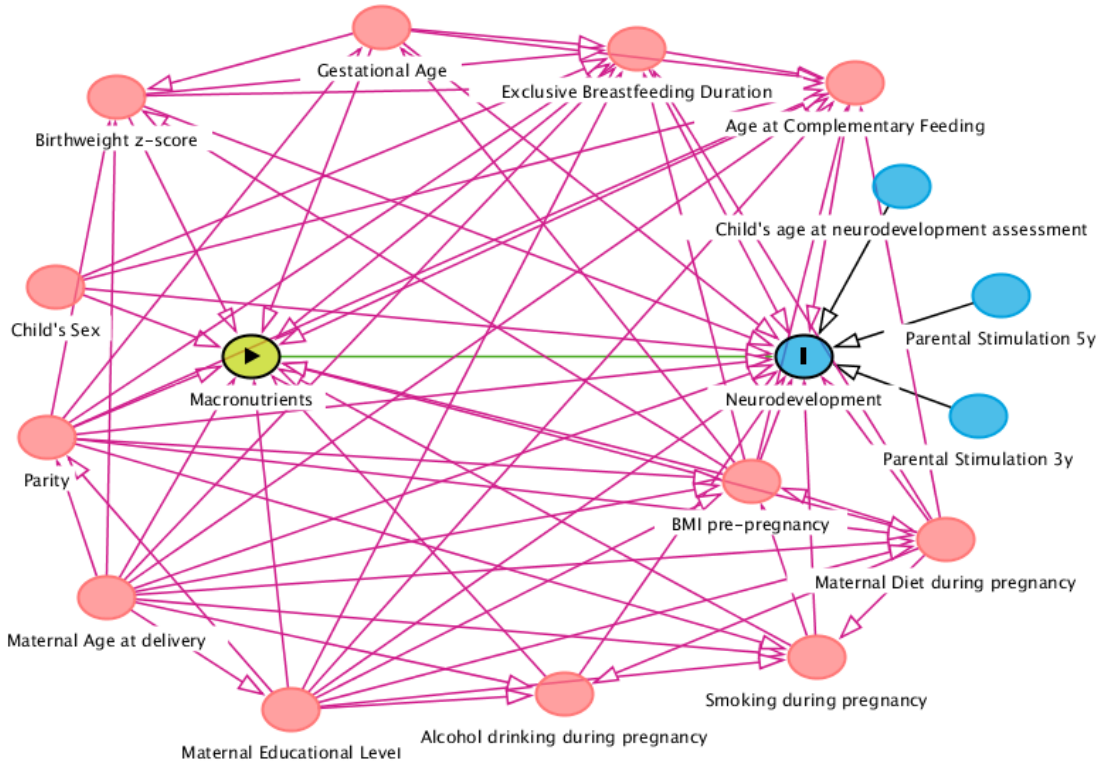


ON-LINE SUPPLEMENTARY MATERIAL

**Macronutrient intake during infancy and neurodevelopment
in preschool children from the EDEN mother-child cohort**

A.R. Marinho, D. Correia, J.Y. Bernard, B. Heude, C. Lopes, B. de Lauzon-Guillain



Supplementary figure S1. Direct Acyclic Graph for the associations between 12-month macronutrient intake and neurodevelopmental outcomes.

Here, the green circle with the triangle is the main exposure (macronutrient intake in infancy) and the blue circle with the “I” is the outcome (neurodevelopmental scores). Potential confounders are depicted by red circles, whilst variables that are not expected to influence maternal diet but are related to the outcome are depicted by blue circles. Arrows denote the direction of causal association.

