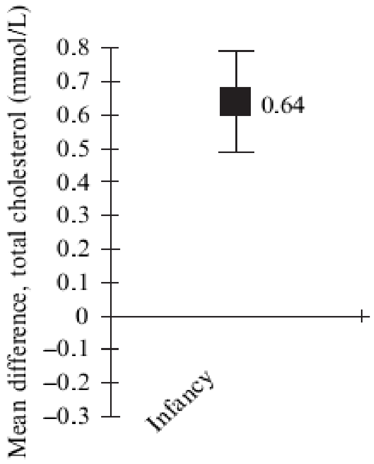
	Linoleic acid	LA/LNA ratio	Fat sources
Starter and follow-up infant formulas			
Milupa	10.1–15.9 (0.37–0.54)	5:1–10.8:1	Palm, coconut, rapeseed, sunflower, high-oleic palm
Nutricia	10.0–13.0 (0.32–0.39)	5.3:1–5.6:1	Palm, coconut, rapeseed, sunflower
Wyeth SMA	16.1–17.8 (0.47–0.58)	10.5:1–10.7:1	Palm, coconut, high-oleic safflower or sunflower, soybean
Nestlé	13.7–18.5 (0.43–0.67)	7.8:1–10.8:1	Palm, palm olein, rapeseed, corn, sunflower, safflower, soybean
Abbott Ross	14.9–29.3 (0.55–1.055)	7.7:1–18.3:1	Palm olein, coconut, high oleic safflower or sunflower, soybean
Mead Johnson	14.6–17.5 (0.51–0.61)	10.0:1	Palm olein, coconut, high-oleic sunflower, soybean
Blédina SA	15.2–18.0 (0.50–0.63)	9.0:10.5	Palm, rapeseed, coconut, sunflower

[a] LA content is expressed as % of total fatty acids (g/100 mL). Total lipid contents were in the ranges 2.5–3.6 g/100 mL prepared milk. Abbott Ross, Nestlé, Nutricia, Mead Johnson, and Milupa have developed formulas enriched in long-chain PUFAs (ARA, 0.10–0.55% of total fatty acids; DHA, 0.2–0.4%). Adapted from Refs. [252–255].

D'après Ailhaud et al, prog lipid res, 2006

Les formules infantiles contiennent moins de cholestérol que le lait maternel (~0.2g/L)

nourrisson alimenté au sein reçoit l'équivalent de 10 fois au moins la quantité quotidienne de cholestérol d'un adulte équivalent.



D'après Owen, et coll, 2002, Pediatrics

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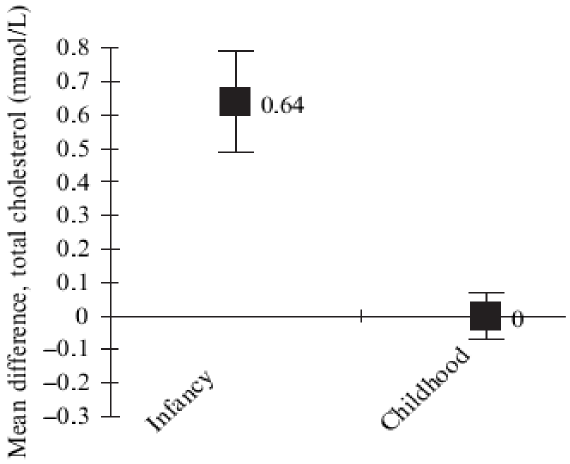

D'après Owen, et coll, 2002, Pediatrics

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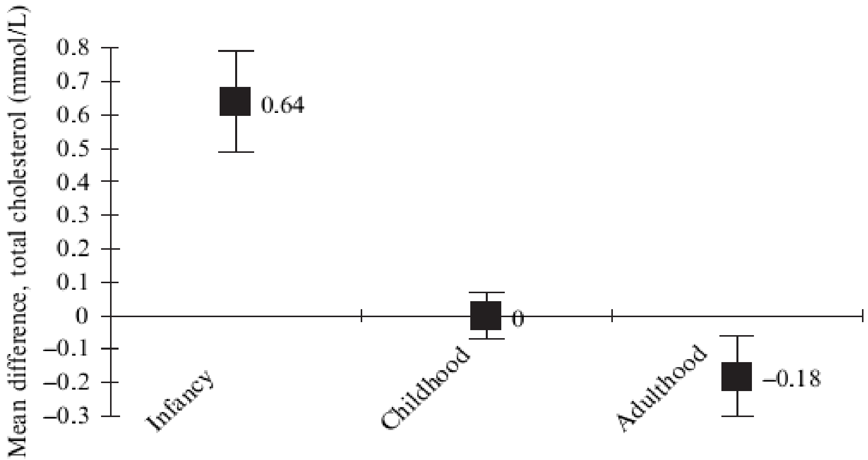


D'après Owen, et coll, 2002, Pediatrics

Effects of Early Cholesterol Intake on Cholesterol Biosynthesis and Plasma Lipids Among Infants Until 18 Months of Age

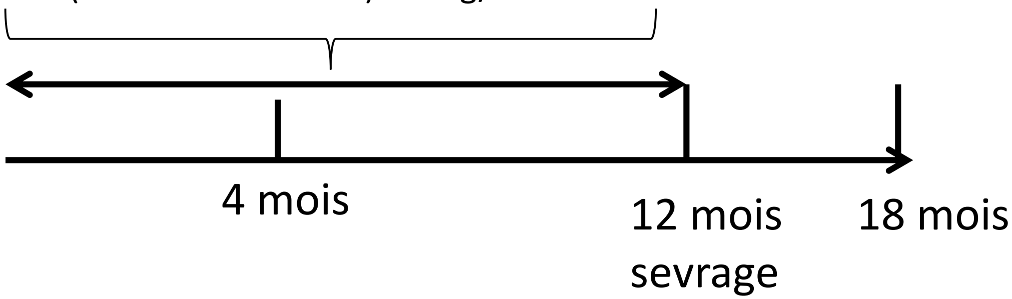
Théa A. Demmers, Peter J. H. Jones, Yanwen Wang, Susan Krug, Vivian Creutzinger and James E. Heubi

