NUTRITION AND DIETETICS

Breastfeeding

Early-Life Nutrition and Long-Term Health Outcomes

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Learning Objectives

The First 1,000 Days

Explain breastfeeding as an early-life nutritional exposure within the **first 1,000 days**, and why this window matters for long-term health risk

Biological Mechanisms

Describe key biological and nutritional pathways through which breastfeeding may influence **metabolic**, **immune/allergic**, and **neurodevelopmental** outcomes.

Gene-Environment Interaction

Recognize how **genetic variability** can modify breastfeeding-health associations (gene × environment interaction).

The First 1,000 Days of Life

- The **first 1,000 days of life**, spanning from **conception to 2 years of age**, are recognized as a **critical period of growth and development**.
- It is well established that **early-life nutrition** is a key environmental factor that strongly influences the risk of developing **cardiovascular and metabolic diseases in adulthood**.
- Nature leads the **first ~500 days** of the offspring's diet - the period from **conception to approximately six months of age -** when the growing offspring is **completely dependent on the mother for nutrition**.
- This adaptive process of nutrition occurs via the **placenta** to the developing embryo and fetus, and then, **ideally**, via **exclusive breastfeeding for the first six months of infancy**.
- At **12 months of age**, an infant's daily **sleep-wake cycle** is moderately stabilized, with increasing **consolidation of sleep during the night** compared to early infancy.
- Using **multivariate logistic regression** with **confounder adjustment**, **exclusive breastfeeding during the first six months of life** was **negatively associated with post-midnight feeding at 12 months of age**.

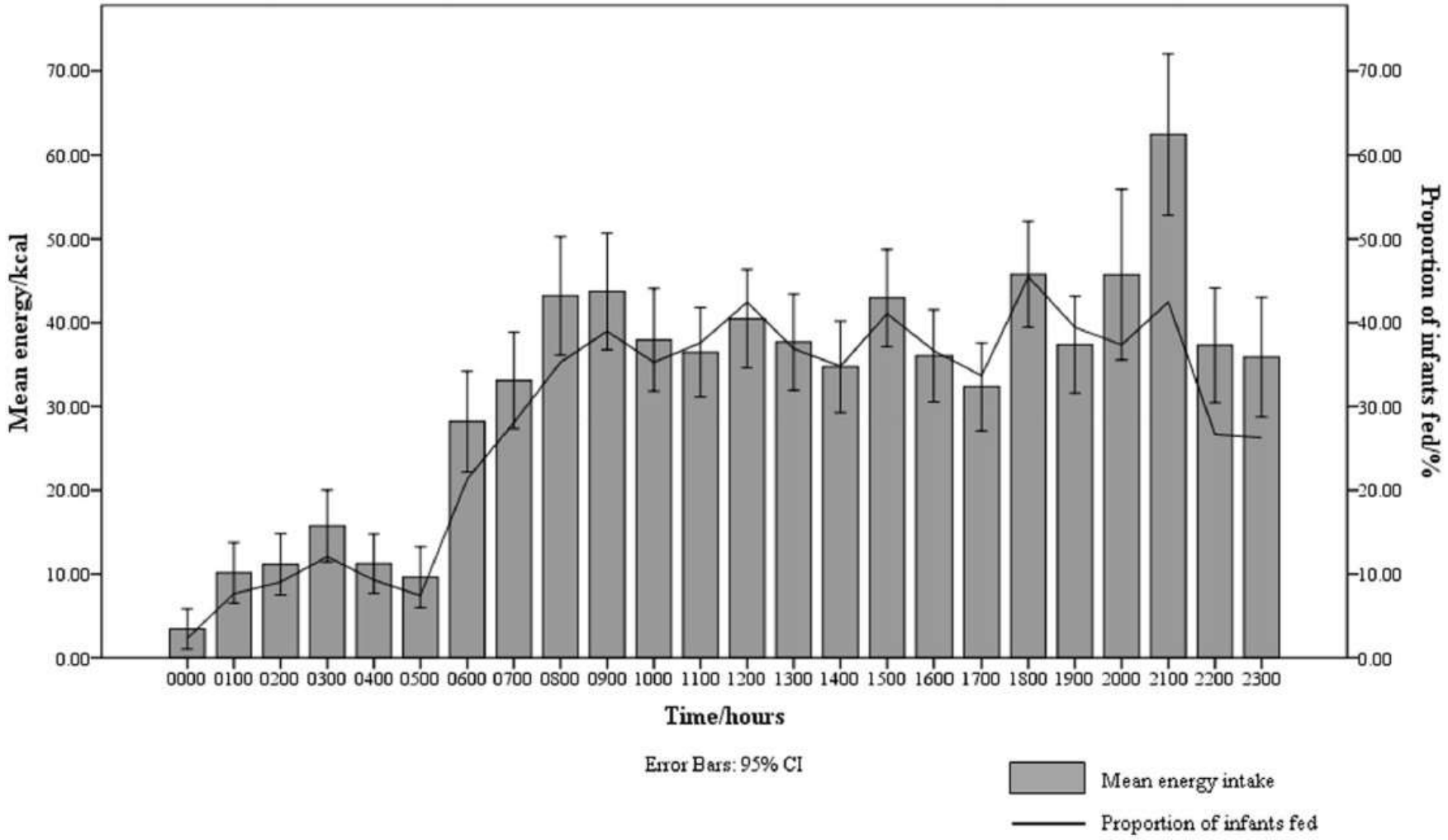


Fig. 1.
Mean hourly energy intake and proportion of infants fed across 24 hours

The Breastfed Baby

Immune system.
Responds better to vaccinations. Human milk helps to mature immune system. Decreased risk of childhood cancer.

Skin.
Less allergic eczema in breastfed infants.

Eyes.
Visual acuity is higher in babies fed human milk.

Higher IQ.
Cholesterol and other types of fat in human milk support the growth of nerve tissue.

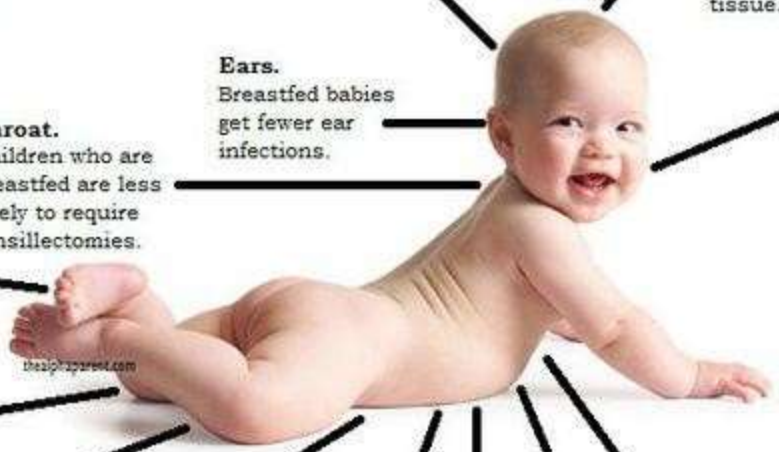
Endocrine system.
Reduced risk of getting diabetes.

Ears.
Breastfed babies get fewer ear infections.

Mouth.
Less need for orthodontics in children breastfed more than a year. Improved muscle development of face from suckling at the breast. Subtle changes in the taste of human milk prepare babies to accept a variety of solid foods.

Joints and muscles.
Juvenile rheumatoid arthritis is less common in children who were breastfed.

Throat.
Children who are breastfed are less likely to require tonsillectomies.



Bowels.
Less constipation.

Urinary tract.
Fewer infections in breastfed infants.

Appendix.
Children with acute appendicitis are less likely to have been breastfed.

Kidneys.
With less salt and less protein, human milk is easier on a baby's kidneys.

Respiratory system.
Breastfed babies have fewer and less severe upper respiratory infections, less wheezing, less pneumonia and less influenza.

Digestive system.
Less diarrhea, fewer gastrointestinal infections in babies who are breastfeeding. Six months or more of exclusive breastfeeding reduces risk of food allergies. Also, less risk of Crohn's disease and ulcerative colitis in adulthood.

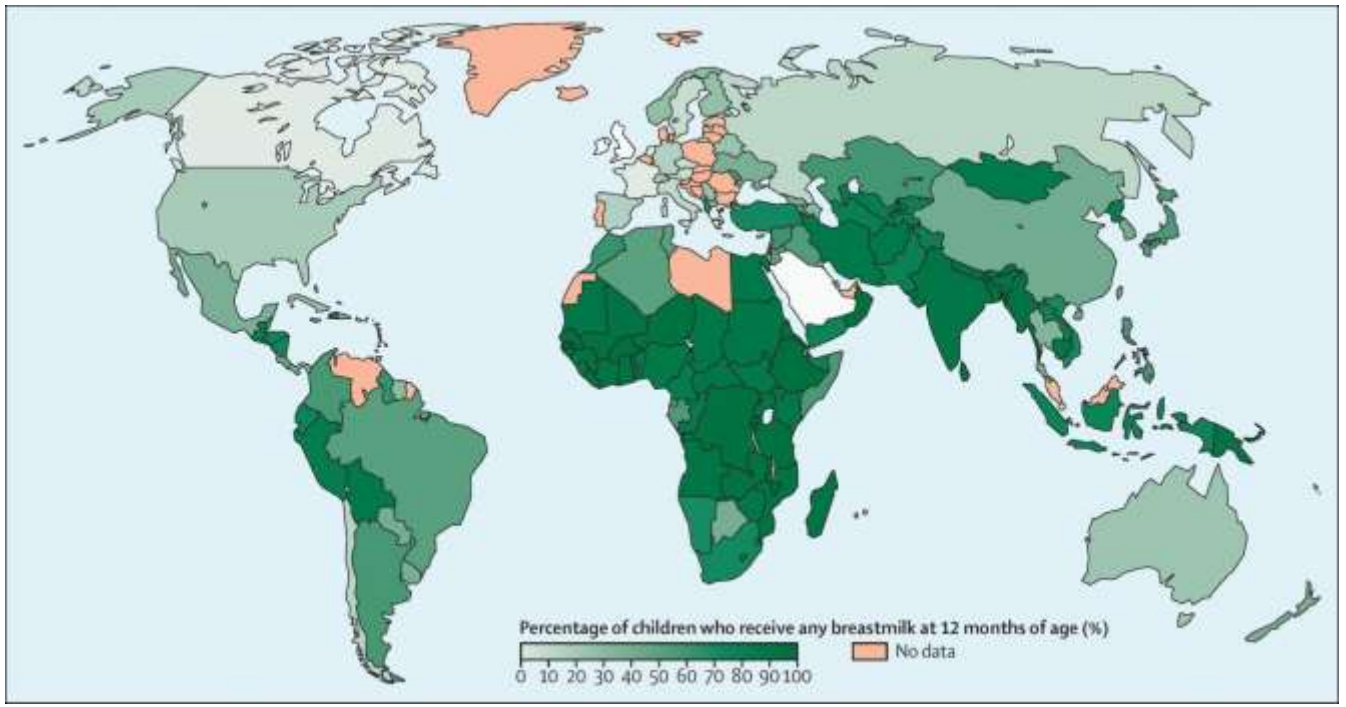
Heart and circulatory system.
Breastfed children have lower cholesterol as adults. Heart rates are lower in breastfed infants.

thealphaparent.com

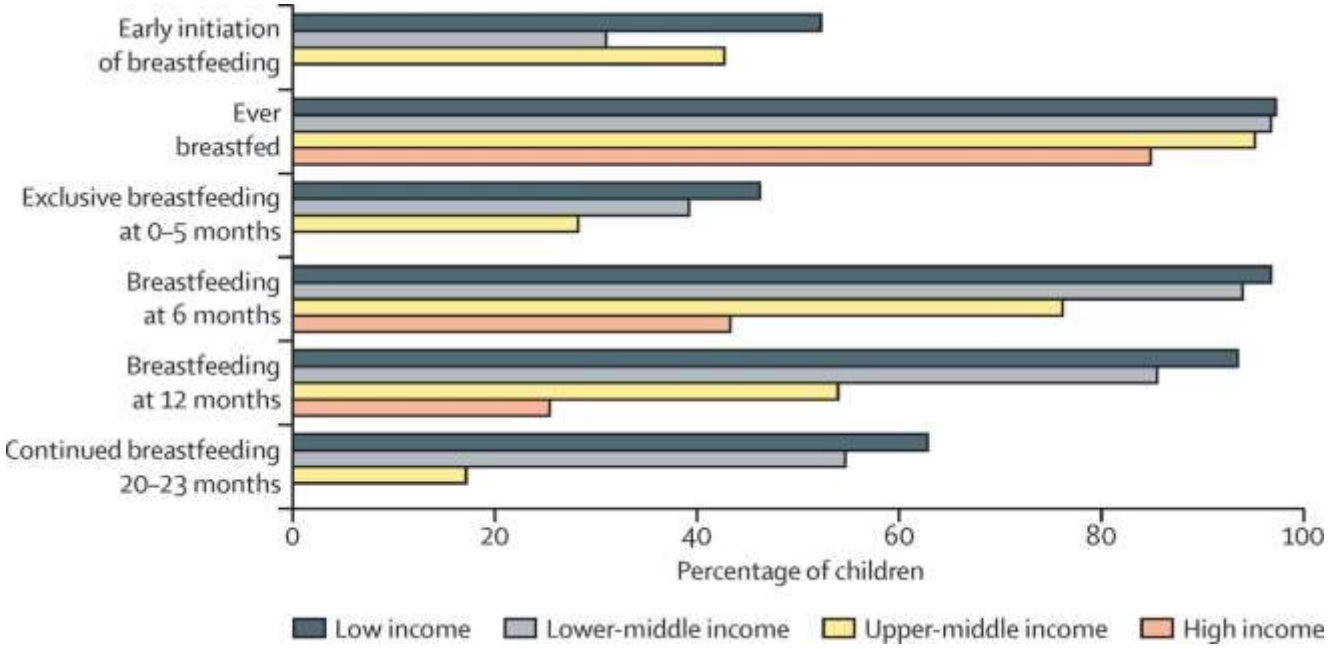
Breastfeeding in the 21st century: epidemiology, mechanisms, and lifelong effect

*Cesar G Victora, Rajiv Bahl, Aluísio J D Barros, Giovanny V A França, Susan Horton, Julia Krasevec, Simon Murch, Mari Jeeva Sankar, Neff Walker, Nigel C Rollins, for The Lancet Breastfeeding Series Group**

In most high-income countries, the prevalence is lower than 20%. We noted important differences- eg, between the UK (<1%) and the USA (27%), and between Norway (35%) and Sweden (16%).