Supplementary table S1. Comparison between included and excluded subjects in the 3-year and 5-6-year samples

N	3-year sample		p-value	5-6-year sample		p-value
	Included	Excluded		Included	Excluded	
	914	1088		785	1217	
Maternal characteristics						
Recruitment in Poitiers, % (n)	51.1 (467)	46.0 (501)	0.02	54.9 (431)	44.1 (537)	<0.001
Maternal age at child's birth, years	30.0 (4.5)	29.0 (5.1)	<0.001	30.2 (4.6)	29.0 (5.1)	<0.001
Maternal educational level, % (n)			<0.001			<0.001
< 12 years	17.7 (162)	35.6 (387)		19.1 (150)	32.8 (399)	
12-14 years	17.5 (160)	16.5 (180)		17.3 (136)	16.8 (204)	
> 14 years	64.4 (589)	39.7 (432)		63.2 (496)	43.1 (525)	
Maternal pre-pregnancy BMI, kg/m ²	23.3 (4.4)	23.3 (4.8)	0.11	23.3 (4.5)	23.2 (4.7)	0.54
Primiparous, % (n)	49.6 (454)	36.2 (394)	<0.001	47.6 (410)	38.9 (474)	0.03
Smoking during pregnancy, % (n)	20.5 (187)	27.2 (297)	<0.001	20.0 (157)	26.7 (327)	<0.001
Alcohol drinking during pregnancy, % (n)	28.1 (257)	20.2 (220)	0.06	27.6 (217)	21.4 (260)	0.18
Diet during pregnancy						
Fruit and vegetable intake, times/day	3.1 (2.3)	3.2 (2.8)	<0.001	3.2 (2.4)	3.2 (2.7)	0.21
Fish and shellfish intake, % (n)			0.05			0.008
<1 time/week	30.5 (279)	30.0 (323)		29.9 (235)	30.2 (367)	
1-2 times/week	30.1 (275)	21.9 (238)		31.5 (247)	21.9 (266)	
>2 times/week	30.7 (281)	24.8 (270)		29.6 (232)	26.2 (319)	
Child's characteristics						
Male, % (n)	51.9 (475)	48.3 (537)	0.65	51.6 (405)	50.0 (595)	0.51
Birthweight, g	3304 (448)	3255 (565)	<0.001	3305 (455)	3260 (545)	0.003
Gestational age, weeks	39.3 (1.4)	39.1 (2.0)	<0.001	39.4 (1.4)	39.1 (1.9)	<0.001
Exclusive breastfeeding duration, months	1.4 (2.0)	1.8 (2.9)	<0.001	1.5 (2.0)	1.8 (2.8)	<0.001
Complementary food introduction, months	4.4 (1.5)	4.4 (1.8)	<0.001	4.4 (1.5)	4.4 (1.7)	<0.001
Maternal stimulation at 3 years, % (n)			0.41			
Every day or almost	20.4 (186)	6.7 (73)		-	-	-
3-5 times/week	49.1 (449)	18.9 (205)		-	-	-
1-2 times/week	21.4 (196)	8.5 (93)		-	-	-
<1 time/week or never	3.9 (36)	2.1 (23)		-	-	-
5-6-year HOME-Score	-	-	-	17.2 (2.3)	17.2 (2.4)	0.79

Supplementary table S2. Associations between 12-month macronutrients intake and neurodevelopmental scores in preschool children, complete-case analysis