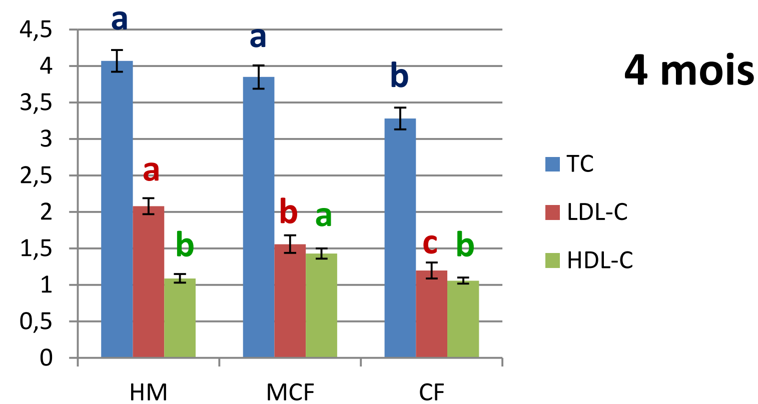
Pediatrics 2005;115:1594

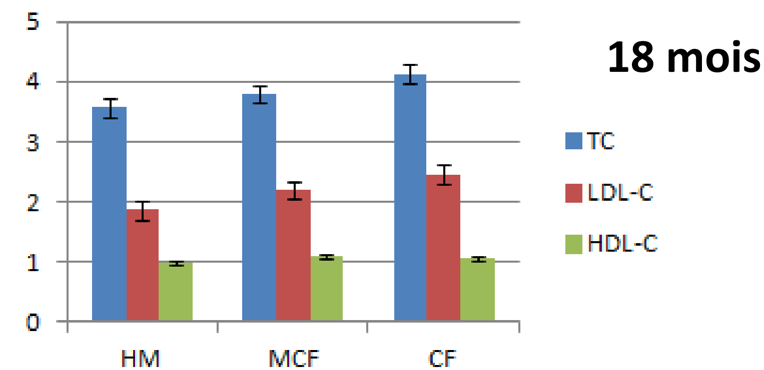
HM (human milk) 120mg/L

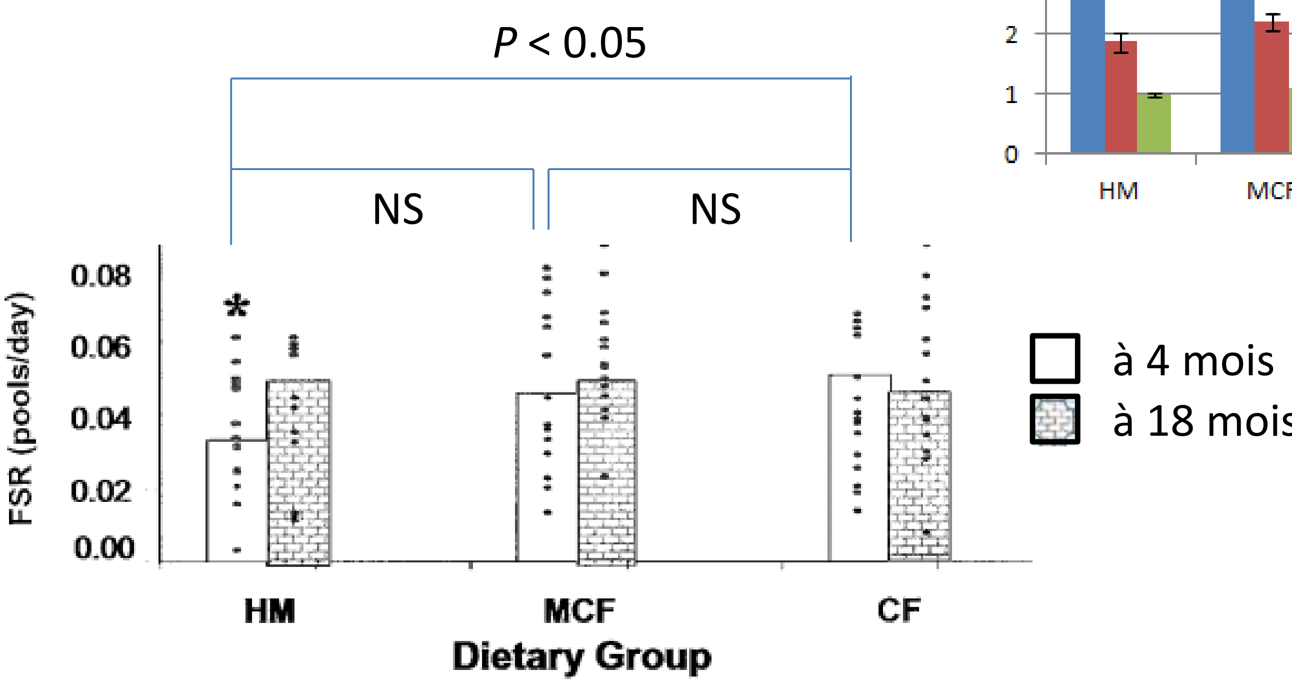
MCF (modified cow's milk formula) 80 mg/L

CF (cow's milk formula) 40 mg/L







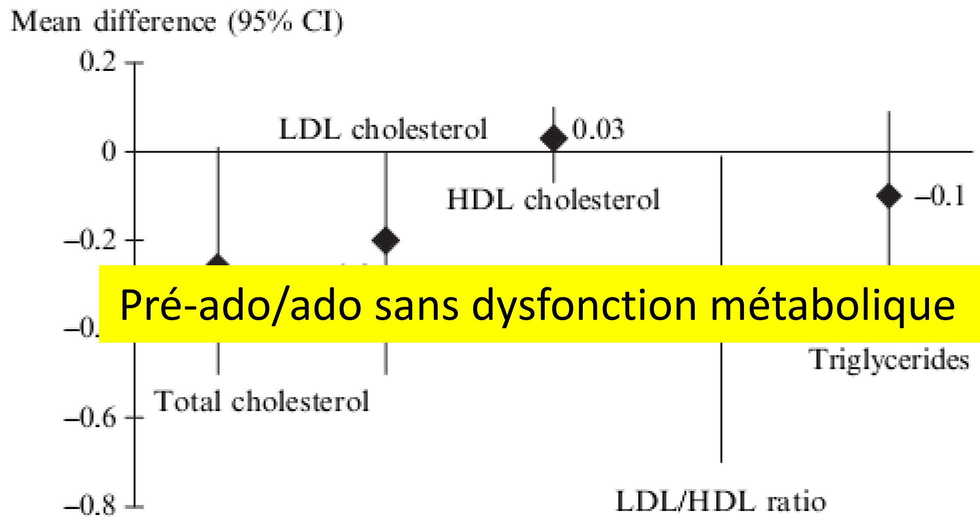


Breastmilk feeding and lipoprotein profile in adolescents born preterm: follow-up of a prospective randomised study

Lancet 2004; **363:** 1571–78

Atul Singhal, Tim J Cole, Mary Fewtrell, Alan Lucas

Prématurés allotés lait maternel (banque du lait, n=66) ou formule (n=64)
Suivi longitudinal pendant 13-16 ans



Pré-ado/ado sans dysfonction métabolique

Fig. 2 Breast milk feeding and lipoprotein profile in adolescents born preterm: banked breast milk (n=66) versus preterm formula (n=64). Mean differences are presented (mmol/L) with 95% confidence intervals (CI) (Based on data presented in Singhal et al. 2004)

Autres composés du lait maternel responsable de l'effet?

Modèles animaux

Mauvais modèle
pour métabolisme
cholestérol et MCV

Apports +/-
cholestérol
pendant
lactation

Rats

Effet cholestérol précoce

Reiser R, et al. Control of serum cholesterol homeostasis by cholesterol in the milk of the suckling rat. *J Nutr 102: 1009-1016, 1972.*

Durée vie 45 ans

Babouin à 4 ans et 7 ans

Pré-ado/ado
Espèce à LDL bas

Effet cholestérol précoce mais contradictoire et non reproductible

- **Lewis DS, eta l.** Deferred effects of preweaning diet on atherosclerosis in adolescent baboons. *Arteriosclerosis, Thrombosis, and Vascular Biology 8: 274-280, 1988.*
- **McGill HC, Jr., et al** Early determinants of adult metabolic regulation: effects of infant nutrition on adult lipid and lipoprotein metabolism. *Nutr Rev 54: S31-40, 1996.*
- **Mott GE,.et al** Cholesterol Metabolism in Adult Baboons Is Influenced by Infant Diet. *The Journal of Nutrition 120: 243-251, 1990.*

Others

Ya BL, et al. Dietary cholesterol alters memory and synaptic structural plasticity in young rat brain. *Neurol Sci 34: 1355-1365, 2013.*

Intermediary conclusion

Suspicion « d'indispensabilité » du cholestérol
Aucune étude exempte de biais, suivi clinique trop court, exposition exacte au cholestérol, état métabolomique sain
Études animales incomplètes, mauvais modèles

JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY

Sterol Composition in Infant Formulas and Estimated Intake

Lorena Claumarchirant,[†] Esther Matencio,[‡] Luis Manuel Sanchez-Siles,[‡] Amparo Alegría,[†] and María Jesús Lagarda*[,†]

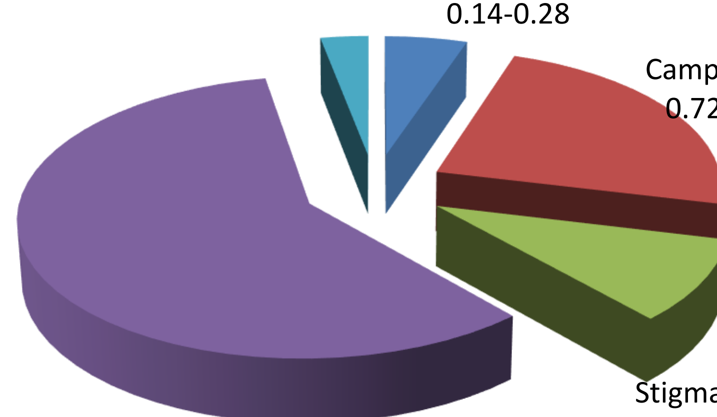
DOI: 10.1021/acs.jafc.5b02647
J. Agric. Food Chem. 2015, 63, 7245−7251

cholesterol (mg/100 mL)		desmosterol (mg/100 mL)	
IFs	human milk	human milk	ref
	9.7−11.0	0.6−1.3	Clark et al.[27]
	15.6−18.9	1.2−1.5	Kallio et al.[28]
	10.0−20.0		Jensen[29]
1.16−4.64	12.0−16.6		Huisman et al.[12]
0.3−25.8	6.5−18.4		Scopesi et al.[13]
	9.0−15.0		Koletzko et al.[7]
7.5−12.8	9.5−29.2	0.5−3.1	Ramalho et al.[14]
0.93−5.45	4.3−21.8[a]		Kamelska et al.[9]

x7

(~6mg/100mL) (~15mg/100mL)