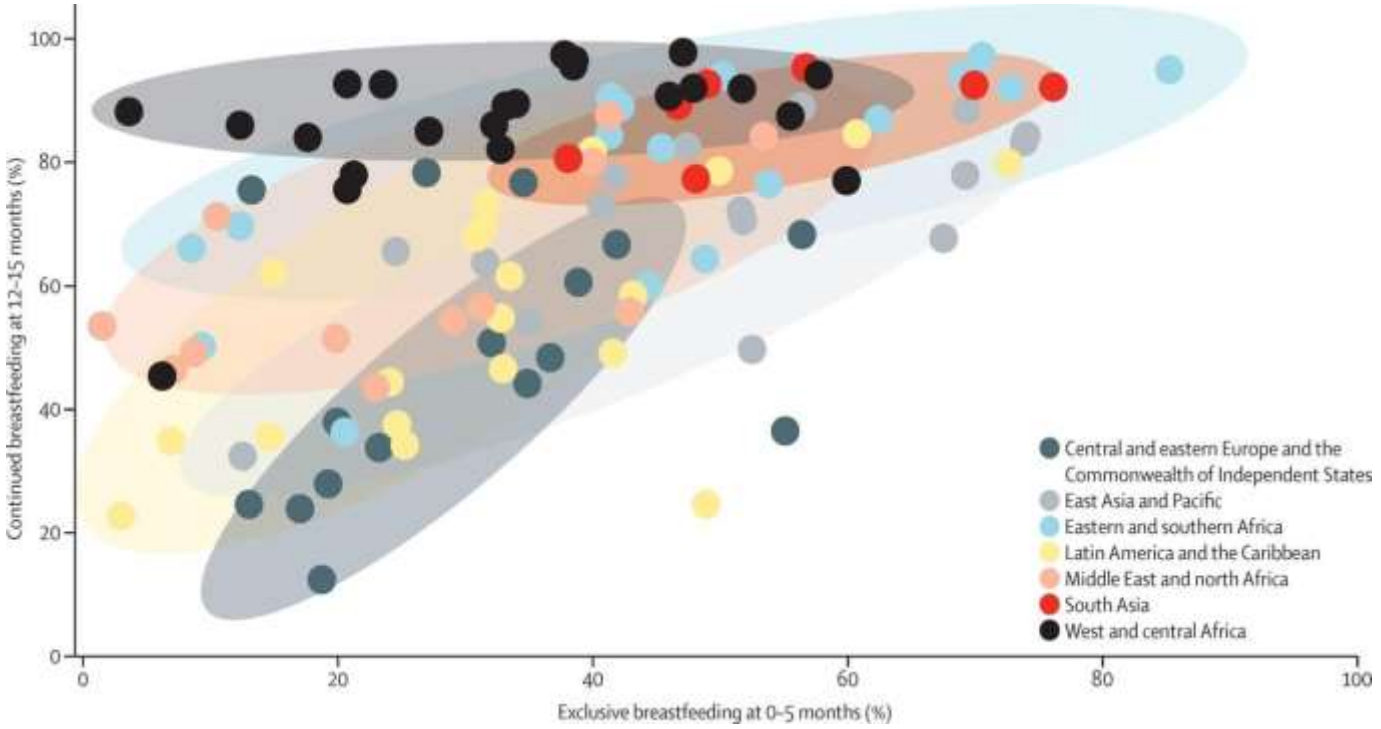
Lancet 2016; 387: 475–90



Global Patterns of Breastfeeding

- In most country groups, the majority of mothers initiated breastfeeding; only **France, Spain, and the USA** reported rates below **80%** for ever breastfeeding.
- Across all settings, **early initiation** and **exclusive breastfeeding** rates were consistently low.
- Breastfeeding at **12 months of age** was common in **low-income and lower-middle-income** settings but relatively uncommon in higher-income contexts.

Lancet 2016; 387: 475–90



Regional Variation in Breastfeeding Practices

- Countries in **eastern and southern Africa** generally showed **lower rates of continued breastfeeding** but **higher rates of exclusive breastfeeding** compared with those in **west Africa**.
- In **Latin America and the Caribbean**, as well as **central and eastern Europe and the Commonwealth of Independent States**, both indicators tended to be **lower than in Africa**.
- **South Asian countries** exhibited **high rates of both exclusive and continued breastfeeding**.
- Countries in the **Middle East and North Africa** generally reported **lower rates** for both indicators.
- **East Asia and the Pacific** showed **moderate to high prevalence** of both exclusive and continued breastfeeding.

Lancet 2016; 387: 475–90

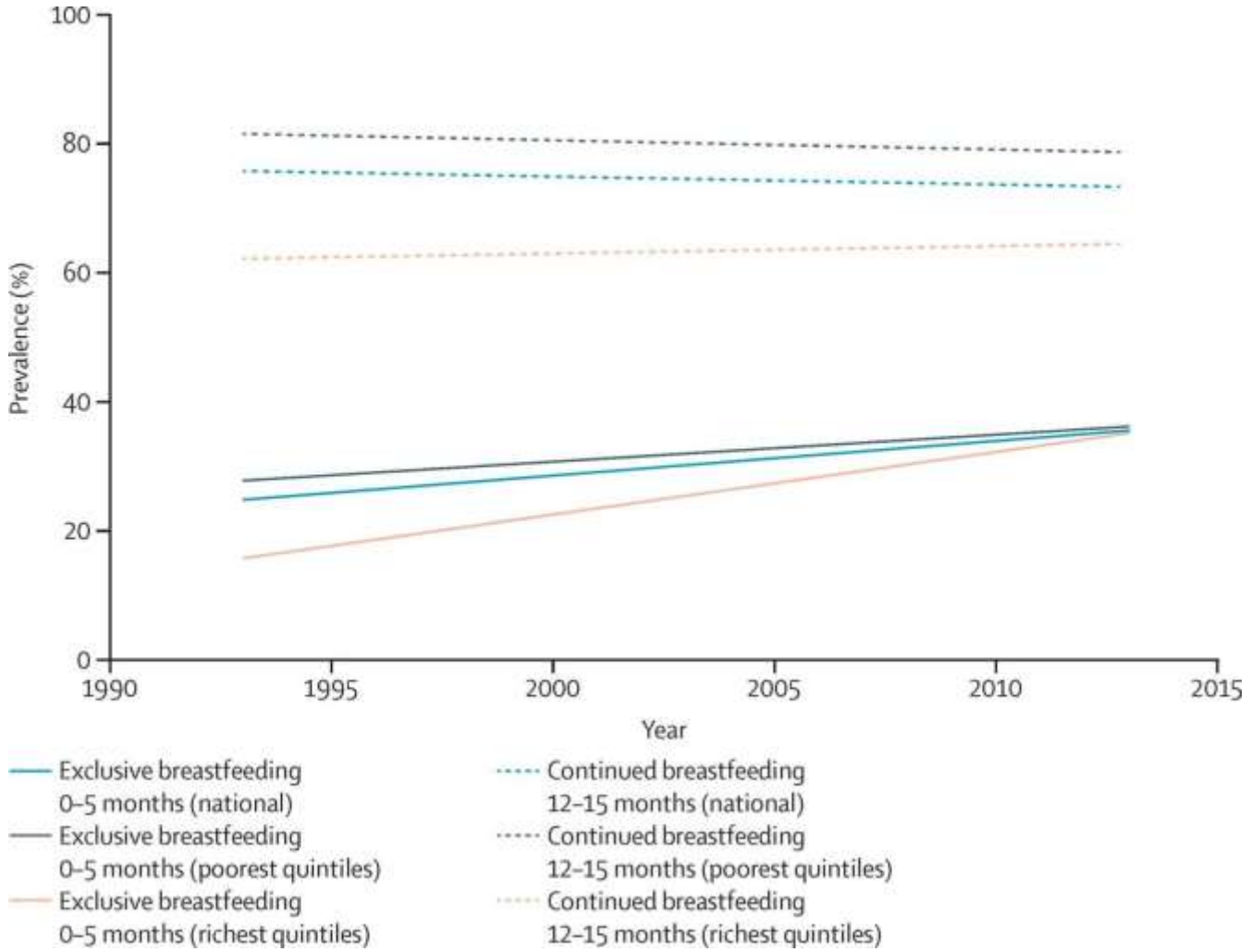
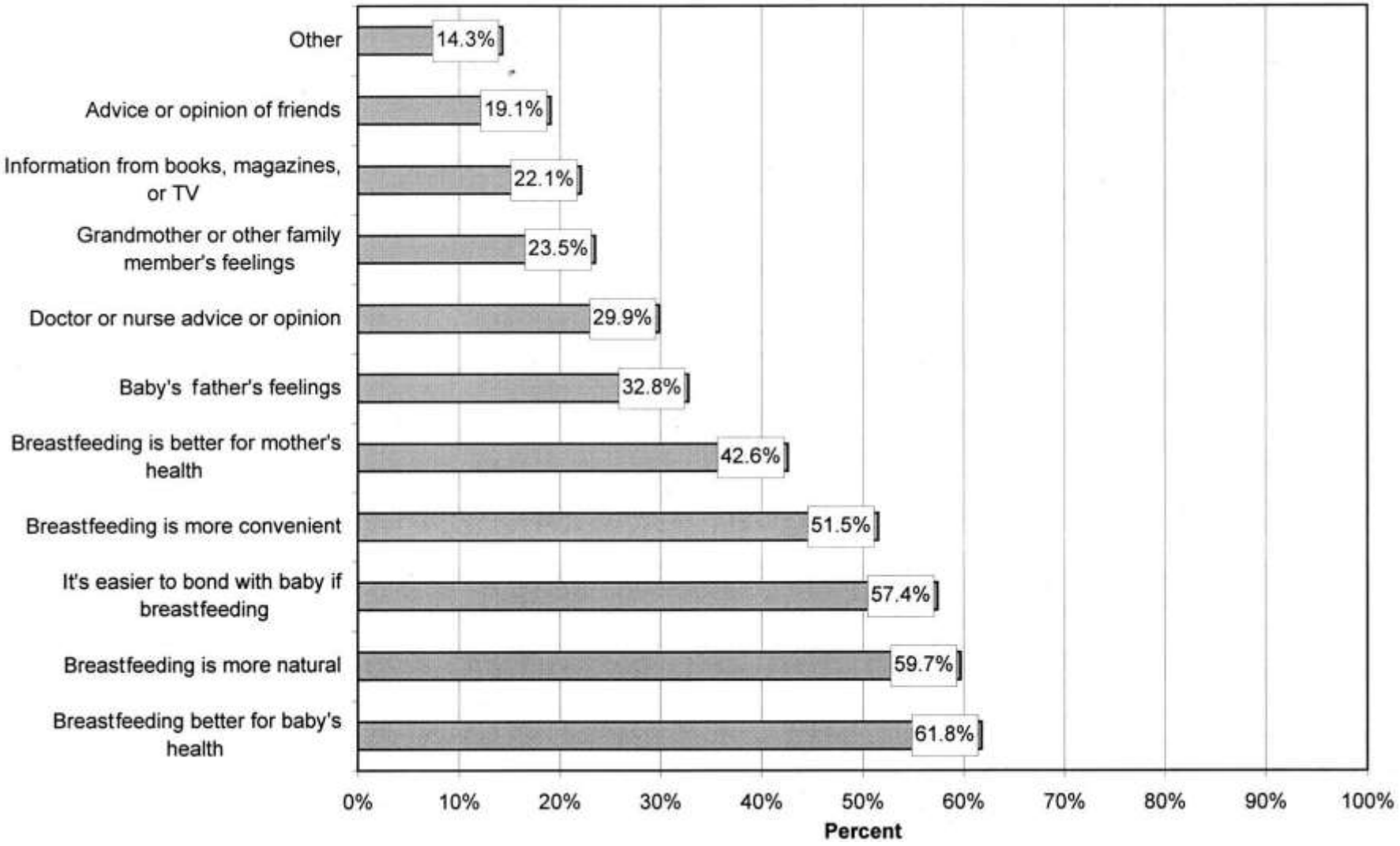


Figure 4: **National and wealth quintile-specific time trends in exclusive and continued breastfeeding, 1993–2013**

Data are weighted by national populations of children younger than 2 years at the time of the survey. Analyses restricted to 66 countries with information about household wealth.

Major Factors Influencing Breastfeeding Rates: Mother's Perception of Father's Attitude and Milk Supply



Pediatrics November 2000, VOLUME 106 / ISSUE 5

Physiology of Lactation and Early Immune Protection

- Under the influence of the hormones **prolactin** and **oxytocin**, milk production is initiated following childbirth to meet the nutritional needs of the newborn.
- The initial milk produced, known as **colostrum**, is rich in **immunoglobulin A (IgA)**, which coats the gastrointestinal tract and provides passive immune protection.
- This immune protection supports the newborn during the early postnatal period, before the infant's own immune system is fully developed.
- Milk production operates on a **supply-demand mechanism**, whereby the frequency of nursing and/or pumping directly influences the volume of milk produced.
- Feeding in response to infant cues, rather than according to a rigid schedule, supports this physiological regulation of milk production

Colostrum vs breastmilk

Fat (g/100 ml)	
total	4.2
fatty acids - length 8C	trace
polyunsaturated fatty acids	0,6
cholesterol	0,016
Protein (g/100 ml)	
total	1.1
casein	0.4
a-lactalbumin	0.3
lactoferrin (apo-lactoferrin)	0.2
IgA	0.1
IgG	0.001
lysozyme	0.05
serum albumin	0.05
ß-lactoglobulin	-
Carbohydrate (g/100 ml)	
lactose	7
oligosaccharides	0.5
Minerals (g/100 ml)	
calcium	0.03
phosphorus	0.014
sodium	0.015
potassium	0.055
chlorine	0.043

Human Milk Oligosaccharides (HMOs)

- Breast milk contains **human milk oligosaccharides (HMOs)**, a unique class of carbohydrates that are **not present in infant formula**.
- HMOs are **not digested by the infant** but contribute to the development of the **intestinal microbiota**.
- They function as **decoy receptors**, inhibiting the attachment of pathogenic microorganisms to the intestinal epithelium and thereby reducing infection risk.
- HMOs also **modulate immune cell responses**, supporting immune development during early life.
- To date, **more than 100 distinct HMOs** have been identified, with substantial **interindividual variation** in both their number and composition, and each HMO may exert **specific biological functions**.

