

Enrichment of infant formula with long-chain polyunsaturated fatty acids and risk of infection and allergy in the nationwide ELFE birth cohort

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Supplementary materials

Supplementary table 1 Details of multiple imputation of missing data

Variable	Type of variable	Model used to predict missing data	Number (proportion) of missing values
DHA enrichment of the formula	Binary	Logistic regression	No missing data
ARA enrichment of the formula	Binary	Logistic regression	No missing data
EPA enrichment of the formula	Binary	Logistic regression	No missing data
Ever lower respiratory tract infection	Binary	Logistic regression	No missing data
Ever upper respiratory tract infection	Binary	Logistic regression	No missing data
Ever gastrointestinal infection	Binary	Logistic regression	No missing data
Ever wheezing	Binary	Logistic regression	No missing data
Ever use of asthma medications	Binary	Logistic regression	No missing data
Ever food allergy	Binary	Logistic regression	No missing data
Ever itchy rash	Binary	Logistic regression	No missing data
Recruitment wave	Categorical	Discriminant function method	No missing data
Maternity size	Ordinal	Logistic regression	No missing data
Family history of allergic diseases	Binary	Logistic regression	No missing data
Sex	Binary	Logistic regression	No missing data
Maternal age	Continuous	Predictive mean matching method	No missing data
Older siblings	Ordinal	Logistic regression	No missing data
Maternal employment status	Categorical	Discriminant function method	2 (0%)
City size	Binary	Logistic regression	2 (0%)
Age at infant formula introduction	Continuous	Predictive mean matching method	3 (0%)
Region of residence	Categorical	Discriminant function method	3 (0%)
Physician type	Categorical	Discriminant function method	49 (0.6%)
Caesarean section	Binary	Logistic regression	64 (0.8%)
Maternal smoking	Categorical	Discriminant function method	100 (1.2%)
Maternal pre-pregnancy BMI	Continuous	Predictive mean matching method	127 (1.5%)
Gestational age	Continuous	Predictive mean matching method	132 (1.6%)
Birth weight	Continuous	Predictive mean matching method	241 (2.9%)
Monthly household income per CU	Continuous	Predictive mean matching method	247 (2.9%)
Maternal education level	Ordinal	Logistic regression	294 (3.5%)
Maternal diet quality during pregnancy (PANDiet)	Continuous	Predictive mean matching method	978 (11.6%)
n-3 fatty acids supplementation during pregnancy	Binary	Logistic regression	1018 (12.1%)

ARA arachidonic acid; *BMI* body mass index; *CU* consumption unit; *DHA* docosahexaenoic acid; *EPA* eicosapentaenoic acid; *PANDiet* Probability of Adequate Nutrient Intake Dietary score

Supplementary table 2 Adjusted associations between consumption of LCPUFA-enriched formula at age 2 months and risk of infection among infants without any change in infant formula or infants without infection or allergy up to age 2 months †