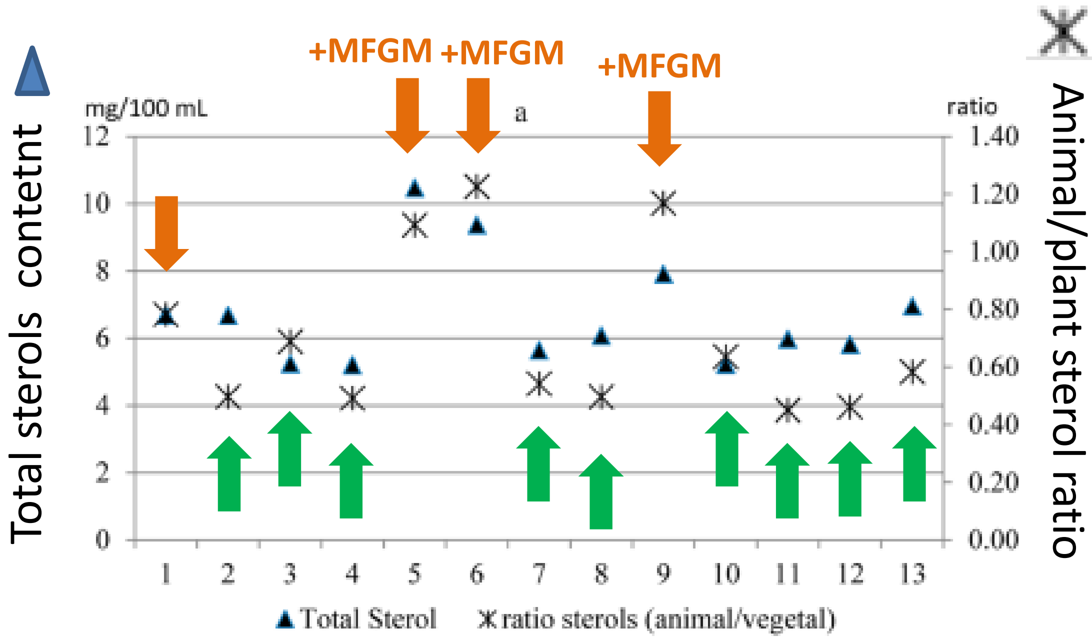
Total plant sterols in IF 3.9 ± 0.5 mg/mL



ANSES, Saisine n°2010-SA-0057, 2014

Sur la base de cette nouvelle évaluation, le CES « Nutrition Humaine » estime que les produits enrichis en phytostérols/stanols ne doivent pas être consommés par les enfants, quel que soit leur âge, sauf avis médical spécifique.

Including dairy fat

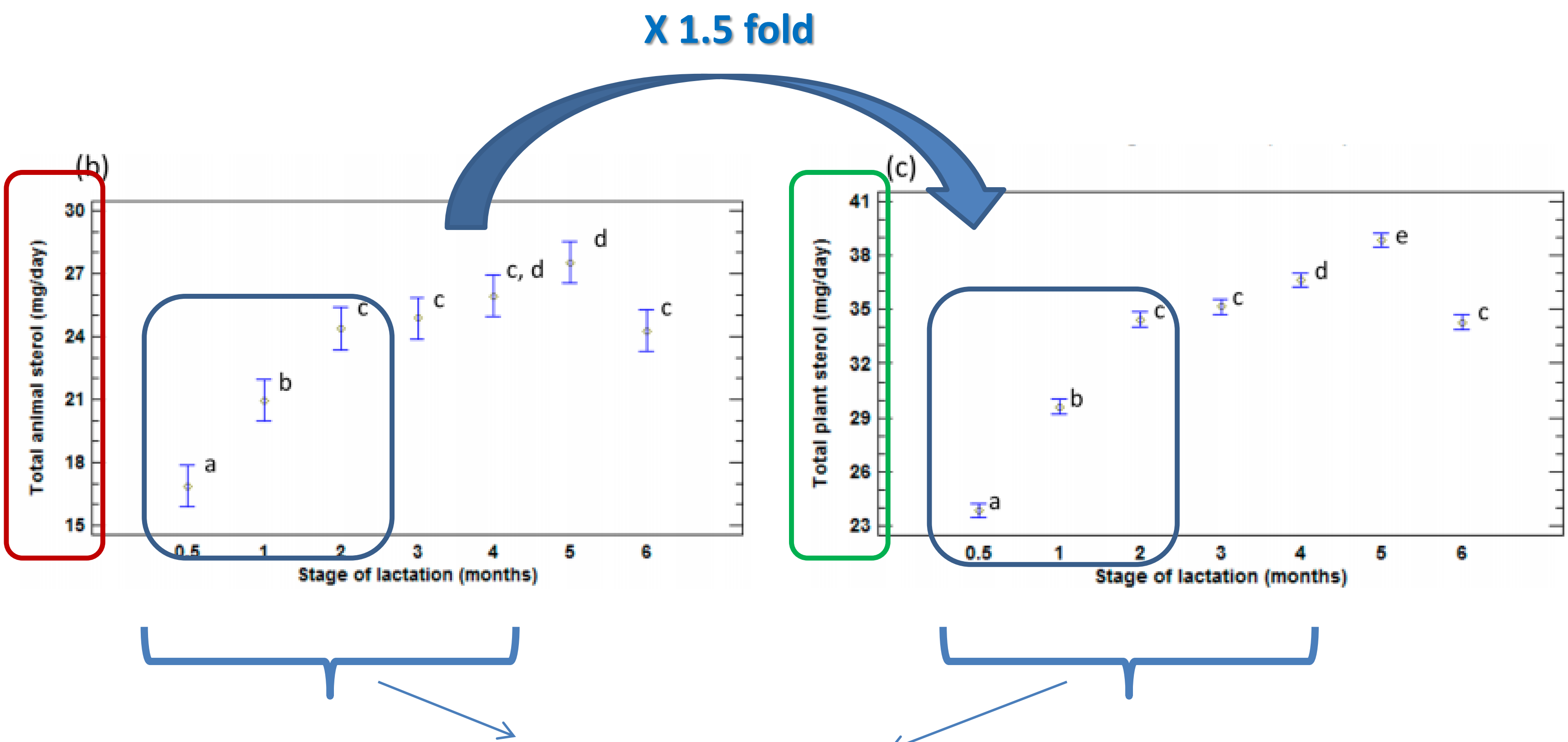


plant

All formulas contained whey proteins and/or skimmed milk that provide cholesterol

Total animal sterols (chol/desmo = 8.2) in IF = 2.78 ± 1.30 mg/mL

Total plant sterols in IF 3.9 ± 0.5 mg/mL



Sensitivity period for cholesterol synthesis

Cruz ML, et al. Effects of infant nutrition on cholesterol synthesis rates. *Pediatr Res 35: 135-140, 1994.*

Demmers T et al. Effects of early cholesterol intake on cholesterol biosynthesis and plasma lipids among infants until 18 months of age. *Pediatrics 115: 1594-1601, 2005.*

Plant sterol and cholesterol absorption in infants?