Nutrient	Human Milk	Cow's Milk	Goat's Milk
Calories	172	146	168
Protein (g)	2.5	7.9	8.7
Fat (g)	10.8	7.9	10.1
Saturated fat (g)	4.9	4.6	6.5
Monounsaturated fat (g)	4.1	2.0	2.7
Polyunsaturated fat (g)	1.2	0.5	0.4
Carbohydrate (g)	17.0	11.0	10.9
Folate (mcg)	12	12	2
Vitamin C (mg)	12.3	0	3.2
Sodium (mg)	42	98	122
Iron (mg)	0.07	0.07	0.12
Calcium (mg)	79	276	327

Place of storage	Temperature	Maximum storage time
In a room	25 °C	Six to eight hours
Insulated thermal bag with ice packs		Up to 24 hours
In a refrigerator	4 °C	Up to five days
Freezer compartment inside a refrigerator	-15 °C	Two weeks
A combined refrigerator and freezer with separate doors	-18 °C	Three to six months
Chest or upright manual defrost deep freezer	-20 °C	Six to twelve months

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PLoS one

Genetic Variants of the *FADS* Gene Cluster and *ELOVL* Gene Family, Colostrums LC-PUFA Levels, Breastfeeding, and Child Cognition

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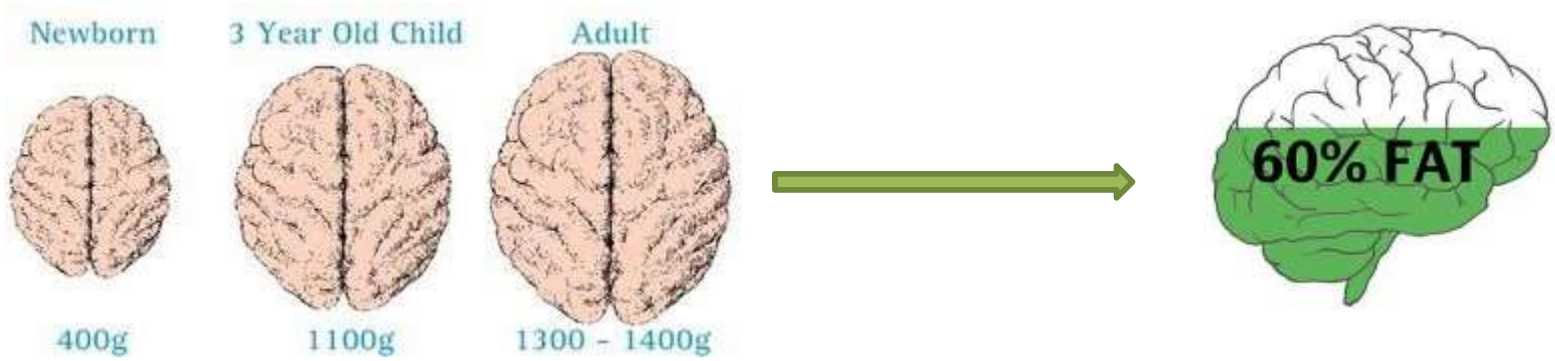
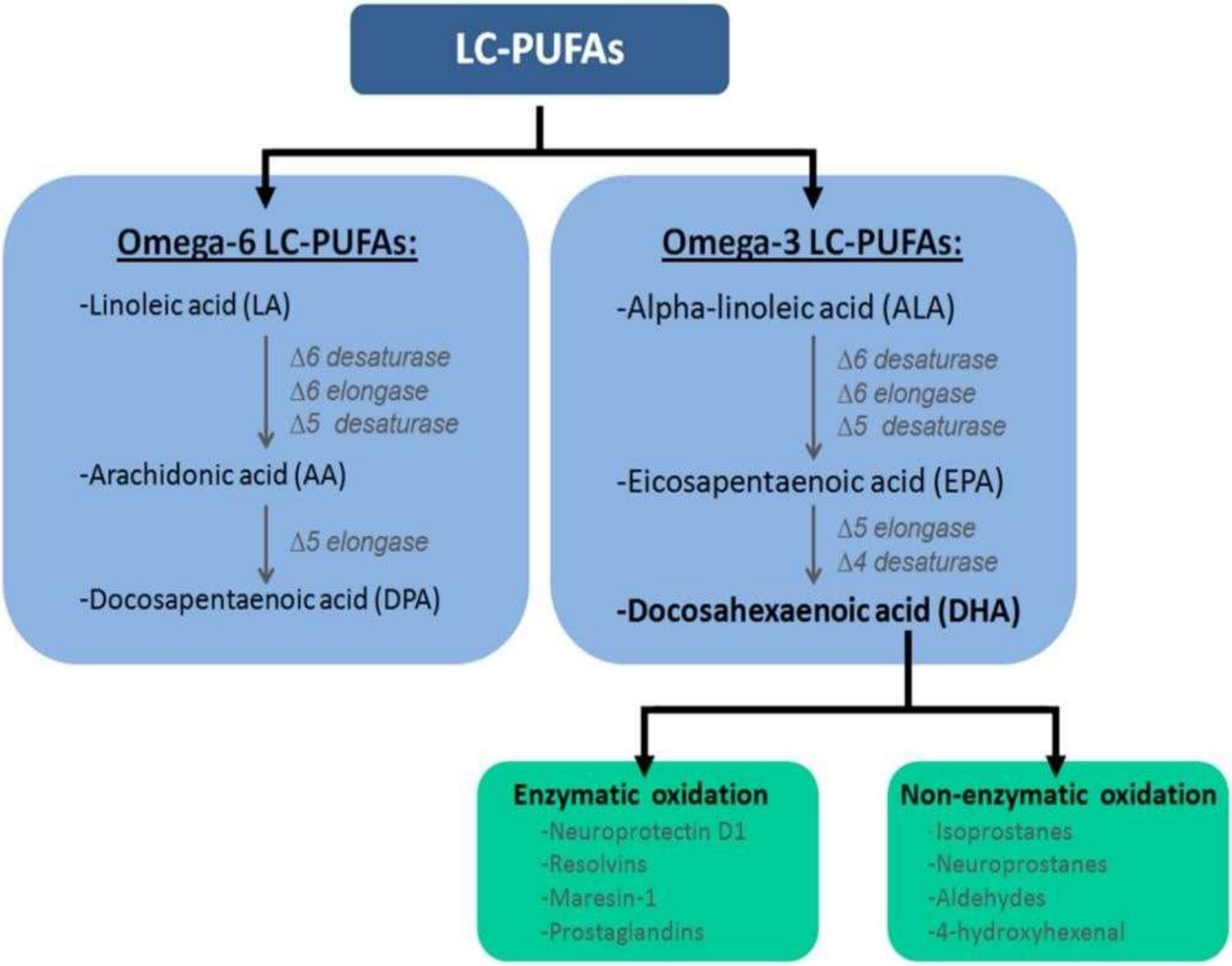
Aims

1. to determine whether maternal genetic variants in the FADS cluster and ELOVL genes contribute to differences in LC-PUFA levels in colostrum
2. to analyze whether these maternal variants are related to child cognition
3. to assess whether children's variants modify breastfeeding effects on cognition.

The majority of dry weight in an adult brain is composed of lipids, **35% of which** are long chain polyunsaturated fatty acids (**LC-PUFAs**)




LC-PUFAs
Omega-6 LC-PUFAs:
-Linoleic acid (LA)
Δ6 desaturase
Δ6 elongase
Δ5 desaturase
-Arachidonic acid (AA)
Δ5 elongase
-Docosapentaenoic acid (DPA)
Omega-3 LC-PUFAs:
-Alpha-linoleic acid (ALA)
Δ6 desaturase
Δ6 elongase
Δ5 desaturase
-Eicosapentaenoic acid (EPA)
Δ5 elongase
Δ4 desaturase
-Docosahexaenoic acid (DHA)
Enzymatic oxidation
-Neuroprotectin D1
-Resolvins
-Maresin-1
-Prostaglandins
Non-enzymatic oxidation
-Isoprostanes
-Neuroprostanes
-Aldehydes
-4-hydroxyhexenal

Long-Chain Polyunsaturated Fatty Acids (LC-PUFAs) and Brain Development

- During pregnancy, the fetus is supplied with **preformed maternal long-chain polyunsaturated fatty acids (LC-PUFAs)** via **placental transfer**.
- Following birth, **breast milk provides a unique postnatal source** of essential LC-PUFAs, including **eicosapentaenoic acid (EPA)**, **arachidonic acid (AA)**, and **docosahexaenoic acid (DHA)**.
- These fatty acids support the **accretion of LC-PUFAs in the developing brain**, contributing to early brain growth and maturation.

Two 25-mL samples of human breast milk:
foremilk (left) and **hindmilk** (right), collected during the same pumping session.

Assessment of Mental Development

- Child cognitive development was assessed at a mean age of **14 months** (range: 12–17 months)
- Assessments were conducted by **two specially trained psychologists** using the **Bayley Scales of Infant Development (first edition)**.
- The primary outcome was the **Mental Development Index**, comprising **163 items** assessing age-appropriate cognitive functioning, including **performance abilities, memory, and early verbal learning**.

Table 1. FADS1, FADS2 and ELOVL5 enzymatic indexes according to maternal genotypes and LC-PUFA levels in colostrum.

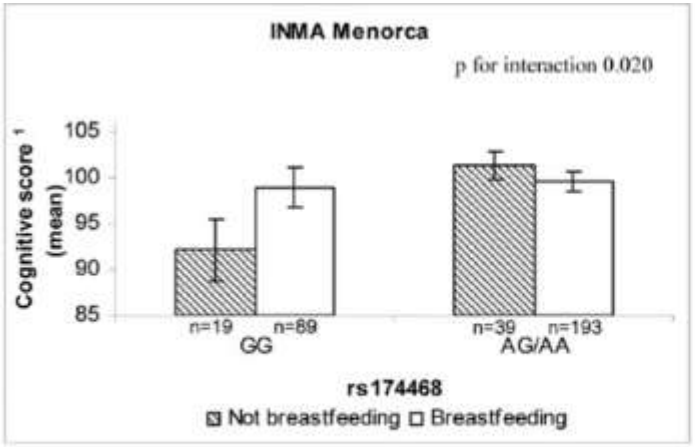
			11		12		22		
		Major/minor allele	N	Mean (sd)	N	Mean (sd)	N	Mean (sd)	p value*
FADS1 index									
AA:DGLA									
Gene	SNP								
FADS	rs174537	G/T	142	1.46 (0.02)	109	1.22 (0.03)	19	0.96 (0.08)	1.0×10^{-20}
FADS	rs968567	G/A	200	1.44 (0.02)	57	1.04 (0.03)	3	0.76 (0.08)	2.4×10^{-29}
FADS	rs2072114	A/G	219	1.35 (0.02)	49	1.23 (0.04)	2	0.93 (0.04)	0.0026
FADS	rs526126	C/G	160	1.37 (0.02)	66	1.25 (0.04)	2	1.06 (0.19)	0.0031
FADS	rs174626	T/C	66	1.43 (0.03)	141	1.32 (0.02)	63	1.25 (0.04)	0.0007
FADS	rs174627	C/T	209	1.37 (0.02)	56	1.20 (0.04)	5	0.99 (0.14)	7.5×10^{-06}
FADS	rs174464	C/T	116	1.41 (0.03)	103	1.26 (0.03)	19	1.20 (0.07)	7.2×10^{-05}
FADS	rs174468	G/A	100	1.28 (0.03)	124	1.34 (0.03)	40	1.43 (0.04)	0.0078
FADS2 indexes									
DGLA:LA									
Gene	SNP								
FADS	rs174537	G/T	142	0.06 (0.001)	109	0.07 (0.002)	19	0.09 (0.008)	8.5×10^{-06}
FADS	rs968567	G/A	200	0.06 (0.001)	57	0.09 (0.003)	3	0.11 (0.016)	1.1×10^{-15}
FADS	rs174627	C/T	209	0.06 (0.001)	56	0.07 (0.003)	5	0.08 (0.020)	0.0129
DHA:EPA									
Gene	SNP								
FADS	rs174602	A/G	209	1.65 (0.03)	56	1.56 (0.03)	5	1.42 (0.05)	0.0039
ELOVL5 index									
DPA:EPA									
Gene	SNP								
ELOVL5	rs2397142	C/G	125	7.81 (0.31)	112	8.08 (0.42)	31	10.02 (1.28)	0.0362

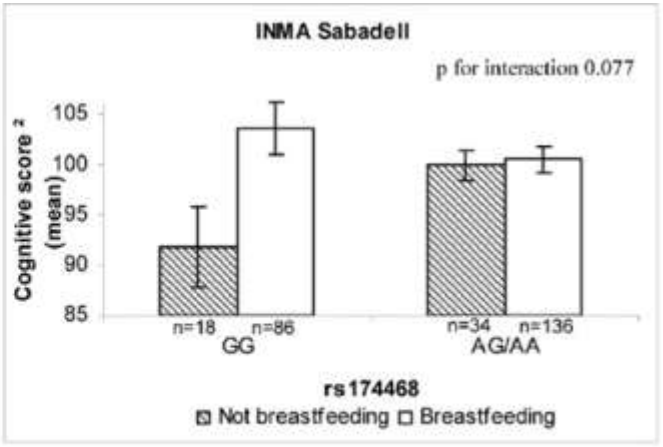
INMA Sabadell cohort.