	Gastrointestinal infection			Lower respiratory tract infection		Upper respiratory tract infection	
	N	OR [95% CI]	NC	OR [95% CI]	NC	OR [95% CI]	NC
Infants without change in infant formula up to age 2 months (n=4,429)							
LCPUFA enrichment							
DHA/ARA							
Not enriched	2689	1.00 [Ref]	325	1.00 [Ref]	960	1.00 [Ref]	786
Enriched	1740	1.11 [0.92; 1.34]	224	1.02 [0.90; 1.17]	632	1.07 [0.94; 1.23]	549
DHA/ARA/EPA							
Not enriched	3769	1.00 [Ref]	464	1.00 [Ref]	1363	1.00 [Ref]	1138
Enriched	660	1.09 [0.84; 1.40]	85	0.94 [0.79; 1.13]	229	0.94 [0.78; 1.13]	197
LCPUFA content ‡							
DHA							
Not enriched	2689	1.00 [Ref]	325	1.00 [Ref]	960	1.00 [Ref]	786
DHA <10 mg/100 kcal	571	1.21 [0.92; 1.58]	81	1.11 [0.91; 1.34]	219	1.07 [0.87; 1.30]	173
DHA ≥10 mg/100 kcal	708	0.93 [0.71; 1.22]	76	0.91 [0.76; 1.09]	238	1.03 [0.86; 1.24]	223
Enriched but DHA content unknown	461	1.26 [0.94; 1.69]	67	1.11 [0.89; 1.37]	175	1.15 [0.93; 1.43]	153
EPA							
Not enriched	3769	1.00 [Ref]	464	1.00 [Ref]	1363	1.00 [Ref]	1138
EPA <3.2 mg/100 kcal	221	1.27 [0.86; 1.87]	34	1.04 [0.78; 1.39]	80	1.00 [0.73; 1.35]	64
EPA ≥3.2 mg/100 kcal	431	1.01 [0.73; 1.38]	51	0.89 [0.72; 1.11]	146	0.90 [0.72; 1.12]	129
Enriched but DHA content unknown	8		0	0.90 [0.21; 3.84]	3	2.11 [0.52; 8.55]	4
Infants without infections or allergies up to age 2 months (n=6,490)							
LCPUFA enrichment							
DHA/ARA							
Not enriched	4037	1.00 [Ref]	495	1.00 [Ref]	1380	1.00 [Ref]	1251
Enriched	2453	1.09 [0.94; 1.28]	319	1.08 [0.97; 1.21]	882	1.07 [0.96; 1.20]	818
DHA/ARA/EPA							
Not enriched	5747	1.00 [Ref]	714	1.00 [Ref]	2015	1.00 [Ref]	1840
Enriched	743	1.13 [0.90; 1.42]	100	0.91 [0.77; 1.08]	247	0.92 [0.78; 1.09]	229
LCPUFA content ‡							
DHA							
Not enriched	4037	1.00 [Ref]	495	1.00 [Ref]	1380	1.00 [Ref]	1251
DHA <10 mg/100 kcal	1129	1.06 [0.87; 1.30]	145	1.24 [1.08; 1.42]	440	1.16 [1.01; 1.34]	390
DHA ≥10 mg/100 kcal	798	0.96 [0.76; 1.23]	91	0.93 [0.78; 1.09]	261	0.96 [0.81; 1.14]	254
Enriched but DHA content unknown	526	1.38 [1.06; 1.78]	83	1.02 [0.84; 1.24]	181	1.06 [0.87; 1.29]	174
EPA							
Not enriched	5747	1.00 [Ref]	714	1.00 [Ref]	2015	1.00 [Ref]	1840
EPA <3.2 mg/100 kcal	240	1.29 [0.89; 1.86]	37	1.02 [0.78; 1.35]	84	0.99 [0.74; 1.32]	73
EPA ≥3.2 mg/100 kcal	449	0.98 [0.72; 1.33]	53	0.80 [0.65; 1.00]	139	0.85 [0.69; 1.05]	135
Enriched but EPA content unknown	54	1.75 [0.86; 3.55]	10	1.49 [0.86; 2.59]	24	1.32 [0.75; 2.30]	21

DHA docosahexaenoic acid; EPA eicosapentaenoic acid; LCPUFA long-chain polyunsaturated fatty acids; NC number of cases

† Values are odd ratios (OR) [95% confidence intervals (CI)] adjusted for child characteristics (sex, gestational age, caesarean section, birth weight category, child's physician type, presence of siblings, age at infant formula introduction), maternal and household characteristics (age, education level, city size, region of residence, employment status in early pregnancy, pre-pregnancy body mass index, smoking status, diet quality during pregnancy, n-3 PUFA supplementation during pregnancy, household income and family history of allergy) and ELFE study design variables (recruitment wave, maternity size). Separate logistic regressions for each outcome and LCPUFA variable.

‡ DHA and EPA enrichment levels were classified by using the median value.

Supplementary table 3 Adjusted associations between consumption of LCPUFA-enriched formula at age 2 months and risk of allergy among infants without any change in infant formula or infants without infection or allergy up to age 2 months †