Joki P, et al. Cholesterol precursors and plant sterols in children with food allergy. ***Am J Clin Nutr 77: 51-55, 2003.***

1.7 year children

High plant sterols diet

High cholesterol neosynthesis

Serum cholesterol precursor and plant sterol concentrations in the 2 study groups and the control subjects[1]

	Group A (n = 21)	Group B (n = 31)	Control subjects (n = 18)	P
Δ^8-Cholestenol ($10^2 \times$ μmol/mmol cholesterol)	10.5 (6.8, 16.2)	12.9 (10.2, 16.3)	6.6 (4.3, 8.9)	0.005
Desmosterol ($10^2 \times$ μmol/mmol cholesterol)	86.2 (76.6, 97.2)	87.6 (78.6, 97.8)	77.3 (75.0, 79.6)	0.059
Lathosterol ($10^2 \times$ μmol/mmol cholesterol)	95.9 (72.5, 126.8)	95.4 (91.7, 123.5)	82.6 (80.3, 84.9)	0.040
Sitosterol ($10^2 \times$ μmol/mmol cholesterol)	202.4 (164.7, 248.6)	200.9 (161.6, 250.1)	140.2 (137.9, 142.5)	0.005
Campesterol ($10^2 \times$ μmol/mmol cholesterol)	363.6 (275.1, 481.1)	396.2 (322.5, 486.9)	244.3 (262.0, 266.6)	0.013

[1] Geometric $\bar{x}$; 95% CI in parentheses. There were no significant differences between group A and group B. P for comparison of data from allergic subjects combined with control subjects.

"Plant sterols may have inhibited cholesterol absorption, which in turn stimulated cholesterol synthesis in compensation, also explaining the increased precursor sterol ratios in serum in our subjects."

Interaction with cholesterol metabolism

Mellies M, Glueck CJ, Sweeney C, Fallat RW, Tsang RC, and Ishikawa TT. Plasma and dietary phytosterols in children. ***Pediatrics 57: 60-67, 1976.***

Age	Diet Group	Cholesterol Intake (mg/day)	Phytosterol Intake (mg/day)	
2 mo	24-oz formula	9.6	300	X 30
8.5 mo	32-oz formula	40.0	400	X 10

Plant sterols (mg/100mL plasma)	Vegetable Formulas (N=26)	Cow milk formula or breast milk (N=36)	
Campesterol	3.56 ± 0.70	0.68 ± 0.08	X 6
Stigmasterol	1.44 ± 0.28	0.66 ± 0.11	X 2
B-sitosterol	4.14 ± 0.44	0.89 ± 0.11	X 4.6

Plasma levels of phytosterols of infants (1-12months) fed with vegetable formulas or cow milk formulas or breast milk

Risques liés aux phytostérols en période néonatale

Syndrome de dysfonction hépatique liée à la dysfonction intestinale:

- cholestase
- Stéatose hépatique
- Bilirubine conjugué > 2mg/mL
- Dysfonction biliaire, cirrhose

***Nghiem-Rao TH**. Potential Hepatotoxicities of Intravenous Fat Emulsions in Infants and Children. Nutr Clin Pract 31: 619-628, 2016.*

Calculs biliaires pigmentaires

Koivusalo A, et al Relation of cholesterol metabolism to pediatric gallstone disease: a retrospective controlled study. *BMC Gastroenterol 15: 74.*

Dépôts vasculaires

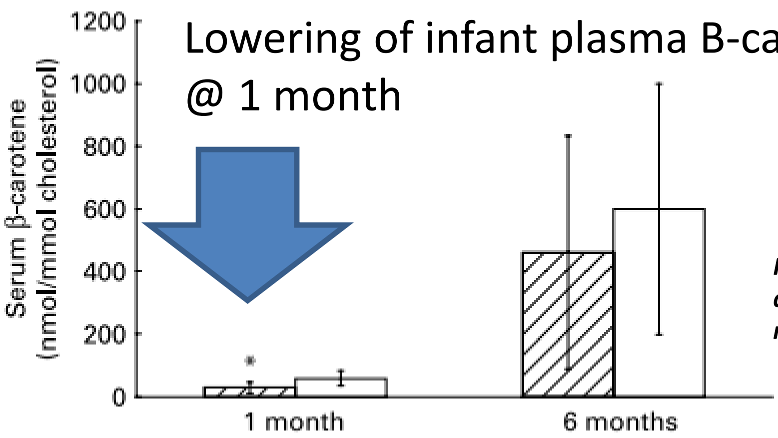
Mellies MJ, et al. Phytosterols in aortic tissue in adults and infants. *J Lab Clin Med 88: 914-921, 1976.*

Laitinen K, et al. Plant stanol ester spreads as components of a balanced diet for pregnant and breast-feeding women: evaluation of clinical safety. *Br J Nutr 101: 1797-1804, 2009.*

	Breast milk with infants' serum	
	R (*n* 20)	*P* value
Total cholesterol	0·234	0·321
Squalene	0·017	0·943
Cholestenol	−0·048	0·842
Desmosterol	0·306	0·189
Lathosterol	−0·082	0·730
Cholestanol	0·079	0·739
Campesterol	0·283	0·226
Sitosterol	0·216	0·361
Avenasterol	−0·404	0·077
Sitostanol	0·072	0·763

Phytosterols in breast milk of stanol-supplemented mothers did not impact the serum level of their breast-fed infant

≠ infant formulas



Lowering of infant plasma B-carotene @ 1 month

Impact on fat soluble vitamins?

Richelle M, et al . Both free and esterified plant sterols reduce cholesterol absorption and the bioavailability of beta-carotene and alpha-tocopherol in normocholesterolemic humans. Am J Clin Nutr 80: 171-177, 2004.

Phytochemicals in neonatal period: towards a new sight in pediatric nutrition?

Early infancy is a period of very high oxidative stress

Friel JK, et al. Evidence of oxidative stress in full-term healthy infants. *Pediatr Res 56: 878-882, 2004.*

Breast milk has antioxidant properties

Yao L, et al. Antioxidant properties of breast milk in a novel in vitro digestion/enterocyte model. *J Pediatr Gastroenterol Nutr 50: 670-676, 2010.*

Phytochemicals & metabolites from recent mother intake can be secreted into breast milk

Khymenets O,. Dietary Epicatechin Is Available to Breastfed Infants through Human Breast Milk in the Form of Host and Microbial Metabolites. *J Agric Food Chem 64: 5354-5360, 2016.*

Song BJ, et al. Assessment of phytochemical content in human milk during different stages of lactation. *Nutrition 29: 195-202, 2013.*

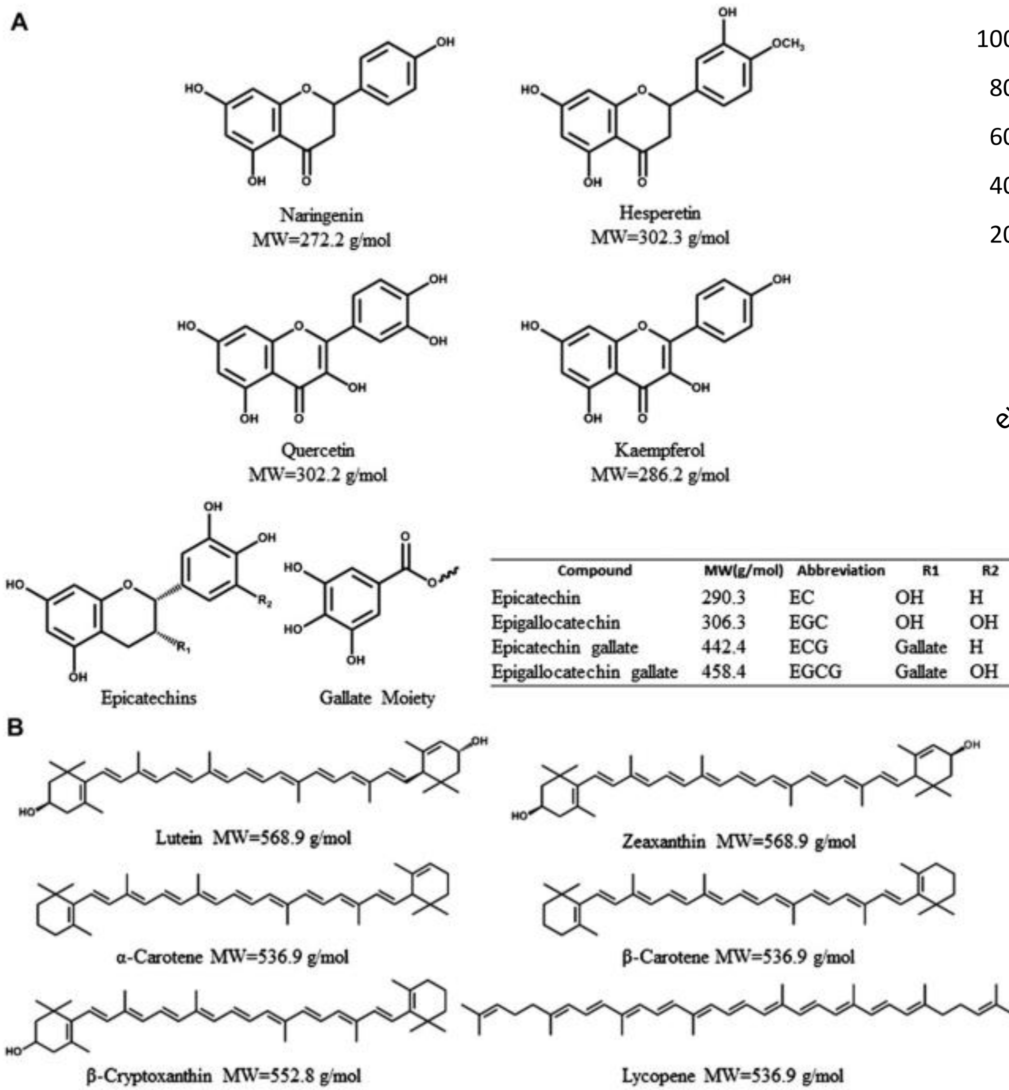
The antioxidant properties of breast milk can be improved by phytochemical intake