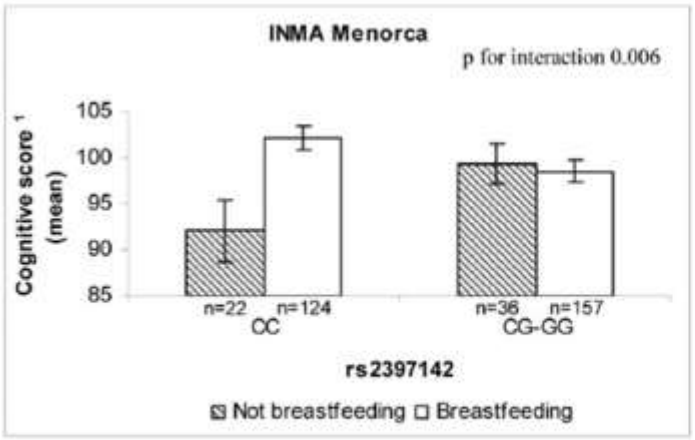
Major allele:1; minor allele:2. Data are means (standard error). *P-values for additive genetic models assuming a trend per copy of the minor allele.
AA: Arachidonic acid; DGLA: Eicosatrienoic acid; LA: Linoleic acid; DHA: Docosahexaenoic acid; DPA: Docosapentaenoic acid; EPA: Eicosapentanoic acid.

Table 2. Association between maternal genetic variants and child cognition at age 14 months.

			11		12		22		
	N	Major/minor allele	N	Score	N	Score	N	Score	p value*
***FADS* cluster**									
rs174537	400	G/T	203	99.5 (1.1)	169	101.0 (1.2)	28	100.7 (2.5)	0.130
rs968567	385	G/A	296	99.4 (0.9)	83	102.6 (1.6)	6	106.3 (4.7)	0.023
rs174570	347	C/T	279	101.0 (0.9)	64	98.5 (2.0)	4	95.8 (3.8)	0.330
rs2072114	399	A/G	310	100.2 (0.9)	87	100.5 (1.5)	2	100.1 (5.7)	0.880
rs174602	393	A/G	230	101.3 (0.9)	137	98.8 (1.4)	26	98.3 (2.9)	0.027
rs526126	336	C/G	234	99.9 (1.0)	99	102.8 (1.6)	3	105.8 (8.3)	0.059
rs174626	399	T/C	102	99.9 (1.4)	209	99.5 (1.1)	88	102.2 (1.7)	0.240
rs174627	399	C/T	313	99.4 (0.9)	82	103.1 (1.5)	4	109.4 (10.3)	<0.001
rs7482316	382	A/G	310	100.7 (0.9)	70	98.0 (2.0)	2	97.2 (20.1)	0.474
rs174464	348	C/T	174	98.3 (1.2)	149	102.2 (1.2)	25	106.6 (2.2)	0.008
rs174468	392	G/A	141	100.4 (1.4)	187	100.1 (1.1)	64	99.9 (1.8)	0.563
ELOVL2									
rs3734397	400	A/G	212	100.9 (0.9)	168	99.1 (1.2)	20	102.7 (4.5)	0.291
rs953413	387	G/A	114	99.2 (1.4)	193	101.1 (1.1)	80	100.0 (1.7)	0.398
rs10498676	392	G/A	288	100.0 (0.9)	94	101.7 (1.6)	10	92.6 (7.6)	0.583
rs6936315	338	T/C	241	100.5 (1.0)	89	101.0 (1.7)	8	102.2 (4.1)	0.844
rs3798719	385	C/T	196	99.7 (1.2)	151	101.6 (1.2)	38	96.3 (2.2)	0.849
rs13204015	389	T/C	356	100.7 (0.8)	32	98.1 (3.1)	1	97.2 (0.0)	0.309
ELOVL5									
rs17544159	383	A/C	332	99.4 (0.8)	51	105.1 (2.0)	-	-	0.016
rs2281274	394	T/C	210	99.7 (1.1)	147	100.6 (1.3)	37	101.7 (2.4)	0.275
rs2294859	392	T/C	332	100.8 (0.9)	56	99.2 (1.7)	4	92.9 (8.3)	0.983
rs9395855	399	T/G	105	98.3 (1.6)	204	101.0 (1.0)	90	100.8 (1.7)	0.633
rs11968589	390	C/T	310	100.5 (0.9)	74	99.1 (1.9)	6	96.2 (5.6)	0.601
rs2397142	397	C/G	173	99.7 (1.1)	178	100.1 (1.2)	46	101.9 (2.1)	0.499
rs12207094	398	A/T	287	99.1 (0.9)	106	102.8 (1.4)	5	119.1 (7.4)	0.003







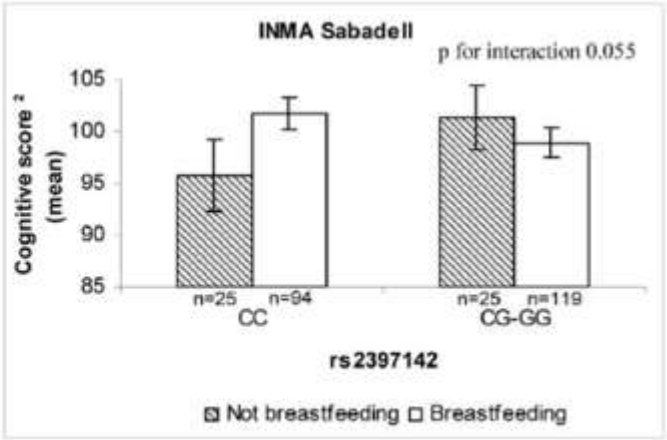


Figure 2. Child cognition scores by child' genetic SNPs in the *FADS* gene cluster (rs174468) and *ELOVL5* gene (rs2397142), by breastfeeding and cohort. Bars represent standard error. [1]Adjusted for sex, school trimester at testing, maternal social class, maternal education,

Not being breastfed resulted in a disadvantage in cognition

- (**9 points in INMA-Menorca** and **8 points in INMA-Sabadell**) among children **GG homozygotes for rs174468** *(low FADS1 index)*, but not among those carrying at least one copy of the **A allele** *(high FADS1 index)*.

- **8 points in INMA-Menorca** and **5 points in INMA-Sabadell**) among children **CC homozygotes for rs2397142** *(low ELOVL5 index)*, but not among those carrying at least one copy of the **G allele** *(high ELOVL5 index)*.

- In contrast, **breastfed children did not differ in cognition score**, irrespective of their genetic variants in these polymorphisms.

Table 3. Child cognition scores* (mean and standard error (SE)) by levels of LC-PUFA in colostrum and by rs2397142 (*ELOVL5* gene) among breast fed children of the INMA Sabadell cohort.

	rs2397142 CC			rs2397142 CG-GG			
	N	Mean	SE	N	Mean	SE	p for interaction
EPA/AA ratio							
Low	25	96.1	3.5	41	100.7	2.3	0.029
High	40	104.8	2.4	37	98.0	2.9	
DHA/AA ratio							
Low	35	96.8	2.8	39	98.6	2.7	0.018
High	30	106.9	2.7	39	100.2	2.4	

AA: Arachidonic acid; EPA: Eicosapentanoic acid; DHA: Docosahexaenoic acid.
*Adjusted for sex, age (days), psychologist, quality of neuropsychological test, maternal education, and use of gas stove at home.

- Results of the present study showed that **LC-PUFA supply during pregnancy and lactation**, genetically determined by **maternal desaturase and elongase activities**, appears to have functional importance for **infant brain development**.

- In addition, breastfeeding effects on **cognition** are modified by **child genetic variants** in desaturase and elongase enzymes involved in the control of **LC-PUFA pathways**.

Does a short breastfeeding period protect from *FTO*-induced adiposity in children?

Dedoussis et al., 2011

Does a short breastfeeding period protect from *FTO*-induced adiposity in children?

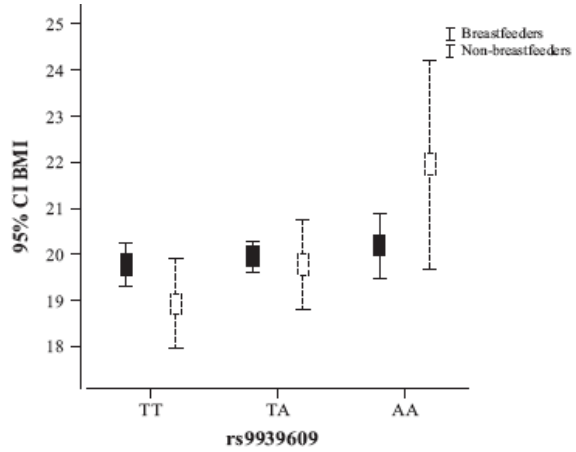
Table I. Anthropometric variables and *FTO* genotyping in all children cohorts.

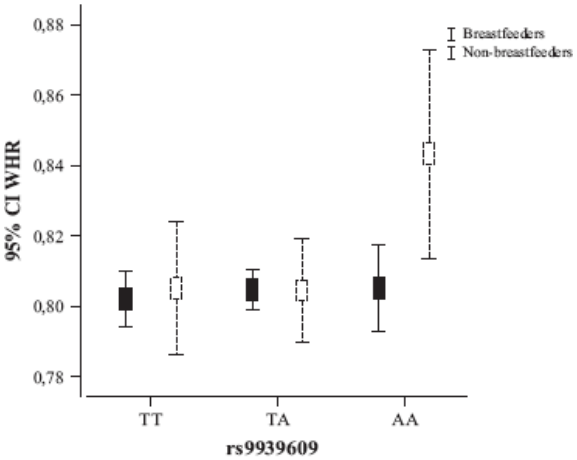
	GENDAI	ALSPAC	GENESIS	
FTO variant	rs9939609 (T>A)		rs17817449 (T>G)	
n	922	6131	394	775
Age (years)	11.2 ± 0.6	11.7 ± 0.22	2–3	3–4
Sex (m/f) (%)	46.9/53.1	51.5/48.5	54.8/45.2	52.9/47.1
BMI (kg/m^2)	20.0 ± 3.4	19.05 ± 3.4	16.4 ± 1.5	16.2 ± 1.6
Waist (cm)	68.7 ± 9.6	68.3 ± 9.4	49.5 ± 3.3	51.4 ± 3.9
WHR	0.8 ± 0.1	0.84 ± 0.06	0.9 ± 0.0	0.9 ± 0.0
Tricept Skinfolds (mm)	19.4 ± 7.5	NA	9.6 ± 2.5	9.5 ± 2.7
Subscapular	11.4 ± 5.3	NA	6.7 ± 2.1	6.7 ± 2.1
Genotype (%)	AA (16.1)	AA (15.50)	GG (20.7)	GG (22.1)
	TA (52.0)	TA (47.17)	TG (32.6)	TG (33.5)
	TT (32.0)	TT (37.33)	TT (46.7)	TT (44.4)
MAF	A(0.421)	A(0.39)	G(0.370)	G(0.388)

Table IV. Multiple linear regression models for the *FTO* polymorphisms *rs9939609* and *rs17817449*.

	GENDAI		ALSPAC		GENESIS			
					2–3 years		3–4 years	
Dependent variable	Beta (SE)	*P*	Beta (SE)	*P*	Beta (SE)	*P*	Beta (SE)	*P*
BMI (kg/m^2)	0.430 (0.166)	**0.009**	**0.542 (0.096)**	**1.961e-08**	–0.046 (0.095)	0.621	0.093 (0.073)	0.203
Waist circumference (cm)	1.067 (0.456)	**0.019**	**1.468 (0.263)**	**2.803e-08**	0.033 (0.213)	0.876	0.473 (0.181)	**0.008**
WHR	0.004 (0.003)	0.061*	**0.005 (0.002)**	**0.004**	–0.001 (0.003)	0.625	0.000 (0.002)	0.989
Triceps skinfold (mm)	0.972 (0.367)	**0.003***	NA	NA	–0.018 (0.163)	0.929	0.221 (0.122)	0.068
Subscapular skinfold (mm)	0.593 (0.261)	**0.023**	NA	NA	–0.099 (0.134)	0.454	0.227 (0.095)	**0.014**

The models in GENDAI and GENESIS were adjusted for the following confounders: age, sex, physical inactivity, Tanner stage. For the same confounders except age all models were adjusted in ALSPAC. Beta coefficients represent the effect of each extra minor allele. P* values are from log transformed variables.


95% CI BMI
25
24
23
22
21
20
19
18
TT
TA
AA
rs9939609
Breastfeeders
Non-breastfeeders


95% CI WHR
0,88
0,86
0,84
0,82
0,80
0,78
TT
TA
AA
rs9939609
Breastfeeders
Non-breastfeeders

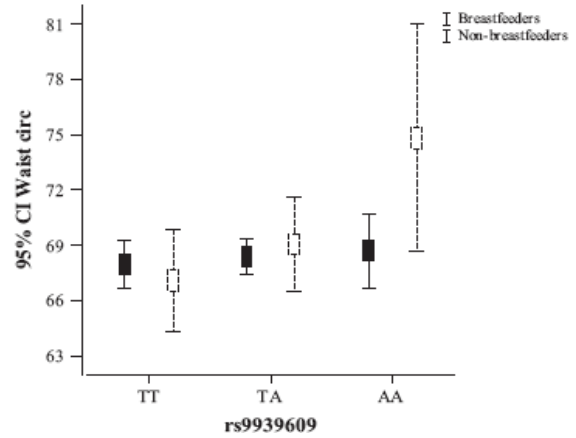

95% CI Waist circ
81
78
75
72
69
66
63
TT
TA
AA
rs9939609
Breastfeeders
Non-breastfeeders

Table V. Multivariate linear regression models for the interaction between breastfeeding (breastfeeders vs. non-breastfeeders) and *FTO* polymorphism *rs9939609*.

	GENDAI		ALSPAC		GENESIS			
					2–3 years		3–4 years	
Dependent variable	Beta (SE)	*P*	Beta	*P*	Beta (SE)	*P*	Beta (SE)	*P*
BMI (kg/m^2)	–0.025 (0.040)	0.528	0.010	0.957	–0.076 (0.028)	**0.007**	–0.005 (0.021)	0.78
Waist circumference (cm)	–0.144 (0.110)	0.190	NA	NA	–0.040 (0.064)	0.51	0.03 (0.051)	0.59
WHR	–0.001 (0.001)	**0.009***	–0.004	0.138	0.001 (0.001)	0.055	0.0003 (0.001)	0.53
Triceps skinfold (mm)	–0.030 (0.089)	0.922*	NA	NA	–0.04 (0.049)	0.42	–0.083 (0.035)	**0.015**
Subscapular skinfold (mm)	–0.076 (0.063)	0.228	NA	NA	0.007 (0.041)	0.85	–0.025 (0.027)	0.35

The models were adjusted for potential confounders: In all cohorts we adjusted for sex, physical inactivity and breastfeeding. ALSPAC and GENDAI were additionally adjusted for Tanner stage while GENDAI peri-adolescents were further adjusted for age. Beta coefficients represent the effect of each extra minor allele. P* values are from log transformed variables. NA: Not available.