	Wheezing		Asthma medications		Itchy rash		Food allergy		
	N	OR [95% CI]	NC	OR [95% CI]	NC	OR [95% CI]	NC	OR [95% CI]	NC
Infants without change in infant formula up to age 2 months (n=4,429)									
LCPUFA enrichment									
DHA/ARA									
Not enriched	2689	1.00 [Ref]	1074	1.00 [Ref]	1061	1.00 [Ref]	1188	1.00 [Ref]	146
Enriched	1740	1.01 [0.89; 1.15]	709	1.02 [0.90; 1.16]	706	0.99 [0.87; 1.12]	784	1.08 [0.82; 1.41]	102
DHA/ARA/EPA									
Not enriched	3769	1.00 [Ref]	1527	1.00 [Ref]	1536	1.00 [Ref]	1672	1.00 [Ref]	217
Enriched	660	0.93 [0.78; 1.11]	256	0.77 [0.65; 0.92]	231	1.01 [0.85; 1.19]	300	0.81 [0.55; 1.20]	31
LCPUFA content ‡									
DHA									
Not enriched	2689	1.00 [Ref]	1074	1.00 [Ref]	1061	1.00 [Ref]	1188	1.00 [Ref]	146
DHA <10 mg/100 kcal	571	1.09 [0.91; 1.32]	243	1.08 [0.90; 1.31]	238	0.95 [0.79; 1.14]	250	1.35 [0.93; 1.95]	40
DHA ≥10 mg/100 kcal	708	0.92 [0.77; 1.10]	273	0.82 [0.69; 0.99]	253	1.00 [0.85; 1.19]	323	0.83 [0.56; 1.23]	33
Enriched but DHA content unknown	461	1.06 [0.86; 1.30]	193	1.32 [1.07; 1.62]	215	1.03 [0.84; 1.26]	211	1.13 [0.74; 1.73]	29
EPA									
Not enriched	3769	1.00 [Ref]	1527	1.00 [Ref]	1536	1.00 [Ref]	1672	1.00 [Ref]	217
EPA <3.2 mg/100 kcal	221	1.01 [0.76; 1.35]	88	0.93 [0.69; 1.24]	84	0.90 [0.68; 1.20]	92	0.72 [0.36; 1.44]	9
EPA ≥3.2 mg/100 kcal	431	0.88 [0.71; 1.09]	163	0.69 [0.55; 0.86]	142	1.05 [0.86; 1.29]	203	0.83 [0.52; 1.33]	21
Enriched but EPA content unknown	8	2.26 [0.53; 9.64]	5	2.07 [0.49; 8.81]	5	2.06 [0.48; 8.94]	5	2.56 [0.3; 21.99]	1
Infants without infections or allergies up to age 2 months (n=6,490)									
LCPUFA enrichment									
DHA/ARA									
Not enriched	4037	1.00 [Ref]	1567	1.00 [Ref]	1577	1.00 [Ref]	1706	1.00 [Ref]	226
Enriched	2453	1.12 [1.01; 1.25]	1024	1.05 [0.95; 1.17]	988	1.00 [0.90; 1.11]	1053	0.94 [0.75; 1.18]	132
DHA/ARA/EPA									
Not enriched	5747	1.00 [Ref]	2307	1.00 [Ref]	2297	1.00 [Ref]	2430	1.00 [Ref]	328
Enriched	743	0.92 [0.79; 1.08]	284	0.84 [0.72; 0.99]	268	1.06 [0.90; 1.24]	329	0.67 [0.45; 0.98]	30
LCPUFA content ‡									
DHA									
Not enriched	4037	1.00 [Ref]	1567	1.00 [Ref]	1577	1.00 [Ref]	1706	1.00 [Ref]	226
DHA <10 mg/100 kcal	1129	1.30 [1.13; 1.49]	506	1.17 [1.02; 1.34]	481	0.98 [0.85; 1.12]	477	1.07 [0.80; 1.42]	67
DHA ≥10 mg/100 kcal	798	0.92 [0.78; 1.08]	300	0.84 [0.71; 0.99]	283	0.96 [0.82; 1.13]	339	0.71 [0.49; 1.04]	34
Enriched but DHA content unknown	526	1.10 [0.91; 1.33]	218	1.17 [0.96; 1.41]	224	1.10 [0.91; 1.32]	237	1.02 [0.69; 1.52]	31
EPA									
Not enriched	5747	1.00 [Ref]	2307	1.00 [Ref]	2297	1.00 [Ref]	2430	1.00 [Ref]	328
EPA <3.2 mg/100 kcal	240	1.03 [0.79; 1.35]	96	0.98 [0.74; 1.28]	94	1.00 [0.76; 1.30]	101	0.55 [0.27; 1.14]	8
EPA ≥3.2 mg/100 kcal	449	0.80 [0.65; 0.99]	160	0.70 [0.57; 0.87]	145	1.04 [0.85; 1.27]	199	0.77 [0.48; 1.22]	21
Enriched but EPA content unknown	54	1.65 [0.95; 2.85]	28	1.82 [1.05; 3.16]	29	1.57 [0.91; 2.72]	29	0.32 [0.04; 2.35]	1

DHA docosahexaenoic acid; EPA eicosapentaenoic acid; LCPUFA long-chain polyunsaturated fatty acids; NC number of cases

† Values are odd ratios (OR) [95% confidence intervals (CI)] adjusted for child characteristics (sex, gestational age, caesarean section, birth weight category, child's physician type, presence of siblings, age at infant formula introduction), maternal and household characteristics (age, education level, city size, region of residence, employment status in early pregnancy, pre-pregnancy body mass index, smoking status, diet quality during pregnancy, n-3 PUFA supplementation during pregnancy, household income and family history of allergy) and ELFE study design variables (recruitment wave, maternity size). Separate logistic regressions for each outcome and LCPUFA variable.