Codoner-Franch P,. Diet supplementation during early lactation with non-alcoholic beer increases the antioxidant properties of breastmilk and decreases the oxidative damage in breastfeeding mothers. *Breastfeed Med 8: 164-169, 2013.*

Perrone S et al. Oxidative stress and antioxidant strategies in newborns. *J Matern Fetal Neonatal Med 23 Suppl 3: 63-65, 2010.*

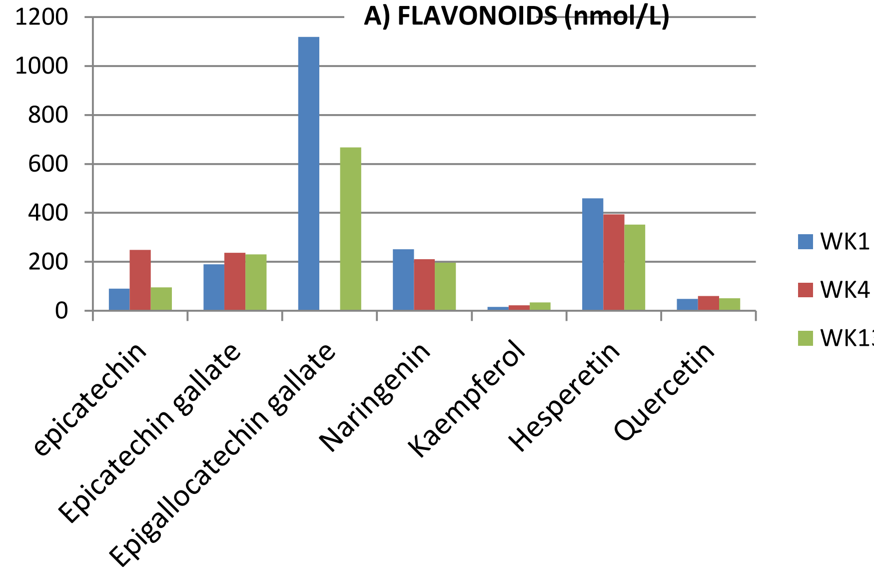
Can phytochemicals found in breast milk _or added to infant formulas_ lower the early infancy oxidative stress?
What kind of phytochemicals (and/or metabolites)?

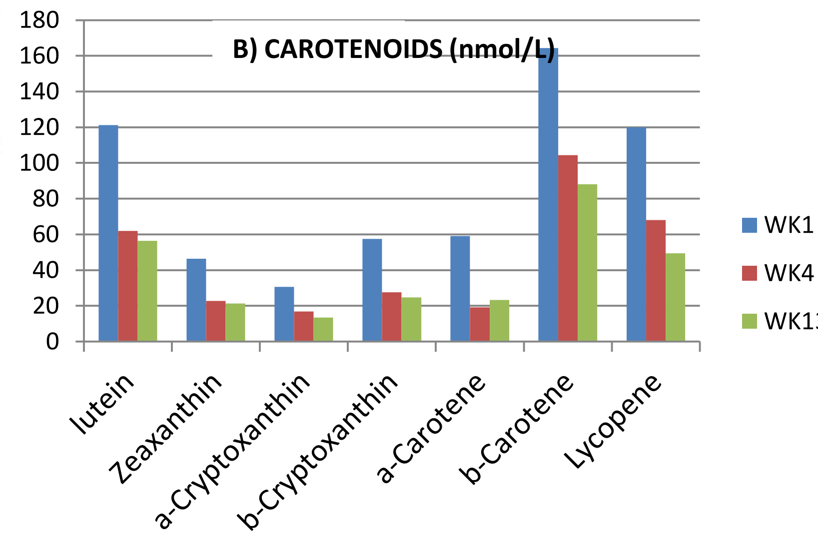
Major phytochemicals found in human breast milk (excluding phytosterols)



Compound	MW(g/mol)	Abbreviation	R1	R2
Epicatechin	290.3	EC	OH	H
Epigallocatechin	306.3	EGC	OH	OH
Epicatechin gallate	442.4	ECG	Gallate	H
Epigallocatechin gallate	458.4	EGCG	Gallate	OH

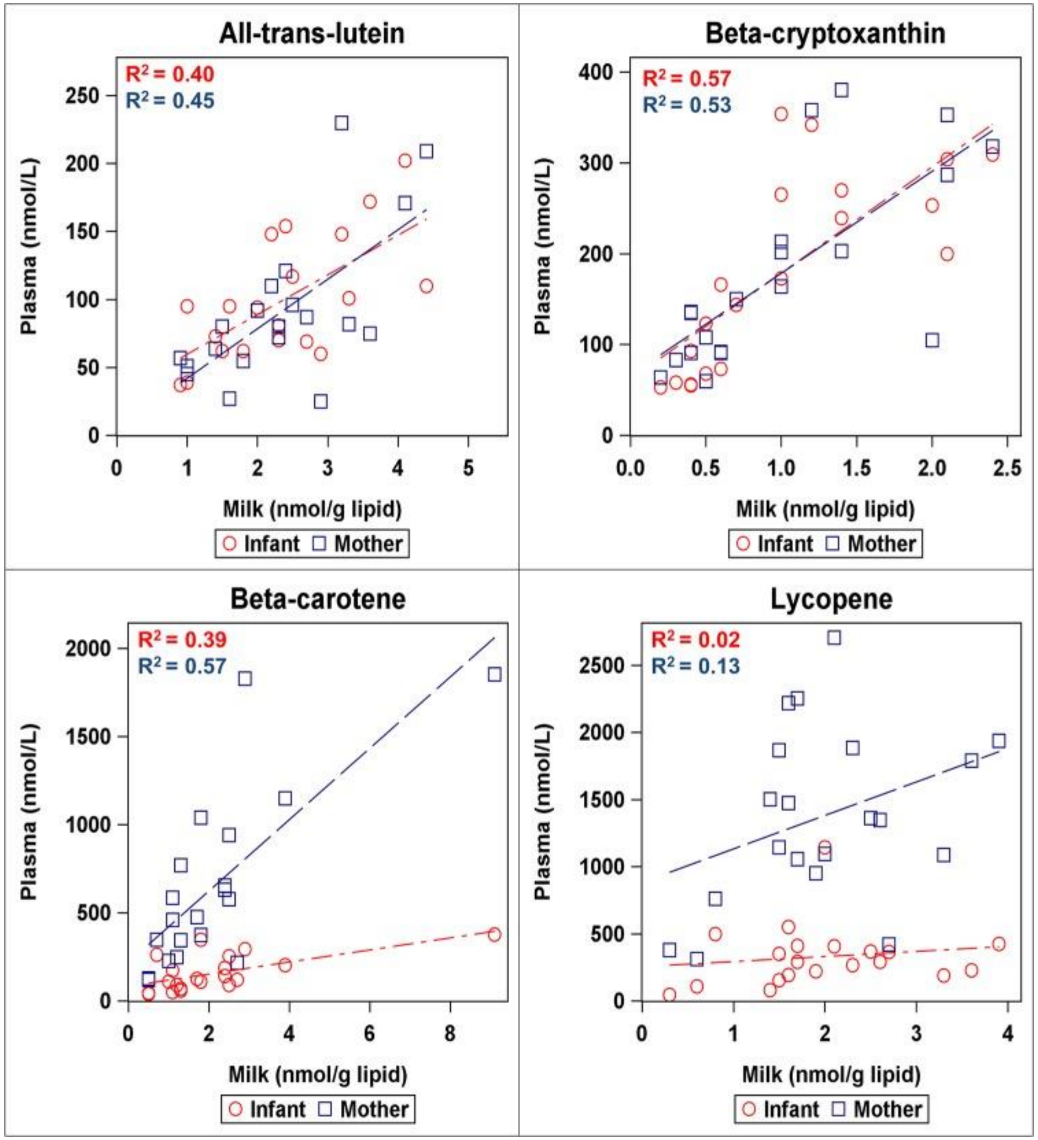
Fig. 1. Structure of (A) major flavonoid and (B) carotenoid compounds commonly found in fruits and vegetables and detected in human milk. MW, molecular weight.