Table VI. Number of obese children included, stratified by genotype and breastfeeding category.

	GENDAI			ALSPAC			GENESIS					
	10–12 years			11–12 years			2–3 years			3–4 years		
	TT	TA	AA	TT	TA	AA	TT	TG	GG	TT	TG	GG
Breastfeeders (BF)	19	24	7	38	84	29	10	8	1	15	32	12
Non-breastfeeders (N-BF)	5	6	4	30	52	21	7	9	4	14	18	13
Ratio BF/N-BF	3.8	4	1.75	1.27	1.61	1.38	1.43	0.9	0.25	0.9	1.8	0.9

In summary, our findings indicate that breastfeeding may exert a modifying effect on the relationship between *FTO* variants and adiposity indices in Greek children from the ages of three upwards. Longitudinal data are needed in order to evaluate whether the breastfeeding protection on the FTO-influenced phenotype is maintained beyond adolescence and whether the breastfeeding protection is also associated with other metabolic and inflammatory markers.

Gene polymorphisms, breast-feeding, and development of food sensitization in early childhood

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- **Food sensitization (FS)** in early childhood is defined by in vitro measurement of **food-specific IgE** (sIgE **>0.35 kUA/L** to a food allergen). FS is an important precursor of **food allergy** and other allergic diseases.
- FS identified at **≥2 years of age** is more likely to represent **persistent** sensitization.
- Follow-up assessments were conducted at **6–12 months**, and at **2, 4, and 6 years**, consistent with routine pediatric visit schedules.

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TABLE I. Population characteristics of 970 children from the Boston Birth Cohort stratified by breast-feeding status

Variable	Never breast-fed (n = 231)	Ever breast-fed (n = 739)	*P* value*
Maternal age (y)	27.7 ± 6.4	28.9 ± 6.2	.01
Maternal BMI (kg/m^2)	26.8 ± 6.0	26.6 ± 6.4	.66
Child's age (y)	2.5 ± 2.3	2.6 ± 2.2	.73
Maternal smoker during pregnancy	56 (24.2)	40 (5.4)	<.001
Maternal smoker after delivery	91 (39.4)	77 (10.4)	<.001
Maternal race			<.001
African American	133 (57.6)	439 (59.4)	
White	31 (13.4)	26 (3.5)	
Hispanic	39 (16.9)	186 (25.2)	
Other	28 (12.1)	88 (11.9)	
Maternal education			.001
Primary or secondary	88 (38.1)	215 (29.1)	
High school	88 (38.1)	257 (34.8)	
College or greater	55 (23.8)	267 (36.1)	
Household income at visits			.11
<$30,000	110 (47.6)	324 (43.8)	
≥$30,000	22 (9.5)	110 (14.9)	
Unknown	99 (42.9)	305 (41.3)	
Maternal history of allergy, yes	95 (41.1)	255 (34.5)	.19
Paternal history of allergy, yes	45 (19.5)	123 (16.6)	.45
Family history of allergy, yes	118 (51.1)	330 (44.7)	.23
Child's sex, boy (%)	124 (53.7)	362 (49.0)	.24
Preterm birth	65 (28.1)	189 (25.6)	.49
Parity, first born	89 (38.5)	304 (41.1)	.53
Cesarean section	80 (34.6)	236 (31.9)	.62
Pets in the first year, yes	47 (20.3)	112 (15.2)	.13
Detectable CBIgE†	119 (51.5)	398 (53.9)	.68
Allergic disease in the first 4 mo‡	43 (18.6)	121 (16.4)	.71

- In early childhood, plasma concentrations of **food-specific IgE** were measured for **eight food allergens** (egg white, cow's milk, peanut, soy, shrimp, walnut, wheat, and cod) using **ImmunoCAP** at **Quest Diagnostics**, following the manufacturer's protocol.
- The assay detection range was **0.35–100 kUA/L**. **Food sensitization (FS)** was defined as **specific IgE ≥0.35 kUA/L** to **any** of the eight food allergens.
- Compared with never breast-fed children, ever breast-fed children were more likely to have a mother who was **nonsmoking**, **Hispanic**, **older at delivery**, and had a **higher education level**.

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TABLE II. Association between breast-feeding and FS in 970 children from the Boston Birth Cohort

Variable	No.	FS (%)	Crude			Adjusted*		
			OR	95% CI	*P* value	OR	95% CI	*P* value
All children								
Breast-feeding								
Never breast-fed	231	29.4	Reference			Reference		
Ever breast-fed	739	39.6	1.6	1.1-2.2	.005	1.5	1.1-2.1	.019
Exclusive breast-feeding duration†								
Never breast-fed	231	29.4	Reference			Reference		
<4 mo	484	38.4	1.5	1.1-2.1	.019	1.5	1.0-2.2	.034
≥4 mo	200	40.4	1.6	1.1-2.4	.022	1.6	1.1-2.5	.029
Children <2 y								
Breast-feeding								
Never breast-fed	139	30.2	Reference			Reference		
Ever breast-fed	414	36.2	1.3	0.9-2.0	.198	1.1	0.7-1.8	.616
Exclusive breast-feeding duration†								
Never breast-fed	139	30.2	Reference					
<4 mo	291	35.7	1.3	0.8-2.0	.259	1.1	0.7-1.8	.743
≥4 mo	97	36.1	1.3	0.8-2.3	.345	1.2	0.7-2.2	.573
Children ≥2 y								
Breast-feeding								
Never breast-fed	92	28.3	Reference			Reference		
Ever breast-fed	325	44.0	2.0	1.2-3.3	.007	2.3	1.3-4.1	.003
Exclusive breast-feeding duration†								
Never breast-fed	92	28.3	Reference			Reference		
<4 mo	193	42.5	1.9	1.1-3.2	.022	2.4	1.3-4.3	.005
≥4 mo	103	43.7	2.0	1.1-3.6	.026	2.6	1.3-5.0	.006

*Adjusted by maternal age at delivery, family history of allergy, maternal education, maternal smoking during pregnancy, maternal smoking after delivery, child's age when FS was defined, sex, ancestral proportion, pets in the first year, and allergic disease during the first 4 months of life.
†Fifty-five ever breast-fed children have missing data on exclusive breast-feeding duration.

The prevalence of FS in breast-fed children (39.6%) was higher than that for never breast-fed children. FS was stronger in children aged 2 or more years

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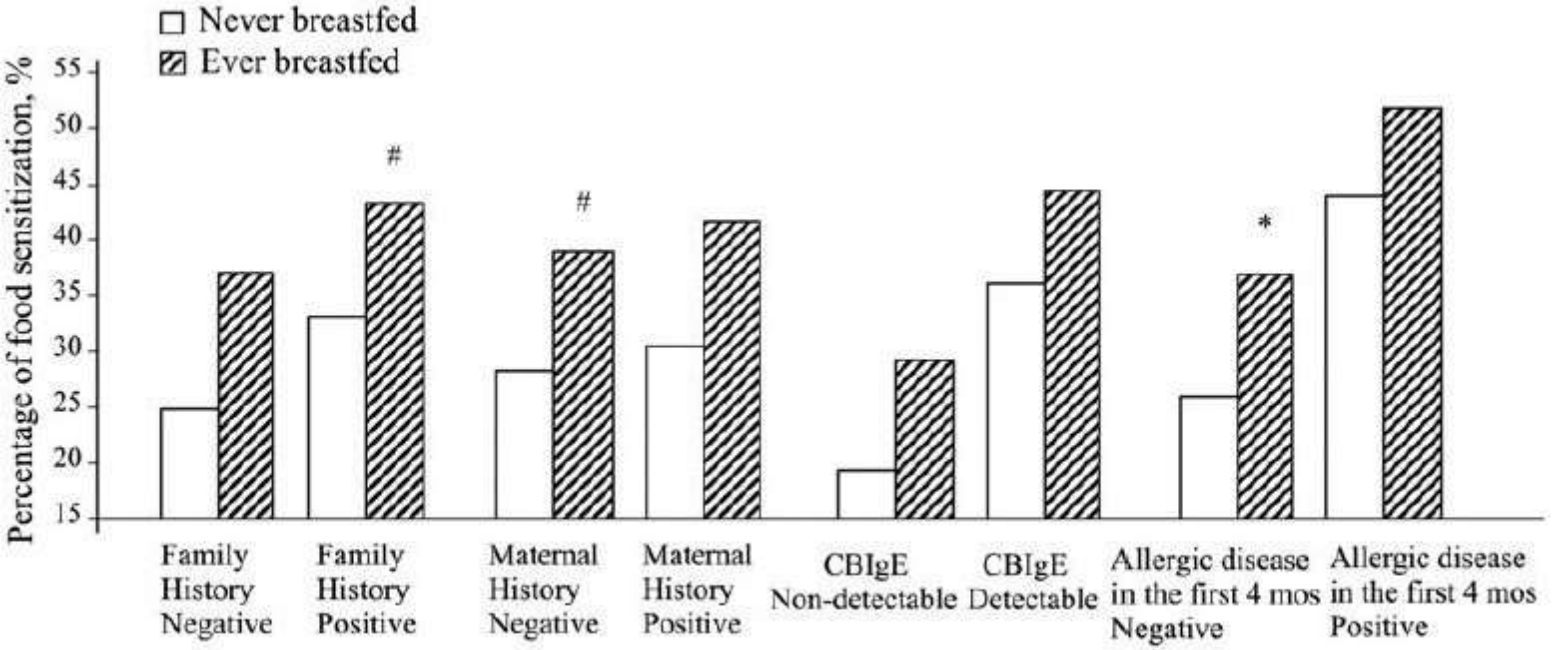

FIG 1. Plot for the association between breast-feeding and FS in 970 children from the Boston Birth Cohort

The relationship between the 2 breast-feeding measures and FS did not vary by family history of allergy, which indicated no effect modification. Similar results were found for the other 2 early signs of allergy

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TABLE III. Gene–breast-feeding interactions on FS in 970 children from the Boston Birth Cohort

SNP*	Genotype	No. (FS [%])		BF-FS association†		*P* value for interaction
		Not BF	BF	OR (95% CI)	*P* value	
IL12RB1						
rs425648	GT+TT	57 (40.4)	189 (31.7)	0.6 (0.3-1.4)	.252	.0007‡
	GG	174 (25.9)	550 (42.4)	2.0 (1.4-3.1)	.0005	
IL-13 receptor α gene *(IL13RA1)*						
rs2495637	AA	29 (48.3)	60 (26.7)	0.2 (0.1-0.8)	.026	.004
	GG+GA	202 (26.7)	678 (40.9)	1.8 (1.2-2.6)	.003	
rs2495619	TT+CT	46 (43.5)	123 (38.2)	0.7 (0.3-1.6)	.433	.035
	CC	185 (25.9)	614 (39.9)	1.9 (1.3-2.8)	.002	
TSLP						
rs3806933	CC	109 (36.7)	342 (37.7)	0.9 (0.6-1.5)	.777	.006
	CT+TT	121 (23.1)	396 (41.4)	2.4 (1.4-4.0)	.0008	
TLR9						
rs352140	CC	83 (36.1)	337 (35.9)	0.9 (0.5-1.6)	.812	.012
	CT	108 (27.8)	296 (41.2)	2.0 (1.2-3.4)	.012	
	TT	40 (20.0)	106 (47.2)	4.7 (1.5-14.9)	.009	
IL4						
rs2243250	CT+CC	150 (32.0)	467 (34.7)	1.1 (0.7-1.7)	.692	
	TT	80 (25.0)	268 (48.5)	2.9 (1.5-5.4)	.001	.022

TABLE IV. Gene-environment interaction between exclusive breast-feeding duration and *IL12RB1*, *TLR9*, and *TSLP* SNPs on FS in 970 children from the Boston Birth Cohort

IL12RB1

	rs425648 = GG		rs425648 = GT/TT		
Duration*	No. (FS [%])	OR (95% CI)†	No. (FS [%])	OR (95% CI)†	*P* for interaction
Never BF	174 (25.9)	Reference	57 (40.4)	Reference	.0007‡
<4 mo	358 (40.2)	1.9 (1.3-3.0)‖	126 (33.3)	0.7 (0.3-1.5)	
≥4 mo	153 (43.8)	2.4 (1.5-4.0)¶	47 (27.7)	0.4 (0.2-1.1)	

TSLP

	rs3806933 = CC		rs3806933 = CT/TT		
Duration*	No. (FS [%])	OR (95% CI)†	No. (FS [%])	OR (95% CI)†	*P* for interaction
Never BF	109 (36.7)	Reference	121 (23.1)	Reference	.001‡
<4 mo	226 (38.1)	1.0 (0.6-1.7)	258 (38.8)	2.2 (1.3-3.7)‖	
≥4 mo	91 (33.0)	0.7 (0.4-1.4)	108 (46.3)	3.1 (1.7-5.8)¶	

TLR9

	rs352140 = CC		rs352140 = CT		rs352140 = TT		
Duration*	No. (FS [%])	OR (95% CI)†	No. (FS [%])	OR (95% CI)†	No. (FS [%])	OR (95% CI)†	*P* for interaction
Never BF	83 (36.1)	Reference	108 (27.8)	Reference	40 (20.0)	Reference	.0007‡
<4 mo	227 (37.9)	1.1 (0.6-2.0)	187 (39.0)	1.7 (1.0-3.1)	70 (38.6)	3.3 (1.0-10.9)	
≥4 mo	85 (30.6)	0.8 (0.4-1.5)	84 (40.5)	2.1 (1.0-4.0)§	31 (64.5)	13.2 (3.0-57.3)¶	

