

## SUPPLEMENTARY MATERIAL

### **LC-PUFA enrichment in infant formula and neurodevelopment up to age 3.5 years in the French nationwide ELFE birth cohort**

Pauline Martinot<sup>a</sup>, Moufidath Adjibade<sup>a</sup>, Marion Taine<sup>a</sup>, Camille Davaisse-Paturet<sup>a</sup>, Sandrine Lioret<sup>a</sup>, Marie-Aline Charles<sup>a,b</sup>, Blandine de Lauzon-Guillain<sup>a,\*</sup>, Jonathan Y. Bernard<sup>a,c,\*</sup>

<sup>a</sup> Université de Paris, Centre for Research in Epidemiology and Statistics (CRESS), Inserm, INRAE, F-75004 Paris, France

<sup>b</sup> Unité mixte Inserm-Ined-EFS ELFE, Ined, F-75020 Paris, France

<sup>c</sup> Singapore Institute for Clinical Sciences (SICS), Agency for Science, Technology and Research (A\*STAR), Singapore, Singapore

\*Blandine de Lauzon-Guillain and Jonathan Bernard contributed equally to this work.

#### **Corresponding author**

Blandine de Lauzon-Guillain, blandine.delauzon@inserm.fr

**Supplementary table 1.** Associations between consumption of LC-PUFA–enriched formula and child’s neurodevelopment up to 3.5 years in complete-case samples.

	Child Development Inventory 1 year (n=7,038)	MacArthur Bates Communicative Development Inventory 2 years (n=6,202)	Child Development Inventory 3.5 years (n=5,707)	British Ability Scale 3.5 years (n=4,556)
<b>2-month LC-PUFA enrichment</b>				
Unadjusted analyses <sup>1</sup>	0.1	0.06	1	0.6
Not enriched	0 [Ref]	0 [Ref]	0 [Ref]	0 [Ref]
Enriched	-0.22 [-0.49 ; 0.05]	1.23 [-0.05 ; 2.52]	0.00 [-0.28 ; 0.27]	-0.45 [-2.20 ; 1.30]
Adjusted analyses <sup>3</sup>	0.1	0.6	0.03	0.1
Not enriched	0 [Ref]	0 [Ref]	0 [Ref]	0 [Ref]
Enriched	-0.19 [-0.44 ; 0.06]	0.29 [-0.94 ; 1.53]	-0.32 [-0.62 ; -0.03]	-1.43 [-3.17 ; 0.31]
Weighted analyses <sup>4</sup>	0.5	0.4	0.1	0.6
Not enriched	0 [Ref]	0 [Ref]	0 [Ref]	0 [Ref]
Enriched	-0.13 [-0.50 ; 0.23]	-0.82 [-2.86 ; 1.22]	-0.42 [-0.94 ; 0.09]	-0.76 [-3.71 ; 2.18]
<b>2-month LC-PUFA enrichment category</b>				
Unadjusted analyses <sup>1</sup>	0.05	0.04	0.6	0.7
Not enriched	0 [Ref]	0 [Ref]	0 [Ref]	0 [Ref]
DHA/ARA only	-0.09 [-0.39 ; 0.20]	1.79 [0.35 ; 3.22]	0.07 [-0.25 ; 0.38]	-0.71 [-2.67 ; 1.25]
DHA/ARA and EPA	-0.53 [-0.95 ; -0.10]	-0.15 [-2.21 ; 1.91]	-0.17 [-0.61 ; 0.27]	0.18 [-2.60 ; 2.97]
Adjusted analyses <sup>3</sup>	<b>0.04</b>	0.2	0.09	0.2
Not enriched	0 [Ref]	0 [Ref]	0 [Ref]	0 [Ref]
DHA/ARA only	-0.06 [-0.34 ; 0.21]	0.81 [-0.57 ; 2.19]	-0.29 [-0.62 ; 0.04]	-1.62 [-3.57 ; 0.32]
DHA/ARA and EPA	-0.51 [-0.91 ; -0.11]	-1 [-2.97 ; 0.97]	-0.41 [-0.88 ; 0.06]	-0.97 [-3.73 ; 1.79]
Weighted analyses <sup>4</sup>	0.06	0.4	0.3	0.3
Not enriched	0 [Ref]	0 [Ref]	0 [Ref]	0 [Ref]
DHA/ARA only	0.05 [-0.36 ; 0.46]	-0.14 [-2.43 ; 2.15]	-0.48 [-1.11 ; 0.14]	-1.76 [-5.09 ; 1.57]