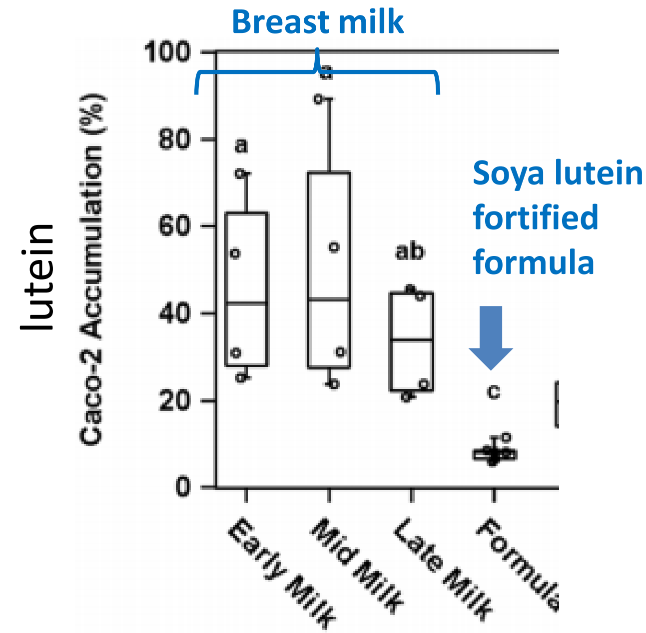


Song BJ, Jouni ZE, and Ferruzzi MG. Assessment of phytochemical content in human milk during different stages of lactation. Nutrition 29: 195-202, 2013.

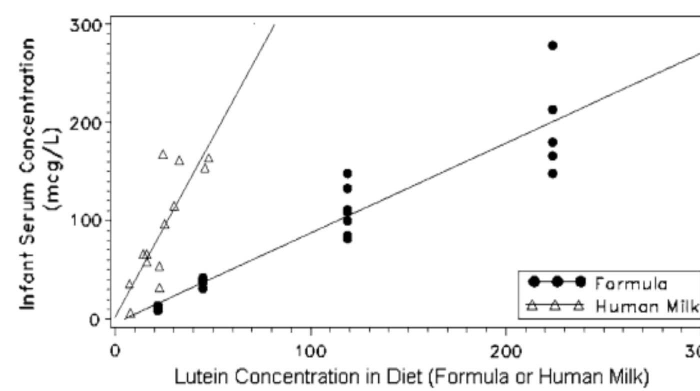
Mother_breast fed infant carotenoids transfer



Lipkie TE, et al. Longitudinal Survey of Carotenoids in Human Milk from Urban Cohorts in China, Mexico, and the USA. *PLoS One 10: e0127729, 2015.*

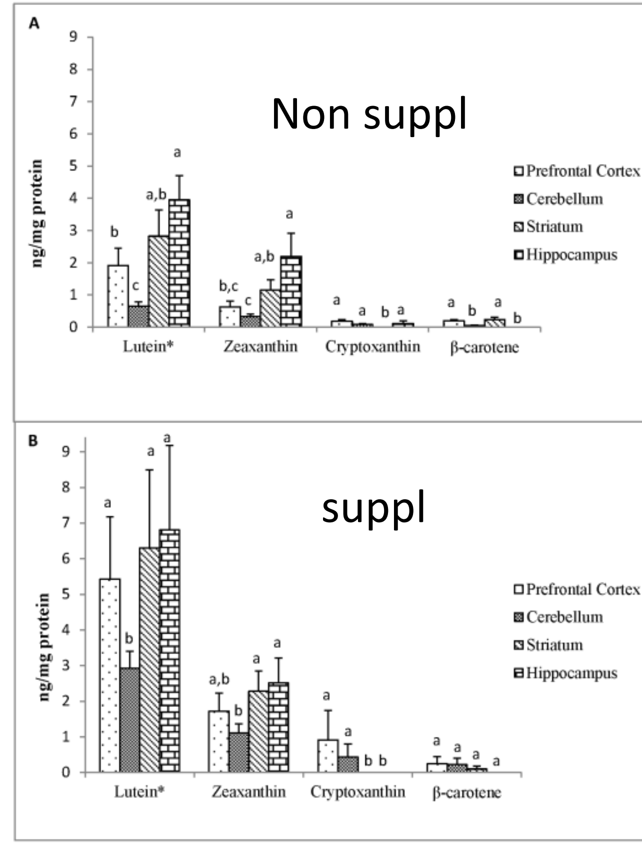


Lipkie TE, et al. Caco-2 accumulation of lutein is greater from human milk than from infant formula despite similar bioaccessibility. *Mol Nutr Food Res 58: 2014-2022, 2014.*



Bettler J,. Serum lutein concentrations in healthy term infants fed human milk or infant formula with lutein. *Eur J Nutr 49: 45-51, 2010.*

Rhesus macaques

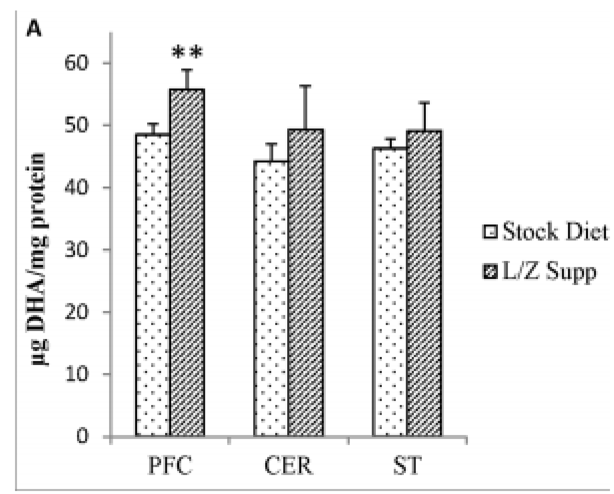


DHA non-enzymatic oxidation products

Table 3. Partial correlations between membrane lutein# and neuroprostanes and isoprostanes from different brain regions of rhesus macaques (n = 11^).