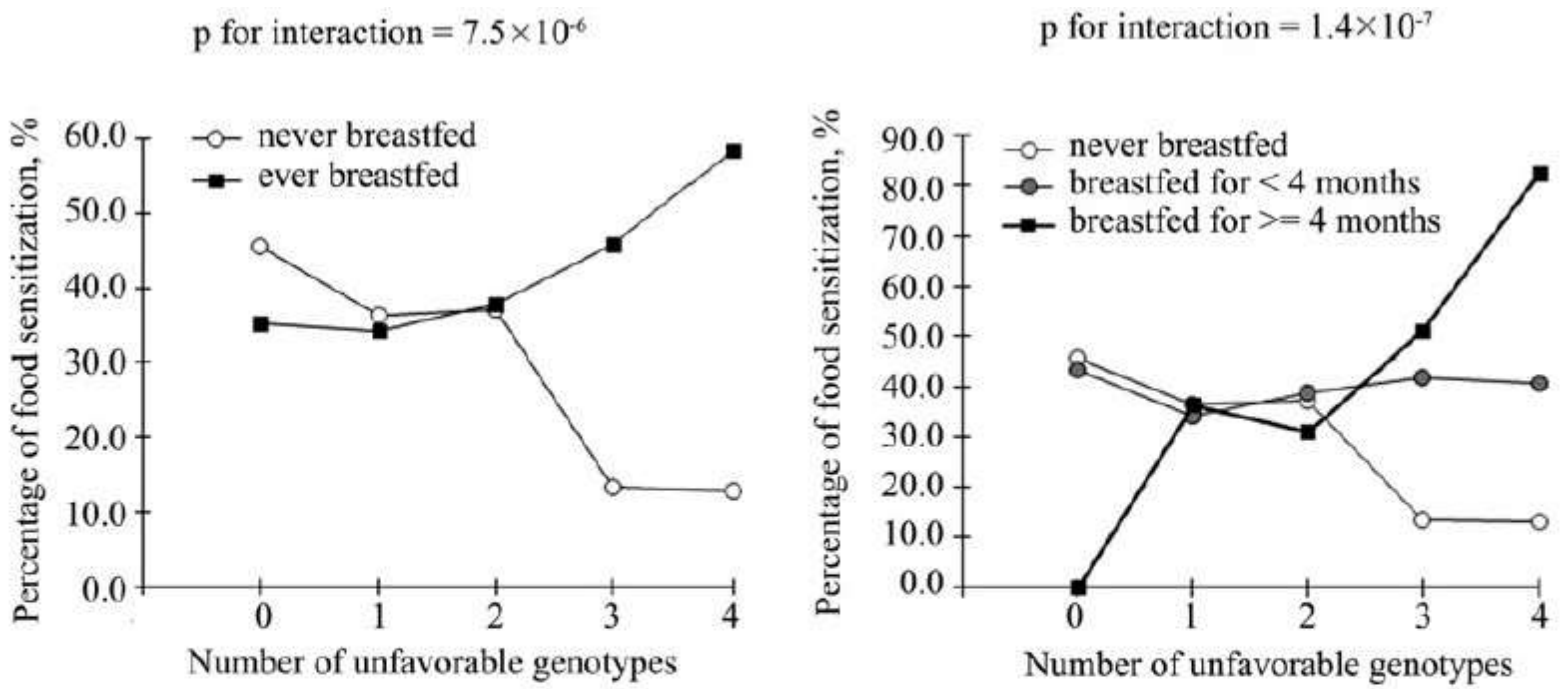

FIG 2. Gene-environment interaction effect between breast-feeding and the number of unfavorable genotypes of the *IL12RB1* (rs425648), *TSLP* (rs3806933), and *TLR9* (rs352140) genetic variants on FS in 970 children from the Boston Birth Cohort. The unfavorable genotype is defined as that for which breast-feeding increased the risk of FS, which is GG for rs425648, CT/TT for rs3806933, and the T allele for rs352140.

- Breastfeeding tended to be associated with a **decreased risk of food sensitization (FS)** among children carrying **0 unfavorable genotypes**. This association was **attenuated** as the number of unfavorable genotypes increased, and it was **significantly reversed** among children carrying **≥3 unfavorable genotypes**.
- These patterns supported a **gene × breastfeeding interaction** (**P for interaction = 7.5×10^{-26}**) and a **gene × exclusive breastfeeding duration interaction** on FS (**P for interaction = 1.4×10^{-27}**).

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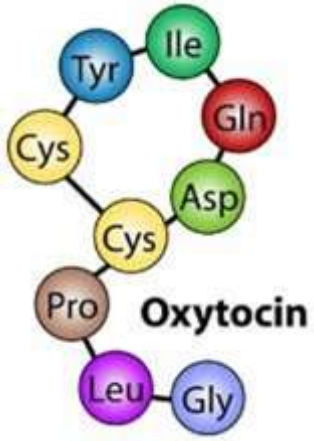
Genetic variation in oxytocin rs2740210 and early adversity associated with postpartum depression and breastfeeding duration

Genes, Brain and Behavior (2013) ***12:*** *681–694*

Oxytocin: Roles in Lactation and Maternal Physiology

- **Oxytocin** is a **nine-amino acid peptide** with a highly conserved structure across mammalian species.
- During **labor**, oxytocin promotes **uterine contractions**.
- During **lactation**, oxytocin triggers **milk ejection (let-down)** by contracting **myoepithelial cells** surrounding the alveoli in response to infant suckling.
- Oxytocin also acts in the central nervous system as a **neuropeptide**, released in brain regions activated during **parturition and caregiving**.



Postpartum Depression and Breastfeeding

Epidemiological studies suggest that **10–20%** of mothers experience **depressive symptoms** during the first postpartum weeks; symptoms often improve within **6–12 months**.

Postpartum depression is associated with:

- more negative maternal cognitions and parenting behaviors, and
- adverse consequences for **infant emotional and developmental outcomes**.

Postpartum depression is also linked to a **reduced likelihood of breastfeeding** and **shorter breastfeeding duration**.

In this study, the authors examined whether:

1. **Oxytocin-related polymorphisms** (OXT **rs2740210**, **rs4813627**, and OXTR **rs237885**) are associated with **breastfeeding initiation** and **breastfeeding duration** during the **first year postpartum**.

1. **Early adversity** and **maternal depressive symptoms** are associated with **breastfeeding duration**.

1. **Maternal depression mediates** the association between **early adversity** and breastfeeding, and whether OXT-related polymorphisms **moderate** this mediation (i.e., a **moderated mediation** model).

Table 1: Overview of the allele distribution of *OXT rs2740210* and *rs4813625* and *OXTR rs237885* and their associations with the occurrence of breastfeeding at 3, 6 and 12 months postpartum in the Hamilton and Montreal samples

Genotype	Exclusive breastfeeding 3 months	Exclusive breastfeeding 6 months	Any breastfeeding 3 months	Any breastfeeding 6 months	Any breastfeeding 12 months	Group comparisons
Hamilton sample						
OXT rs2740210 AA (20), *CA* (77), *CC* (104)	$\chi^2 = 4.68$, df = 1, $P = 0.022$	$\chi^2 = 6.43$, df = 1, $P = 0.010$			$\chi^2 = 4.05$, df = 1, $P = 0.033$	>Proportions of mothers with an A allele (*AA*/*AC*) breastfeed at these time points
OXT rs4813625 AA (44), *AG* (71), *GG* (44)						ns
OXTR rs237885 GG (41), *CG* (72), *CC* (49)						ns
Montreal sample						
OXT rs2740210 AA (12), *CA* (63), *CC* (76)					$\chi^2 = 3.581$, df = 1, $P = 0.074$	
OXT rs4813625 AA (45), *AG* (74), *GG* (34)	$\chi^2 = 7.735$, df = 2, $P = 0.021$		$\chi^2 = 7.265$, df = 2, $P = 0.026$			>Proportions of mothers with an A allele (*AA*/*AG*) breastfeed at these time points
OXTR rs237885 GG (37), *CG* (68), *CC* (47)					$\chi^2 = 4.844$, df = 2, $P = 0.089$	

No significant associations were observed between **exclusive breastfeeding** or **any breastfeeding** and maternal depression for **OXT rs4813627** or **OXTR rs237885**. Therefore, all subsequent analyses focused on **OXT rs2740210** only.

Early life adversity

- The self-report **Childhood Trauma Questionnaire (CTQ)** was used for measuring childhood abuse experiences
- It consists of **28 items** that assess early adverse experiences (physical, emotional and sexual abuse and emotional and physical neglect) during childhood and adolescence.
- **It quantifies** the frequency of these experiences on a 5-point scale (from 0=never to 5=very often).
- Cutoff scores define the **severity of the early adverse experiences** (none or minimal, minor, moderate and severe)

Maternal mood

The Center for Epidemiological Studies Depression Scale (CES-D) (Radloff 1977) was used to assess maternal mood at 6months postpartum.

This self-assessment scale has 20 items in a 4-point response format between 0 and 3, for an overall score ranging from 0 (no depression) to 60 (highest level of depression).

Scores of 27 or more indicate a major depression

Table 2: Means and standard deviations of breastfeeding duration, demographic variables, early experience (CTQ) and depression (CES-D) scores in mothers as a function of *OXT rs2740210* genotype in the (a) MAVAN Hamilton sample and (b) Montreal replication sample

	OXT rs2740210			
(a)	*AA* ($n = 14–20$)	*CA* ($n = 58–77$)	*CC* ($n = 79–104$)	Group comparisons
Breastfeeding duration (weeks)	31.57 (20.87)	29.18 (18.43)	23.93 (18.28)	ns
Birth weight (g)	3620 (329)	3552 (591)	3395 (451)	$F_{2,166} = 2.650$, $P = 0.074$
Maternal age	30 (5.04)	30 (5.08)	30 (5.24)	ns
Family income*	14.13 (2.16)	13.94 (3.64)	13.45 (4.04)	ns
Maternal education†	15.65 (2.47)	15.96 (3.01)	16.08 (3.04)	ns
CTQ scores during pregnancy	1.41 (0.53)	1.51 (0.62)	1.50 (0.56)	ns
CES-D scores at 6 months postpartum	27.29 (10.25)	26.16 (9.58)	26.72 (10.54)	ns
Partner (% yes)	85	85	80	ns
Parity (% primiparae)	31	29	32	ns
Boys (%)	69	51	65	ns

	OXT rs2740210			
(b)	*AA* ($n = 9–12$)	*CA* ($n = 43–63$)	*CC* ($n = 63–76$)	Group comparisons
Breastfeeding duration (weeks)	31.75 (19.7)	22.85 (19.02)	27.95 (20.23)	ns
Birth weight (g)	2918 (438)	3187 (357)	3273 (385)	$F_{2,144} = 4.404$, $P = 0.014$
Maternal age	29.8 (8.47)	28.96 (4.03)	29.01 (4.51)	ns
Low SES and low education (%)‡	22.2	19.3	26.9	ns
CTQ at 24 months postpartum	1.26 (0.31)	1.38 (0.42)	1.51 (0.57)	ns
CES-D scores at 6 months postpartum	10.58 (10.63)	8.66 (7.56)	11.95 (9.61)	ns
EPDS scores 6 months	4.11 (3.76)	4.74 (3.47)	5.95 (4.57)	ns
Boys (%)	25	42.9	51.3	ns

SES, socioeconomic status.

*Combined family income during pregnancy, where 12 = at least $40 000, 13 = between $40 000 and $50 000, 14 = between $50 000 and $60 000 and 15 = between $60 000 and $80 000 per year.

†Maternal education, where 15 = high school (HS) diploma + 1 year of college or trade, 16 = HS diploma + diploma in trade or college, 17 = HS diploma plus some university but without completion and 18 = Bachelor degree.

Table 3: Correlations between breastfeeding, maternal demographic variables, early adversity (CTQ) and depression (CES-D) in the (a) Hamilton sample and (b) Montreal sample

(a)*	Breastfeeding duration (weeks)	Birth weight (g)	Maternal age	Family income	Maternal education	CTQ scores
Birth weight (g)	0.002					
Maternal age	0.257**	−0.042				
Family income	0.164*	−0.089	0.481**			
Maternal education	0.304**	−0.041	0.529**	0.465**		
CTQ scores during pregnancy	−0.189*	−0.01	−0.081	−0.111	−0.200**	
CES-D scores at 6 months postpartum	−0.216**	−0.04	−0.223**	−0.159	−0.237**	0.455**

(b)†	Breastfeeding duration (weeks)‡	Birth weight (g)	Maternal age	SES	CTQ scores
Birth weight (g)	0.103				
Maternal age	0.243**	0.029			
SES	0.170*	0.112	0.156*		
CTQ scores at 24 months postpartum	0.004	0.093	−0.087	−0.136	
CES-D scores at 6 months postpartum	−0.173*	0.02	−0.156*	−0.329**	0.337**

They found significant associations between the two variants of OXT rs2740210 (CC vs. AA/AC carriers) and exclusive breastfeeding at 3 and 6months postpartum ($\chi 2 = 4.68$, df=1, $P = 0.022$ and $\chi 2 = 6.43$, df=1, $P = 0.010$) as well as partial breastfeeding at 12 months postpartum ($\chi 2 = 4.05$, df=1, $P = 0.033$).

Duration of breastfeeding correlated significantly with maternal age ($r = 0.257$), CTQ score ($r = -0.189$) and CES-D score ($r = -0.216$).