DHA/ARA and EPA	-0.59 [-1.12 ; -0.07]	-2.48 [-5.86 ; 0.90]	-0.28 [-0.91 ; 0.35]	1.65 [-2.63 ; 5.92]	
2- to 10-month LC-PUFA enrichment <sup>2</sup>					
Unadjusted analyses <sup>1</sup>		0.2	0.9	0.4	0.5
Never enriched	0 [Ref]	0 [Ref]	0 [Ref]	0 [Ref]	
Enrichment up to 6 months	-0.12 [-0.45 ; 0.21]	-0.09 [-1.68 ; 1.50]	-0.23 [-0.57 ; 0.11]	-1.27 [-3.38 ; 0.84]	
Enrichment from 2 to 10 months	-0.44 [-0.94 ; 0.05]	-0.52 [-2.88 ; 1.85]	-0.08 [-0.58 ; 0.41]	-0.39 [-3.49 ; 2.71]	
Adjusted analyses <sup>3</sup>		0.3	0.2	0.07	0.2
Never enriched	0 [Ref]	0 [Ref]	0 [Ref]	0 [Ref]	
Enrichment up to 6 months	-0.19 [-0.50 ; 0.12]	-0.74 [-2.27 ; 0.78]	-0.39 [-0.75 ; -0.04]	-1.76 [-3.86 ; 0.35]	
Enrichment from 2 to 10 months	-0.30 [-0.77 ; 0.16]	-1.92 [-4.21 ; 0.37]	-0.34 [-0.87 ; 0.18]	-1.64 [-4.77 ; 1.48]	
Weighted analyses <sup>4</sup>		0.1	0.09	0.03	0.6
Never enriched	0 [Ref]	0 [Ref]	0 [Ref]	0 [Ref]	
Enrichment up to 6 months	-0.15 [-0.57 ; 0.27]	-2.06 [-4.45 ; 0.34]	-0.75 [-1.44 ; -0.06]	-1.93 [-5.54 ; 1.68]	
Enrichment from 2 to 10 months	-0.60 [-1.19 ; 0.00]	-3.05 [-6.49 ; 0.38]	-0.98 [-1.90 ; -0.05]	-0.53 [-5.29 ; 4.24]	

Data are estimates (95% confidence interval) from <sup>1</sup> simple linear regressions; <sup>2</sup> linear regressions adjusted for familial characteristics (maternal age, education level, migration status, employment during pregnancy, smoking status, pre-pregnancy BMI, household income and, number of older children, rural/urban area and region of residence), maternal diet during pregnancy (fish intake, consumption of dietary supplements with LC-PUFA), infant characteristics (sex, gestational age, birth weight category, type of physician consulted after discharge), 2-month breastfeeding status, maternal stimulation and variables related to study design (maternity size and recruitment wave), as well as the child's exact age at neurodevelopmental assessment, except for the British Ability Scale; <sup>3</sup> linear regressions were adjusted for the same variables as the previous models, but applying weighting to take the inclusion procedure and biases related to non-consent and attrition into account; <sup>4</sup> for 2- to 10-month trajectories of LC-PUFA enrichment, the sample size was 5,613 for the 1-year Child Development Inventory, 5,121 for the 2-year McArthur Bates Communicative Development Inventory, 3,038 for the 3.5-year Child Development Inventory and 3,038 for the 3.5-year British Ability Scale.

**Supplementary table 2.** Adjusted associations between consumption of LC-PUFA–enriched formula and child neurodevelopment up to 3.5 years in specific complete-case subsamples.