	Total	Nuclear	Myelin	Neuronal	Mitochondrial
			Neuroprostanes		
Prefrontal Cortex	-0.48	--	-0.48	--	**-0.69****
Cerebellum	--	--	--	--	-0.48
Striatum	-0.59*	--	-0.59*	-0.48	**-0.68****
			Isoprostanes		
Prefrontal Cortex	-0.60*	--	--	-0.51	-0.53
Cerebellum	--	--	--	--	--
Striatum	--	--	--	--	--

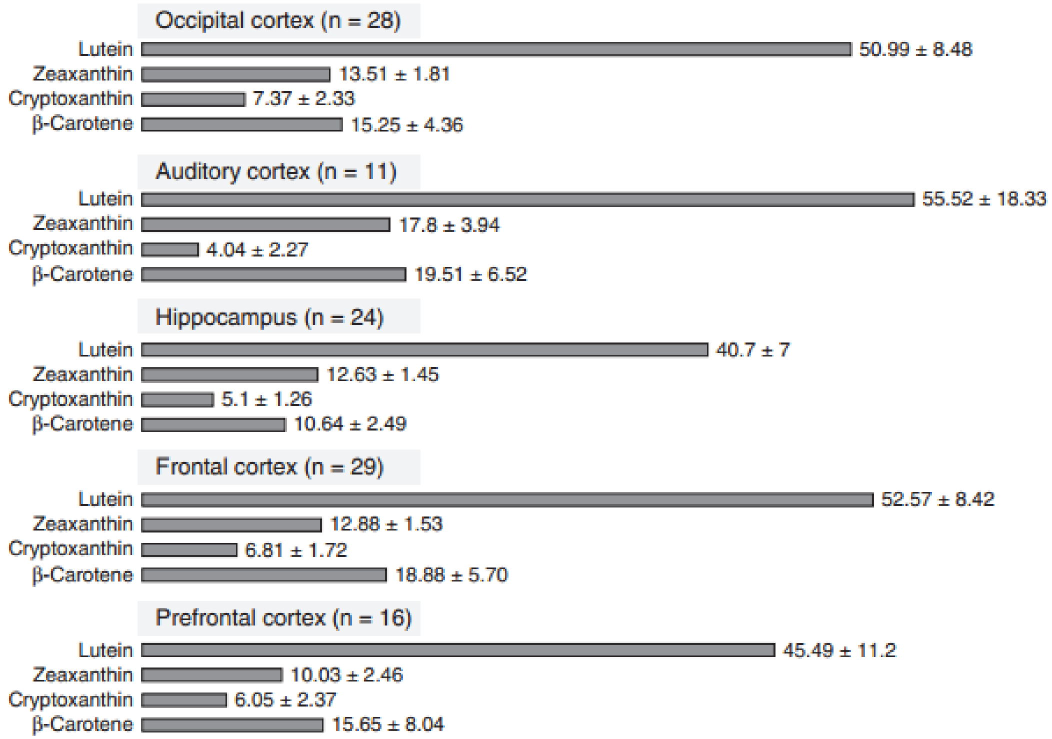
log transformed;



Mohn ES, et al. Lutein accumulates in subcellular membranes of brain regions in adult rhesus macaques: Relationship to DHA oxidation products. PLoS One 12: e0186767, 2017.

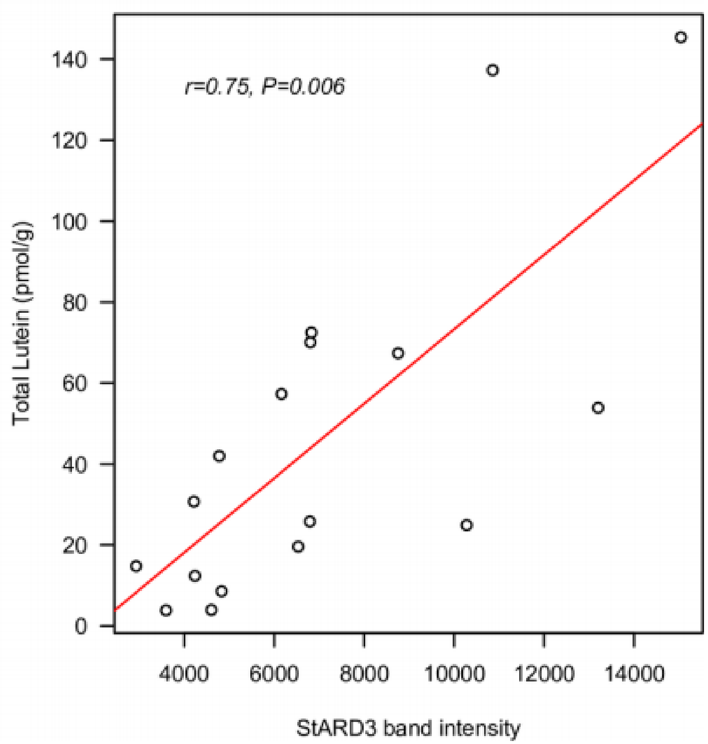
Carotenoids in infant brain

(Decedent age ranged 1-488 days)

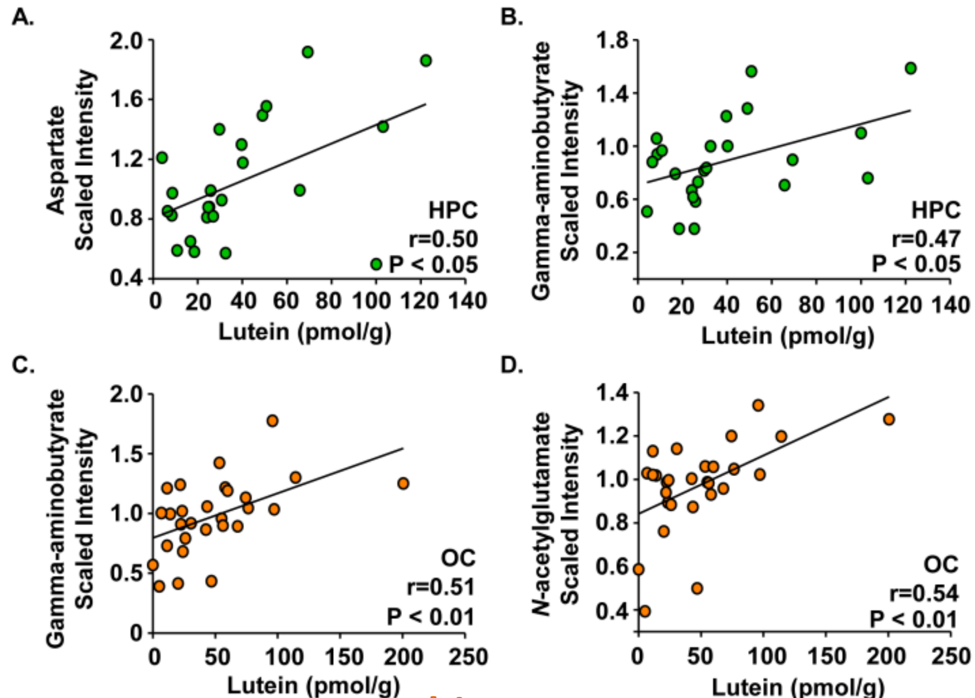


Vishwanathan R, et al. Lutein and preterm infants with decreased concentrations of brain carotenoids. *J Pediatr Gastroenterol Nutr 59: 659-665, 2014.*

Lutein in infant brain



Occipital cortex



hippocampus

Tanprasertsuk J, et al. Relationship between Concentrations of Lutein and StARD3 among Pediatric and Geriatric Human Brain Tissue. *PLoS One 11: e0155488, 2016.*

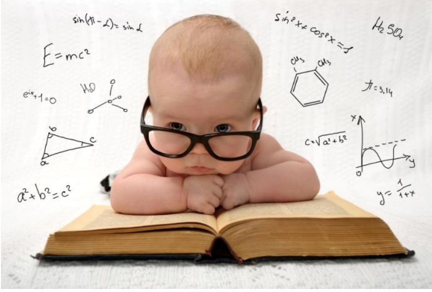
Lieblein-Boff JC, et al. Exploratory Metabolomic Analyses Reveal Compounds Correlated with Lutein Concentration in Frontal Cortex, Hippocampus, and Occipital Cortex of Human Infant Brain. *PLoS One 10: e0136904, 2015.*

carotenoids, cognition and neurological outcome (adults & elderly)

Renzi-Hammond LM et al. Effects of a Lutein and Zeaxanthin Intervention on Cognitive Function: A Randomized, Double-Masked, Placebo-Controlled Trial of Younger Healthy Adults. ***Nutrients 9: 2017.***

Johnson EJ, et al. Cognitive findings of an exploratory trial of docosahexaenoic acid and lutein supplementation in older women. ***Nutr Neurosci 11: 75-83, 2008.***