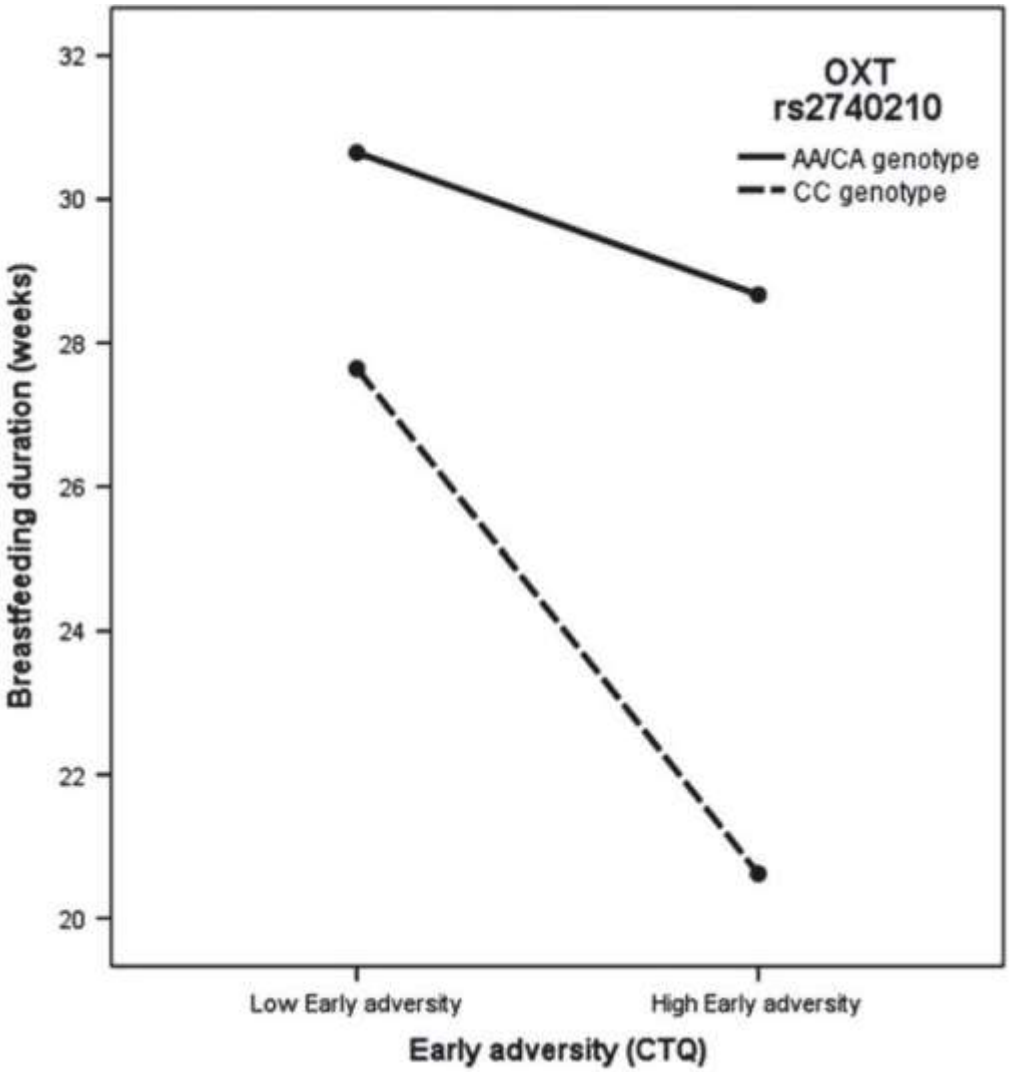


Figure 1: Interaction between *OXT rs2740210* and early adversity on breastfeeding duration during the first postpartum year in mothers (primary sample, $n = 127$). In mothers possessing the *CC* genotype, high early adversity is associated with lower breastfeeding duration. Breastfeeding duration

Thus, *OXT rs2740210* moderates the duration of breastfeeding in the context of early adversity (high levels on the CTQ scale): mothers who score higher on the CTQ breastfeed longer [38.6 (SD 19.8) weeks] if they possess the *AA/AC* genotype and breastfeed for a shorter duration [20.6 (SD 17.3) weeks] if they are homozygous for the *C* allele. This model explained 7.6% of the variance in breastfeeding duration.

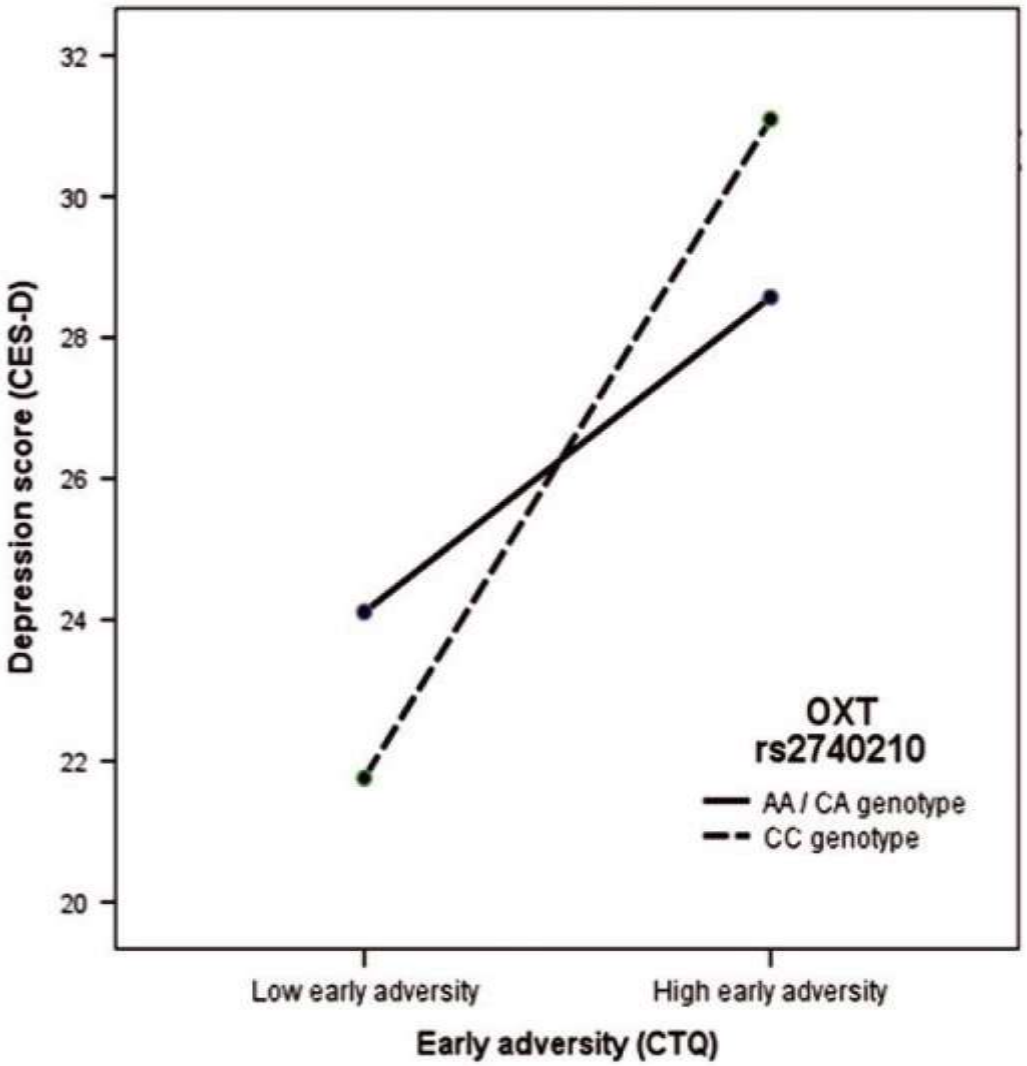


Figure 2: Interaction between *OXT rs2740210* genotype and early adversity on CES-D depression scores at 6 months postpartum in mothers (primary sample, *n* = 134). In mothers who carry the *CC* genotype, high adversity is associated with higher postpartum depression.

(Table 4b). This model explained 23.2% of the variance in depression scores.

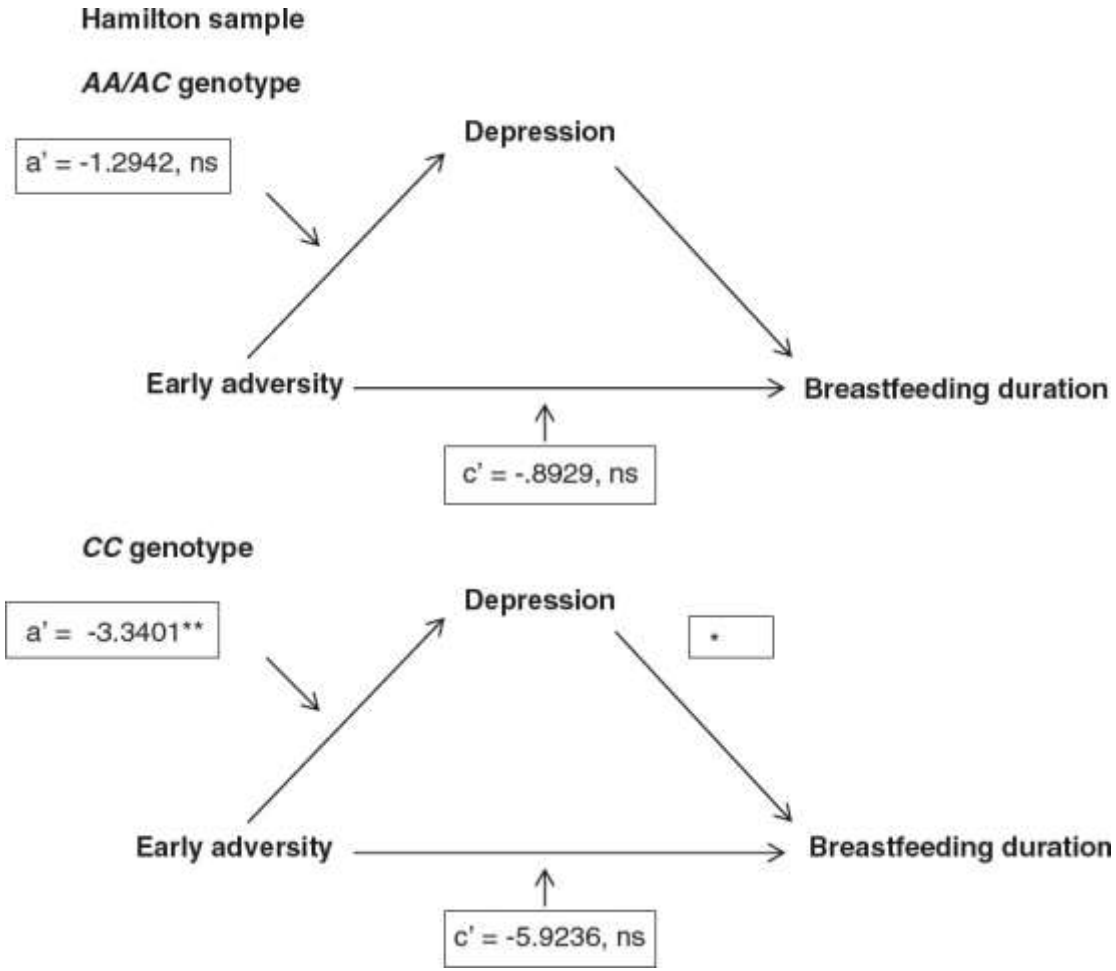


Figure 3: Moderated mediation model (PROCESS model 8) (Hayes 2013**) of the relationship between early experience, depression and breastfeeding duration and its moderation by *OXT rs2740210* genotype (*CC* genotype) in the Hamilton sample.** This model tests whether early adversity and the *OXT rs2740210* genotype (*CC* vs. *AA/AC* genotypes) interactively influence the mediator depression, which then influences the outcome variable breastfeeding duration. In this model ($n = 148$), there was no significant *direct* association of CTQ × *OXT rs2740210* [neither of *CC* ($c' = -5.9236$, ns) nor *AA/AC* ($c' = -0.8929$, ns) genotypes] on breastfeeding duration. However, there was a significant *indirect* path: the association between early adversity on breastfeeding duration was mediated through mothers' depression, but only among women possessing the *CC* genotype,

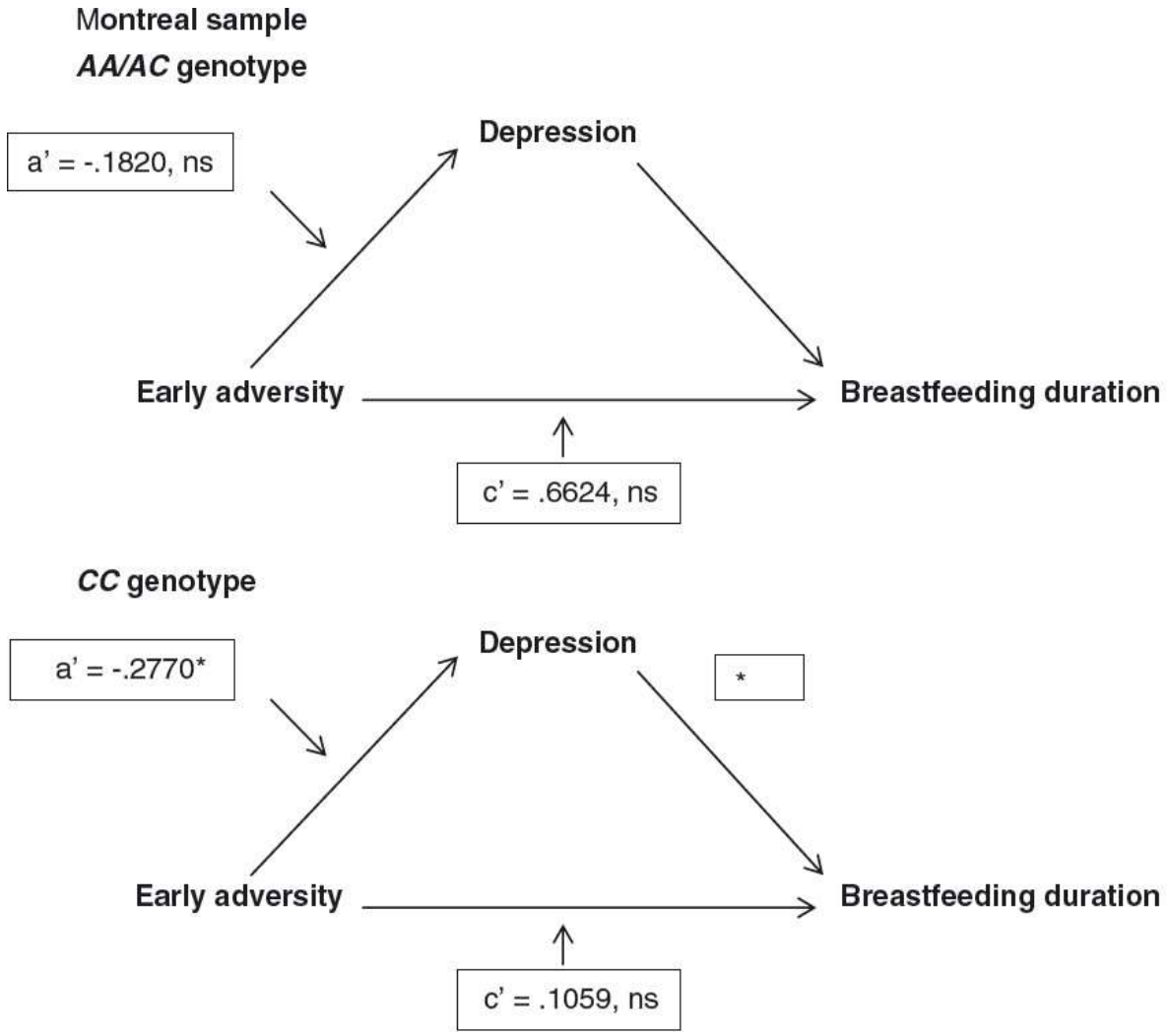


Figure 4: Moderated mediation model (PROCESS model 8) (Hayes 2013**) of the relationship between early experience, depression and breastfeeding duration and its moderation by *OXT rs2740210* genotype (*CC* genotype) in the Montreal sample.** In this model ($n = 111$), there was no significant *direct* association of CTQ × *OXT rs2740210*, but there was a significant *indirect* path: as in the Hamilton sample, the association between early adversity on breastfeeding duration was mediated through mothers' depression, but only among women possessing the *CC* genotype, $*P \leq 0.05$ [effect *a'* (unstandardized regression coefficients) = −0.2770*, 95% CI = −0.7987 to −0.0348] and not in the women with the *AA/AC* genotype (*a'* = −0.1820, ns).