‡ DHA and EPA enrichment levels were classified by using the median value.

Supplementary table 4 Adjusted associations between consumption of LCPUFA-enriched formula at age 2 months and risk of infection (analyses using multiple imputation and weighted analyses), ELFE study [†]

	Gastrointestinal infection	Lower respiratory tract infection	Upper respiratory tract infection
	OR [95% CI]	OR [95% CI]	OR [95% CI]
Analyses using multiple imputation (n=8,389) [‡]			
LCPUFA enrichment			
DHA/ARA			
Not enriched	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]
Enriched	1.06 [0.93; 1.21]	1.02 [0.93; 1.12]	1.07 [0.97; 1.17]
DHA/ARA/EPA			
Not enriched	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]
Enriched	1.08 [0.88; 1.32]	0.89 [0.77; 1.03]	0.90 [0.78; 1.05]
LCPUFA content [§]			
DHA			
Not enriched	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]
DHA <10 mg/100 kcal	1.06 [0.89; 1.26]	1.15 [1.02; 1.30]	1.13 [1.00; 1.28]
DHA ≥10 mg/100 kcal	0.92 [0.75; 1.14]	0.88 [0.76; 1.01]	0.99 [0.85; 1.14]
Enriched but DHA content unknown	1.27 [1.01; 1.59]	0.97 [0.82; 1.15]	1.05 [0.88; 1.24]
EPA			
Not enriched	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]
EPA <3.2 mg/100 kcal	1.21 [0.87; 1.68]	0.94 [0.74; 1.21]	0.90 [0.70; 1.17]
EPA ≥3.2 mg/100 kcal	0.94 [0.72; 1.23]	0.82 [0.68; 0.99]	0.86 [0.71; 1.04]
Enriched but EPA content unknown	1.62 [0.89; 2.96]	1.22 [0.76; 1.97]	1.27 [0.79; 2.06]
Weighted analyses (n=8,351)			
LCPUFA enrichment			
DHA/ARA			
Not enriched	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]
Enriched	1.07 [0.90; 1.26]	1.06 [0.94; 1.19]	1.13 [1.00; 1.27]
DHA/ARA/EPA			
Not enriched	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]
Enriched	1.23 [0.95; 1.60]	0.89 [0.74; 1.07]	0.96 [0.79; 1.17]
LCPUFA content [§]			
DHA			
Not enriched	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]
DHA <10 mg/100 kcal	1.08 [0.87; 1.33]	1.15 [0.98; 1.34]	1.16 [0.99; 1.35]
DHA ≥10 mg/100 kcal	1.00 [0.76; 1.32]	0.97 [0.80; 1.16]	1.11 [0.92; 1.34]
Enriched but DHA content unknown	1.14 [0.87; 1.49]	1.00 [0.81; 1.23]	1.09 [0.89; 1.35]
EPA			
Not enriched	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]
EPA <3.2 mg/100 kcal	1.36 [0.91; 2.03]	0.88 [0.64; 1.20]	0.96 [0.69; 1.34]
EPA ≥3.2 mg/100 kcal	1.13 [0.79; 1.61]	0.89 [0.69; 1.13]	0.92 [0.72; 1.17]
Enriched but EPA content unknown	1.46 [0.69; 3.09]	0.94 [0.50; 1.78]	1.37 [0.71; 2.64]

DHA docosahexaenoic acid; EPA eicosapentaenoic acid; LCPUFA long-chain polyunsaturated fatty acids

[†] Values are odd ratios (OR) [95% confidence intervals (OR)] adjusted for child characteristics (sex, gestational age, caesarean section, birth weight category, child's physician type, presence of siblings, age at infant formula introduction), maternal and household characteristics (age, education level, city size, region of residence, employment status in early pregnancy, pre-pregnancy body mass index, smoking status, diet quality during pregnancy, n-3 PUFA supplementation during pregnancy, household income and family history of allergy) and ELFE study design variables (recruitment wave, maternity size). Separate logistic regressions for each outcome and LCPUFA variable.

[‡] Five databases imputed from available data (only missing covariates were handled).

[§] DHA and EPA enrichment levels were classified by using the median value.