	ASQ at 3 years (n=761)						IQ at 5-6 years (n=654)		
	Full score	Risk of having a poor score (1st tercile vs other terciles)					Full IQ	Verbal IQ	Performance IQ
	β (95% CI)	Communication OR (95% CI)	Gross Motor OR (95% CI)	Fine Motor OR (95% CI)	Problem Solving OR (95% CI)	Personal-Social OR (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)
<i>Unadjusted Model</i>									
Protein, g/day, for 1 SD	-2.4 (-4.6; -0.1)	1.03 (0.88; 1.21)	1.06 (0.91; 1.23)	1.10 (0.94; 1.29)	1.11 (0.94; 1.30)	1.09 (0.93; 1.28)	-0.9 (-2.0; 0.2)	-0.5 (-1.7; 0.6)	-1.1 (-2.2; 0.0)
Carbohydrates, g/day, for 1 SD	-1.4 (-3.7; 0.8)	1.08 (0.93; 1.27)	1.06 (0.91; 1.23)	1.06 (0.90; 1.24)	1.04 (0.89; 1.23)	1.14 (0.97; 1.34)	0.0 (-1.1; 1.1)	-0.5 (-1.7; 0.6)	0.5 (-0.6; 1.6)
Lipids, g/day, for 1 SD	-1.8 (-3.9; 0.4)	1.03 (0.89; 1.20)	0.98 (0.84; 1.13)	1.10 (0.95; 1.28)	1.14 (0.98; 1.34)	1.10 (0.94; 1.28)	0.4 (-0.6; 1.5)	0.2 (-0.9; 1.3)	0.7 (-0.3; 1.8)
<i>Model 1</i>									
Protein, g/day, for 1 SD	-1.5 (-3.7; 0.7)	0.99 (0.84; 1.17)	1.03 (0.87; 1.20)	1.04 (0.88; 1.23)	1.06 (0.89; 1.25)	1.05 (0.88; 1.24)	-0.4 (-1.4; 0.7)	-0.0 (-1.2; 1.1)	-0.6 (-1.7; 0.5)
Carbohydrates, g/day, for 1 SD	-0.7 (-2.9; 1.5)	1.07 (0.91; 1.26)	1.03 (0.88; 1.21)	1.01 (0.85; 1.20)	1.03 (0.87; 1.22)	1.10 (0.93; 1.31)	0.3 (-0.8; 1.3)	-0.3 (-1.4; 0.8)	0.7 (-0.4; 1.7)
Lipids, g/day, for 1 SD	-1.6 (-3.8; 0.5)	1.05 (0.90; 1.23)	0.98 (0.84; 1.14)	1.09 (0.93; 1.28)	1.17 (0.99; 1.37)	1.11 (0.94; 1.30)	-0.2 (-1.2; 0.8)	-0.4 (-1.5; 0.6)	0.2 (-0.9; 1.2)
<i>Model 2</i>									
Protein, g/day, for 1 SD	-1.5 (-3.7; 0.7)	0.99 (0.84; 1.17)	1.03 (0.87; 1.21)	1.04 (0.88; 1.24)	1.06 (0.89; 1.26)	1.05 (0.89; 1.25)	-0.4 (-1.4; 0.7)	-0.0 (-1.1; 1.1)	-0.6 (-1.7; 0.5)
Carbohydrates, g/day, for 1 SD	-0.8 (-3.0; 1.4)	1.07 (0.91; 1.27)	1.03 (0.88; 1.21)	1.01 (0.86; 1.20)	1.04 (0.87; 1.23)	1.11 (0.93; 1.31)	0.2 (-0.8; 1.3)	-0.3 (-1.4; 0.8)	0.7 (-0.4; 1.7)
Lipids, g/day, for 1 SD	-1.7 (-3.8; 0.4)	1.06 (0.90; 1.24)	0.98 (0.84; 1.14)	1.09 (0.93; 1.28)	1.17 (0.99; 1.38)	1.11 (0.94; 1.31)	-0.2 (-1.2; 0.8)	-0.4 (-1.4; 0.7)	0.2 (-0.9; 1.2)

ASQ: Ages and Stages Questionnaire; IQ: Intelligence quotient; β : regression coefficient; OR: Odds-ratio; CI: confidence interval.

Macronutrients were standardized and mutually adjusted for each other. Model 1: Multivariable linear regression models adjusted children's characteristics (sex, gestational age, birth weight z-scores, exclusive breastfeeding duration, age at complementary feeding introduction, age at neurodevelopmental assessment) and maternal characteristics (parity, age at delivery, educational level, BMI pre-pregnancy, smoking habits during pregnancy, alcohol drinking during pregnancy, frequency of fruit and vegetables intake during pregnancy, fish intake during pregnancy and recruitment center). Model 2: Further adjusted for maternal stimulation at 3 years for the ASQ outcomes and parental home stimulation (HOME-score) at 5 years for the IQ outcomes.