	Child Development Inventory at 1 year	MacArthur Bates Communicative Development Inventory at 2 years	Child Development Inventory at 3.5 years	British Ability Scale at 3.5 years
<b>Among never-breastfed children</b>				
N	2729	2332	1622	1653
2-month LC-PUFA enrichment	0.4	0.9	0.1	0.2
Not enriched	0 [Ref]	0 [Ref]	0 [Ref]	0 [Ref]
Enriched	-0.20 [-0.61 ; 0.22]	0.18 [-1.91 ; 2.27]	-0.39 [-0.90 ; 0.13]	-2.11 [-5.13 ; 0.91]
2-month LC-PUFA enrichment category	0.1	0.03	0.3	0.1
Not enriched	0 [Ref]	0 [Ref]	0 [Ref]	0 [Ref]
DHA/ARA only	0 [-0.46 ; 0.45]	1.48 [-0.82 ; 3.79]	-0.31 [-0.88 ; 0.26]	-0.94 [-4.28 ; 2.40]
DHA/ARA and EPA	-0.77 [-1.48 ; -0.06]	-3.64 [-7.19 ; -0.08]	-0.61 [-1.49 ; 0.28]	-5.56 [-10.76 ; -0.36]
2- to 10-month LC-PUFA enrichment	1	0.9	0.3	0.7
Never enriched	0 [Ref]	0 [Ref]	0 [Ref]	0 [Ref]
Enrichment up to 6 months	-0.05 [-0.56 ; 0.46]	-0.70 [-3.29 ; 1.89]	-0.52 [-1.15 ; 0.10]	-0.95 [-4.63 ; 2.72]
Enrichment from 2 to 10 months	-0.07 [-0.86 ; 0.72]	-0.03 [-3.92 ; 3.86]	-0.07 [-1.01 ; 0.87]	1.82 [-3.77 ; 7.40]
<b>Among children consuming the same formula from birth or breastfeeding cessation to 2 months</b>				
N	3698	3231	2330	2370
2-month LC-PUFA enrichment	0.8	0.4	0.3	0.2
Not enriched	0 [Ref]	0 [Ref]	0 [Ref]	0 [Ref]
Enriched	-0.05 [-0.39 ; 0.29]	0.72 [-1 ; 2.45]	-0.21 [-0.62 ; 0.20]	-1.43 [-3.83 ; 0.98]
2-month LC-PUFA enrichment category	0.6	0.3	0.6	0.5

Not enriched	0 [Ref]	0 [Ref]	0 [Ref]	0 [Ref]
DHA/ARA only	0.05 [-0.35 ; 0.45]	1.42 [-0.59 ; 3.43]	-0.21 [-0.69 ; 0.28]	-1.24 [-4.06 ; 1.58]
DHA/ARA and EPA	-0.21 [-0.70 ; 0.27]	-0.42 [-2.85 ; 2.01]	-0.21 [-0.78 ; 0.36]	-1.72 [-5.07 ; 1.63]
2- to 10-month LC-PUFA enrichment	0.4	0.5	0.7	0.9
Never enriched	0 [Ref]	0 [Ref]	0 [Ref]	0 [Ref]
Enrichment up to 6 months	-0.24 [-0.68 ; 0.20]	-1.32 [-3.53 ; 0.90]	-0.21 [-0.72 ; 0.31]	-0.69 [-3.71 ; 2.33]
Enrichment from 2 to 10 months	-0.27 [-0.85 ; 0.31]	-0.52 [-3.41 ; 2.38]	-0.06 [-0.72 ; 0.60]	0.32 [-3.59 ; 4.23]

Data are estimates (95% confidence interval) from linear regressions adjusted for familial characteristics (maternal age, education level, migration status, employment during pregnancy, smoking status, pre-pregnancy BMI, household income and, number of older children, rural/urban area and region of residence), maternal diet during pregnancy (fish intake, consumption of dietary supplements with LC-PUFA), infant characteristics (sex, gestational age, birth weight category, type of physician consulted after discharge), 2-month breastfeeding status, maternal stimulation and variables related to study design (maternity size and recruitment wave), as well as the child's exact age at neurodevelopmental assessment, except for the British Ability Scale.