Discussion

- **The main findings** of this study suggest that exposure to **early life adversity** in family of origin was associated with **elevated depression levels** in the mothers at **6 months postpartum**; depression levels were, in turn, associated with **reduced breastfeeding duration** across the **first postpartum year.**
- Moreover, variants in the **OXT rs2740210 moderated** the effects of early adversity on depression, such that mothers who experienced early adversity showed increased depression and reduced breastfeeding if they possessed the **CC genotype** of OXT rs2740210 but not if they possessed the **A allele (AA/AC genotypes).**
- Thus, depression plays an important role in determining the relationship between early adversity and breastfeeding outcome, **but only among women who are homozygous for the C allele**.
- The mechanism behind the association between OXT genotype and breastfeeding is less clear. OXT rs2740210 may be linked to breastfeeding performance through its association with the **milk ejection reflex** and to the **oxytocin release pattern** which is associated with the **amount of milk expressed** during a breastfeeding session. Mothers carrying at least one A allele may have a **more efficient milk release** in response to the suckling stimulus to facilitate further breastfeeding.
- OXT rs2740210 may also associate with breastfeeding beyond 'lactation' through an effect on **maternal behavior**, i.e. an effect moderated by **brain oxytocin.**

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ORIGINAL ARTICLE

EPIDEMIOLOGY AND GENETICS

FADS gene cluster modulates the effect of breastfeeding on asthma. Results from the GINIplus and LISAplus studies

M. Standl[1], S. Sausenthaler[1], E. Lattka[2], S. Koletzko[3], C.-P. Bauer[4], H.-E. Wichmann[1,5], A. von Berg[6], D. Berdel[6], U. Krämer[7], B. Schaaf[8], I. Lehmann[9], O. Herbarth[10], N. Klopp[2], B. Koletzko[3] & J. Heinrich[1] for the GINIplus* and LISAplus† Study Group

Table 1 Basic characteristics of the study population

	LISAplus (n = 789)	GINIplus (n = 1456)	Total (n = 2245)
Boys	56%	50%	52%
Intervention group	0%	50%	32%
High maternal education	58%	50%	53%
Presence of older siblings	47%	48%	48%
Study centre			
München	53%	56%	55%
Leipzig	25%	0%	9%
Bad Honnef	13%	0%	5%
Wesel	9%	44%	32%
Breastfeeding (BF)			
Number of months of exclusive BF	18%	26%	23%
1–2	13%	11%	12%
3–4	18%	16%	17%
5–6	51%	47%	48%
Asthma (DD)	9%	12%	11%
Atopic asthma (DD)	7%	8%	8%
Nonatopic asthma (DD)	1%	3%	2%

Table 2 Characteristics of the SNPs in the *FADS* gene cluster

SNP	Alleles (major/minor) 1/2	*N*	Number of subjects with Genotype (%) 11	12/22	Allele (%) 1	2
rs174545	G/C	2047	931 (45%)	1116 (55%)	2757 (67%)	1337 (33%)
rs174546	G/A	2076	946 (46%)	1130 (54%)	2799 (67%)	1353 (33%)
rs174556	G/A	2069	1033 (50%)	1036 (50%)	2927 (71%)	1211 (29%)
rs174561	A/G	2082	1040 (50%)	1042 (50%)	2951 (71%)	1213 (29%)
rs174575	C/G	2212	1236 (56%)	976 (44%)	3300 (75%)	1124 (25%)
rs3834458	T/del	2211	1016 (46%)	1195 (54%)	2995 (68%)	1427 (32%)

SNP, single-nucleotide polymorphisms.

Table 3 Prevalence of doctor-diagnosed asthma stratified by number of months of exclusive breastfeeding

	Number of months of exclusive BF	1–2	3–4	5–6	
	% (*n*/*N*)	% (*n*/*N*)	% (*n*/*N*)	% (*n*/*N*)	*P*-value*
Asthma ever (DD)					
No	86.0 (442/513)	87.0 (233/268)	89.0 (338/379)	91.0 (988/1085)	0.0172
Yes	14.0 (71/513)	13.0 (35/268)	11.0 (41/379)	9.0 (97/1085)	

Table 4 Prevalence of doctor-diagnosed asthma stratified by genotype

	Asthma ever (DD)	
	% (*n*/*N*)	*P*-value*
rs174545		
Allele 12/22	10.5 (117/1116)	0.3372
Allele 11	11.9 (111/931)	
rs174546		
Allele 12/22	10.4 (118/1130)	0.3105
Allele 11	11.9 (113/946)	
rs174556		
Allele 12/22	10.0 (104/1036)	0.1190
Allele 11	12.3 (127/1033)	
rs174561		
Allele 12/22	10.1 (105/1042)	0.1790
Allele 11	12.0 (125/1040)	
rs174575		
Allele 12/22	10.2 (100/976)	0.4944
Allele 11	11.2 (139/1236)	
rs3834458		
Allele 12/22	10.0 (120/1195)	0.2062
Allele 11	11.8 (120/1016)	

Figure 1 shows the association between asthma prevalence and the number of months of exclusive BF stratified by genotype for each of the six SNPs. The asthma prevalence is reduced in children who were exclusively breastfed for at least 3 months and are carrying the minor allele, whereas no effect is observed in homozygous major allele carriers.

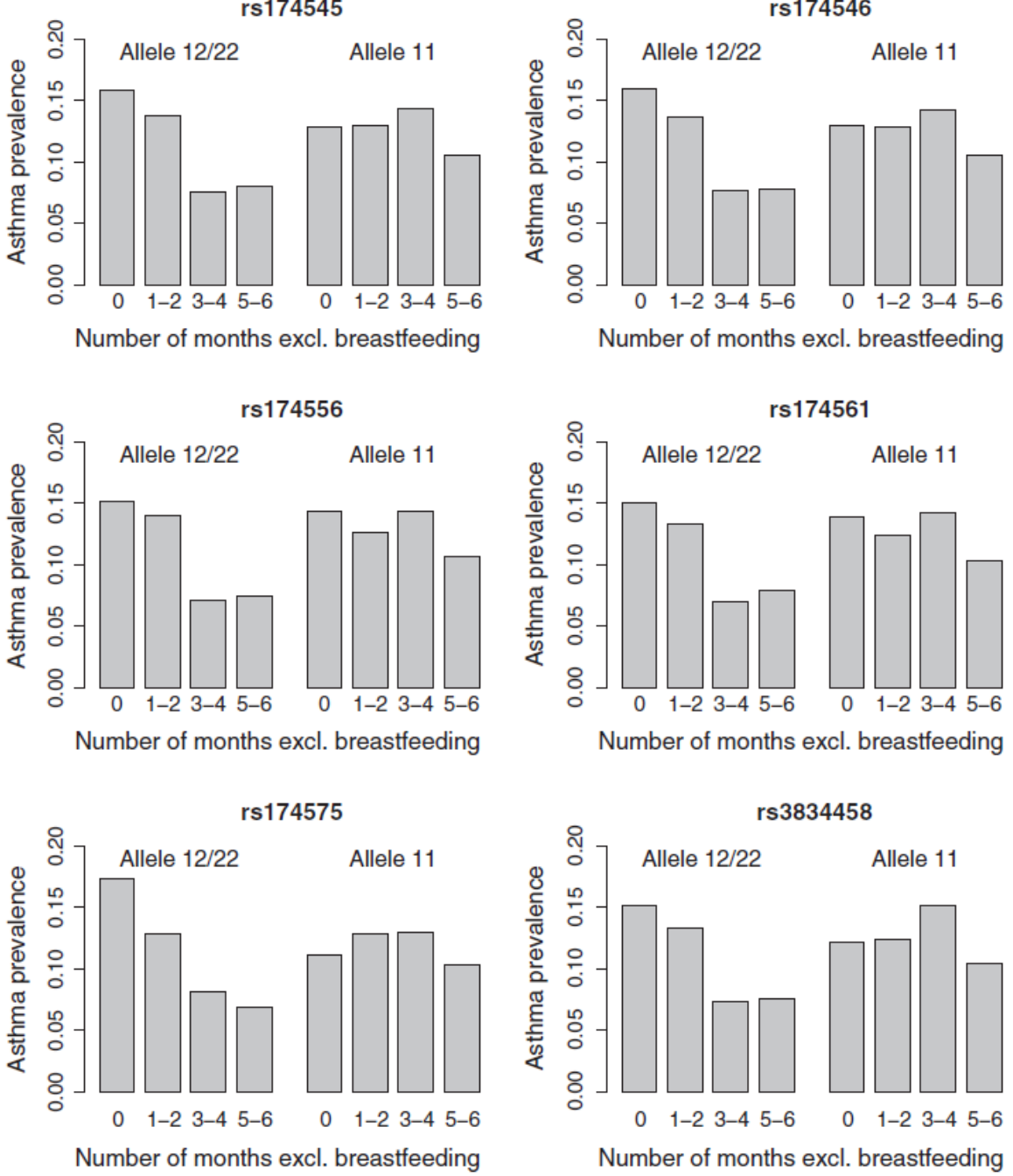


Figure 1 Asthma prevalence stratified by *FADS* genotype and breastfeeding (1: major allele, 2: minor allele).

Table 5 Results of logistic regression models of breastfeeding (BF) on asthma stratified by genotype, adjusted for gender, study centre, maternal education level, study (GINI intervention, GINI nonintervention, LISA) and presence of older siblings (reference category: never exclusive breastfeeding)

		Never exclusive BF	1–2 months exclusive BF		3–4 months exclusive BF		5–6 months exclusive BF	
	N	aOR	aOR (95% CI)	*P*-value*	aOR(95% CI)	*P*-value*	aOR (95% CI)	*P*-value*
rs174545								
Allele 12/22	1073	1	0.89 (0.48, 1.66)	0.7120	**0.38** (0.19, 0.76)	0.0062	**0.41** (0.24, 0.69)	0.0007
Allele 11	905	1	1.33 (0.61, 2.89)	0.4686	1.47 (0.75, 2.92)	0.2639	1.07 (0.60, 1.91)	0.8177
rs174546								
Allele 12/22	1085	1	0.90 (0.48, 1.68)	0.7462	**0.38** (0.19, 0.77)	0.0073	**0.41** (0.24, 0.68)	0.0006
Allele 11	919	1	1.33 (0.62, 2.89)	0.4640	1.48 (0.75, 2.92)	0.2600	1.09 (0.61, 1.94)	0.7725
rs174556								
Allele 12/22	997	1	0.98 (0.51, 1.87)	0.9413	**0.37** (0.18, 0.80)	0.0107	**0.41** (0.24, 0.72)	0.0018
Allele 11	1000	1	1.16 (0.56, 2.38)	0.6947	1.37 (0.73, 2.57)	0.3308	0.95 (0.56, 1.62)	0.8609
rs174561								
Allele 12/22	1003	1	1.02 (0.53, 1.95)	0.9624	**0.39** (0.18, 0.83)	0.0148	**0.47** (0.27, 0.81)	0.0065
Allele 11	1008	1	1.14 (0.55, 2.34)	0.7224	1.38 (0.73, 2.59)	0.3200	0.94 (0.55, 1.59)	0.8039
rs174575								
Allele 12/22	934	1	0.81 (0.41, 1.59)	0.5388	**0.42** (0.20, 0.88)	0.0224	**0.32** (0.18, 0.57)	0.0001
Allele 11	1204	1	1.44 (0.74, 2.81)	0.2844	1.32 (0.72, 2.41)	0.3706	1.17 (0.71, 1.94)	0.5372
rs3834458								
Allele 12/22	1149	1	0.94 (0.51, 1.73)	0.8338	**0.40** (0.20, 0.81)	0.0104	**0.42** (0.25, 0.71)	0.0011
Allele 11	988	1	1.25 (0.59, 2.68)	0.5609	1.44 (0.75, 2.76)	0.2745	1.07 (0.61, 1.86)	0.8189

aOR, adjusted odds ratios; 1, major allele; 2, minor allele.

*Estimates reaching significance after correcting for multiple testing (α_{corr} = 0.05/2 = 0.025) are marked in bold.

Individuals carrying the minor allele have a significant decreased asthma risk if they are exclusively breastfed for 3 or 4 months or more than 5 months

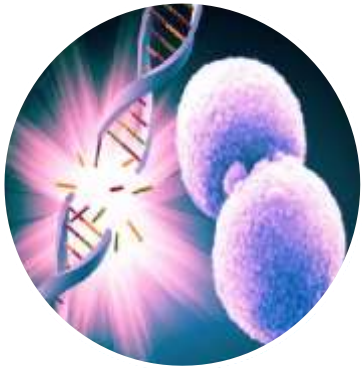
Mechanism

The underlying biological mechanism that causes the association between BF, FADS1 FADS2 genotype and asthma is not completely clear although there are a number of biologically plausible indicators.

Minor allele carriers have a lower proportion of products of the fatty acid metabolism and therefore a lower proportion of AA, a product of the n-6 pathway which may reduce the risk of asthma.

Conclusion

The association between **exclusive BF** and **asthma** is modified by the genetic variants of FADS genotypes in children. The results suggest that **only minor allele** carriers benefit from exclusive BF in regard to asthma development, while homozygous major allele carriers have no advantage in this respect.



This might explain the partly inconsistent results from previous studies on BF and asthma prevalence, which suggests the inclusion of genetic data in future studies