Supplementary table 5 Adjusted associations between consumption of LCPUFA-enriched formula at age 2 months and risk of allergy (analyses using multiple imputation and weighted analyses), Elfe study [†]

	Wheezing	Asthma medications	Itchy rash	Food allergy
	OR [95% CI]	OR [95% CI]	OR [95% CI]	OR [95% CI]
Analyses using multiple imputation (n=8,389) [‡]				
LCPUFA enrichment				
DHA/ARA				
Not enriched	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]
Enriched	1.08 [0.98; 1.18]	1.04 [0.95; 1.14]	0.99 [0.91; 1.09]	1.01 [0.84; 1.22]
DHA/ARA/EPA				
Not enriched	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]
Enriched	0.91 [0.79; 1.05]	0.84 [0.73; 0.97]	1.02 [0.89; 1.18]	0.73 [0.53; 1.00]
LCPUFA content [§]				
DHA				
Not enriched	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]
DHA <10 mg/100 kcal	1.20 [1.06; 1.35]	1.13 [1.00; 1.27]	0.98 [0.87; 1.10]	1.12 [0.89; 1.42]
DHA ≥10 mg/100 kcal	0.93 [0.81; 1.07]	0.88 [0.76; 1.01]	0.99 [0.87; 1.14]	0.81 [0.60; 1.09]
Enriched but DHA content unknown	1.05 [0.89; 1.24]	1.13 [0.96; 1.34]	1.03 [0.88; 1.22]	1.09 [0.79; 1.52]
EPA				
Not enriched	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]
EPA <3.2 mg/100 kcal	0.90 [0.71; 1.15]	0.91 [0.71; 1.16]	0.91 [0.72; 1.16]	0.62 [0.34; 1.11]
EPA ≥3.2 mg/100 kcal	0.85 [0.71; 1.02]	0.74 [0.61; 0.89]	1.04 [0.87; 1.24]	0.81 [0.55; 1.18]
Enriched but EPA content unknown	1.56 [0.97; 2.52]	1.62 [1.00; 2.60]	1.42 [0.88; 2.27]	0.63 [0.20; 2.01]
Weighted analyses (n=8,351)				
LCPUFA enrichment				
DHA/ARA				
Not enriched	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]
Enriched	1.06 [0.95; 1.19]	1.05 [0.93; 1.17]	0.94 [0.84; 1.05]	1.05 [0.83; 1.33]
DHA/ARA/EPA				
Not enriched	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]
Enriched	0.92 [0.77; 1.10]	0.83 [0.69; 0.99]	0.93 [0.78; 1.11]	0.77 [0.51; 1.16]
LCPUFA content [§]				
DHA				
Not enriched	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]
DHA <10 mg/100 kcal	1.15 [0.99; 1.34]	1.12 [0.96; 1.30]	0.92 [0.80; 1.06]	1.24 [0.92; 1.67]
DHA ≥10 mg/100 kcal	0.97 [0.81; 1.15]	0.90 [0.75; 1.07]	0.93 [0.79; 1.11]	0.87 [0.58; 1.29]
Enriched but DHA content unknown	1.02 [0.84; 1.24]	1.12 [0.92; 1.37]	0.99 [0.81; 1.22]	0.92 [0.63; 1.34]
EPA				
Not enriched	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]	1.00 [Ref]
EPA <3.2 mg/100 kcal	0.88 [0.64; 1.20]	0.85 [0.63; 1.14]	0.87 [0.65; 1.17]	0.99 [0.47; 2.08]
EPA ≥3.2 mg/100 kcal	0.86 [0.69; 1.08]	0.74 [0.59; 0.93]	0.96 [0.77; 1.19]	0.68 [0.43; 1.06]
Enriched but EPA content unknown	1.77 [0.97; 3.23]	1.58 [0.86; 2.90]	1.07 [0.57; 1.99]	0.44 [0.11; 1.73]

DHA docosahexaenoic acid; EPA eicosapentaenoic acid; LCPUFA long-chain polyunsaturated fatty acids

[†] Values are odd ratios (OR) [95% confidence intervals (OR)] adjusted for child characteristics (sex, gestational age, caesarean section, birth weight category, child's physician type, presence of siblings, age at infant formula introduction), maternal and household characteristics (age, education level, city size, region of residence, employment status in early pregnancy, pre-pregnancy body mass index, smoking status, diet quality during pregnancy, n-3 PUFA supplementation during pregnancy, household income and family history of allergy) and ELFE study design variables (recruitment wave, maternity size). Separate logistic regressions for each outcome and LCPUFA variable.

[‡] Five databases imputed from available data (only missing covariates were handled).

[§] DHA and EPA enrichment levels were classified by using the median value.