Supplementary table S3. Associations between 12-month ALA and LA intake and neurodevelopmental scores in preschool children, complete-case analysis

	ASQ at 3 years (n=761)						IQ at 5-6 years (n=654)		
	Full score	Risk of having a poor score (1st tercile vs other terciles)					Full IQ	Verbal IQ	Performance IQ
	β (95% CI)	Communication OR (95% CI)	Gross Motor OR (95% CI)	Fine Motor OR (95% CI)	Problem Solving OR (95% CI)	Personal-Social OR (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)
<i>Unadjusted Model</i>									
ALA, g/day, for 1 SD	-1.9 (-5.3; 1.5)	1.11 (0.88; 1.40)	1.05 (0.83; 1.33)	1.06 (0.84; 1.35)	1.18 (0.92; 1.50)	1.16 (0.91; 1.48)	-1.7 (-3.1; -0.2)*	-1.2 (-2.8; 0.4)	-1.1 (-2.6; 0.4)
LA, g/day, for 1 SD	3.1 (-0.3; 6.5)	0.99 (0.78; 1.25)	0.81 (0.64; 1.03)	0.90 (0.70; 1.14)	0.86 (0.67; 1.10)	0.77 (0.60; 0.99)*	2.2 (0.7; 3.7)*	1.6 (0.1; 3.2)	2.2 (0.7; 3.7)
<i>Model 1</i>									
ALA, g/day, for 1 SD	-2.1 (-5.3; 1.2)	1.15 (0.90; 1.46)	1.07 (0.85; 1.36)	1.05 (0.82; 1.35)	1.21 (0.94; 1.54)	1.14 (0.88; 1.47)	-1.7 (-3.1; -0.3)*	-1.5 (-3.0; 0.1)	-1.1 (-2.6; 0.3)
LA, g/day, for 1 SD	2.9 (-0.5; 6.3)	0.97 (0.75; 1.26)	0.83 (0.64; 1.06)	0.95 (0.73; 1.23)	0.88 (0.68; 1.15)	0.75 (0.57; 0.98)*	1.4 (-0.1; 2.9)	1.2 (-0.4; 2.7)	1.3 (-0.2; 2.8)
<i>Model 2</i>									
ALA, g/day, for 1 SD	-1.3 (-4.6; 1.9)	1.12 (0.88; 1.43)	1.04 (0.82; 1.32)	1.03 (0.80; 1.32)	1.16 (0.91; 1.49)	1.09 (0.85; 1.41)	-1.5 (-2.9; -0.1)*	-1.1 (-2.6; 0.4)	-1.1 (-2.6; 0.4)
LA, g/day, for 1 SD	2.4 (-1.0; 5.7)	0.99 (0.77; 1.28)	0.84 (0.65; 1.08)	0.96 (0.74; 1.25)	0.91 (0.70; 1.18)	0.77 (0.59; 1.01)	1.3 (-0.2; 2.7)	0.9 (-0.6; 2.5)	1.3 (-0.3; 2.8)

ASQ: Ages and Stages Questionnaire; IQ: Intelligence Quotient; β : regression coefficient; OR: Odds Ratio; CI: confidence interval; ALA: α -linolenic acid; LA: linoleic acid.

ALA and LA were standardised and mutually adjusted for each other. Model 1: Multivariable linear regression models adjusted for total lipid intake, children's characteristics (sex, gestational age, birth weight z-scores, exclusive breastfeeding duration, age at complementary feeding introduction, age at the neurodevelopmental assessment) and maternal characteristics (parity, age at delivery, educational level, BMI pre-pregnancy, smoking habits during pregnancy, alcohol drinking during pregnancy, frequency of fruit and vegetable intake during pregnancy, fish intake during pregnancy and recruitment centre). Model 2: Further adjusted for maternal stimulation at 3 years for the ASQ outcomes and parental home stimulation (HOME-score) at 5 years for the IQ outcomes. *after accounting for the multiple testing using false discovery rate method, this association was not significant (q-value>0.1).