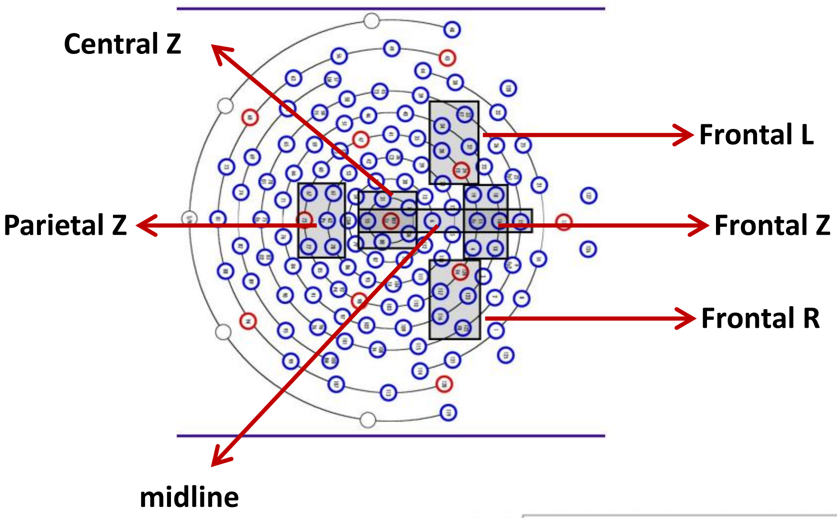
Results: Following supplementation, verbal fluency scores improved significantly in the DHA, lutein, and combined treatment groups ($P < 0.03$). Memory scores and rate of learning improved significantly in the combined treatment group ($P < 0.03$), who also displayed a trend toward more efficient learning ($P = 0.07$). Measures of mental processing speed, accuracy and mood were not



carotenoids, cognition and neurological outcome

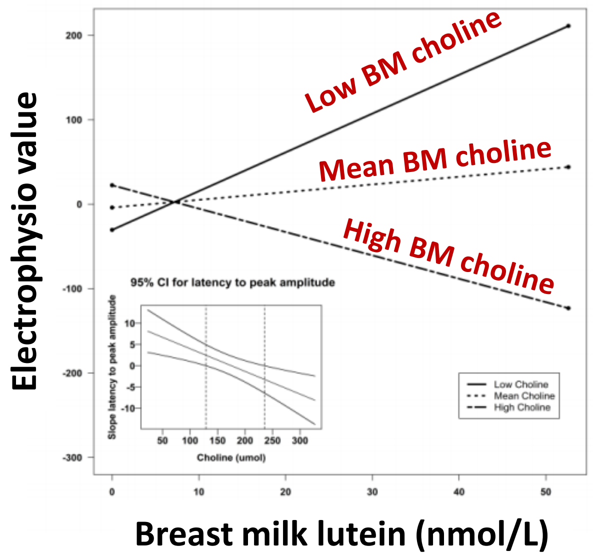
Cheatham CL, et al. Synergistic Effects of Human Milk Nutrients in the Support of Infant Recognition Memory: An Observational Study. ***Nutrients 7: 9079-9095, 2015.***

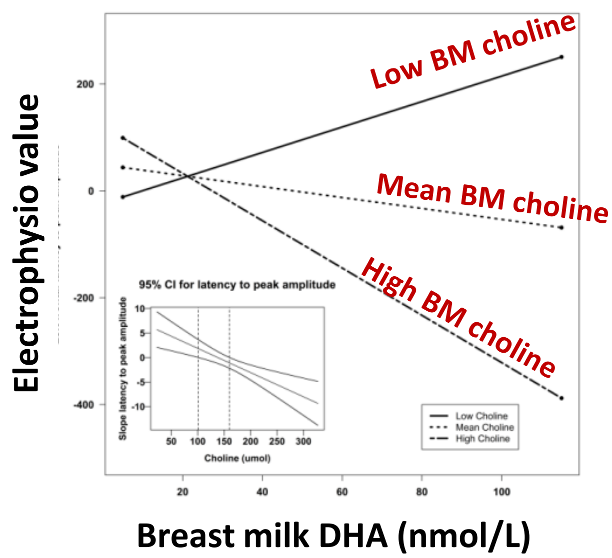
55 six months old infants



5. Conclusions

The finding that choline and DHA as well as choline and lutein are working together in support of infant brain development and subsequent cognitive development is important. Since both lines of

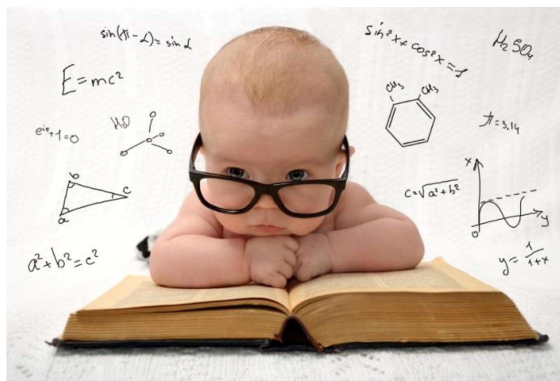




Polyphenols (flavonoids), cognition and neurological outcome

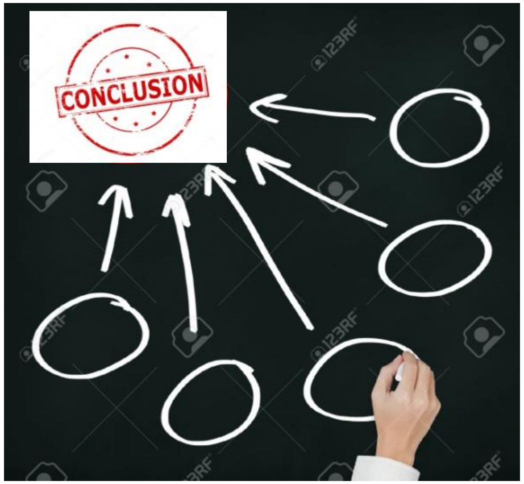
Bell Let al. A Review of the Cognitive Effects Observed in Humans Following Acute Supplementation with Flavonoids, and Their Associated Mechanisms of Action. ***Nutrients 7: 10290-10306, 2015.***

8-10 years children
Adult
Elderly



Infants?

Soja flavonoids (vegetal nd genistein (phytoestrogens)



Breast fed infant is hypercholesterolemic whereas formula fed is not = impact on early life chol neosynthesis

Is this first hit responsible of the lesser CVD risk of BF infants vs FF infants ? (cholesterol imprinting theory)

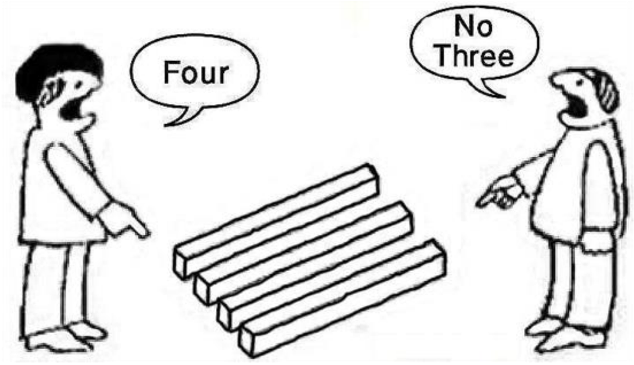
Cholesterol intake can modulate neurodevelopment in early life (rat)

In FF infants Phystosterols intake of 1.5 fold higher than cholesterol intake = increase plasma phytosterol, impact on cholesterol metabolism and on absorption of (some?) fat-soluble vitamins

Aside phytosterols, flavonoids and carotenoids are the major phytochemicals in breast milk= improve antioxidant capabilities

Lutein is the main carotenoids accumulated in the CNS= improve oxidant stress defense and neurodevelopment in human infants

Innovative perspectives



Public safety

Resolve the cholesterol imprinting theory

ANR BabyChol (Isabelle Luron),
epidemiology (EDEN, ELFE)

Characterize the health effects of high intake of phystosterols in infant fed vegetable based formulas (else **remove**!!!)

Gain new results of the effects of phytochemical on infant neurodevelopment and antioxidant status (including formula protection)

Flavonoids = brand new!

Impact of nutrients interaction (DHA & Lutein)


Merci de votre ATTENTION
(Les calanques, Marseille)
jean-charles.martin@univ-amu.fr
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