Supplementary table S4. Associations between 12-month LA/ALA ratio and neurodevelopmental scores in preschool children, complete-case analysis

	ASQ at 3 years (n=761)						IQ at 5-6 years (n=654)		
	Full score	Risk of having a poor score (1st tercile vs other terciles)					Full IQ	Verbal IQ	Performance IQ
	β (95% CI)	Communication OR (95% CI)	Gross Motor OR (95% CI)	Fine Motor OR (95% CI)	Problem Solving OR (95% CI)	Personal-Social OR (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)
<i>Unadjusted Model</i>									
<7.6	0 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	0 (Ref)	0 (Ref)	0 (Ref)
7.6 to 10.0	3.7 (-1.5; 9.0)	0.73 (0.51; 1.05)	0.68 (0.48; 0.97)	0.85 (0.59; 1.23)	0.72 (0.49; 1.06)	1.29 (0.90; 1.87)	1.8 (-0.7; 4.3)	2.2 (-0.5; 4.8)	0.8 (-1.7; 3.4)
≥ 10.0	1.8 (-3.3; 6.9)	0.78 (0.55; 1.11)	0.95 (0.68; 1.35)	0.84 (0.59; 1.20)	0.88 (0.61; 1.26)	0.91 (0.63; 1.32)	0.0 (-2.4; 2.4)	-1.6 (-4.1; 1.0)	1.1 (-1.3; 3.6)
<i>Model 1</i>									
<7.6	0 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	0 (Ref)	0 (Ref)	0 (Ref)
7.6 to 10.0	2.9 (-2.2; 8.0)	0.73 (0.50; 1.07)	0.70 (0.48; 1.01)	0.92 (0.62; 1.36)	0.71 (0.48; 1.06)	1.42 (0.96; 2.11)	2.2 (-0.2; 4.6)	2.7 (0.2; 5.2)*	1.3 (-1.2; 3.7)
≥ 10.0	1.5 (-3.5; 6.5)	0.74 (0.51; 1.07)	0.90 (0.63; 1.29)	0.89 (0.60; 1.30)	0.85 (0.58; 1.25)	1.02 (0.69; 1.50)	0.6 (-1.7; 2.9)	-0.5 (-3.0; 1.9)	1.6 (-0.8; 4.0)
<i>Model 2</i>									
<7.6	0 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	0 (Ref)	0 (Ref)	0 (Ref)
7.6 to 10.0	2.4 (-2.6; 7.5)	0.75 (0.51; 1.09)	0.71 (0.49; 1.03)	0.93 (0.63; 1.38)	0.73 (0.49; 1.08)	1.48 (1.00; 2.20)	2.2 (-0.2; 4.6)	2.8 (0.3; 5.2)*	1.3 (-1.2; 3.8)
≥ 10.0	0.9 (-4.0; 5.9)	0.75 (0.52; 1.09)	0.92 (0.64; 1.32)	0.90 (0.62; 1.33)	0.88 (0.60; 1.28)	1.05 (0.71; 1.56)	0.4 (-1.9; 2.7)	-0.8 (-3.2; 1.6)	1.5 (-0.9; 3.9)

ASQ: Ages and Stages Questionnaire; IQ: Intelligence Quotient; β : regression coefficient; OR: odds ratio; CI: confidence interval; ALA: α -linolenic acid; LA: linoleic acid.

Model 1: Multivariable linear regression models adjusted for total lipid intake, child's characteristics (sex, gestational age, birth weight z-scores, exclusive breastfeeding duration, age at complementary feeding introduction, age at the neurodevelopmental assessment) and maternal characteristics (parity, age at delivery, educational level, BMI pre-pregnancy, smoking habits during pregnancy, alcohol drinking during pregnancy, frequency of fruit and vegetables intake during pregnancy, fish intake during pregnancy and recruitment center). Model 2: Further adjusted for maternal stimulation at 3 years for the ASQ outcomes and parental home stimulation (HOME-score) at 5 years for the IQ outcomes. *after accounting for the multiple testing using false discovery rate method, this association was not significant (q-value>0.1).