Impact de la consommation de lait cru et de fromage sur la protection contre les allergies et l'asthme

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CHRU NANCY

L'étude PASTURE

(Protection against Allergy: STUdy in Rural Environments)

- **Objectifs** :
  - Confirmer l'influence de l'environnement fermier sur la survenue des maladies allergiques
  - Evaluer les facteurs de prévention des maladies allergiques associés à l'environnement fermier
- Etude longitudinale de cohorte de naissance, multicentrique
- 1133 enfants vivant en milieu rural
  - 1/2 milieu fermier d'élevage bovin de production laitière
- 5 pays européens :
  - Allemagne, Autriche, Finlande, France et Suisse

Mutius E, Schmid S. The PASTURE project: EU support for the improvement of knowledge about risk factors and preventive factors for atopy in Europe. Allergy. 2006;61(4):407–13.

L'étude PASTURE

(Protection against Allergy: STUdy in Rural Environments)

- Suivi : 3ème trimestre de grossesse → 16 ans
  - Visite à 16 ans en cours
- Journaux alimentaires (lait de ferme, yaourt, fromage, beurre…) et environnement dès les premières semaines de vie
- Maladies allergiques, sensibilisation atopique, prélévements sg à 1, 4.5, 6 et 10 ans
- 3 contrats européens - 60 publications

Vuitton DA, Divaret-Chauveau A, Dalphin M-L et al. **Protection contre l'allergie par l'environnement de la ferme : en 15 ans, qu'avons-nous appris de la cohorte européenne « PASTURE »?** Bull Acad Nat Med. 2019 ; 603 : 618-630.

La spécificité de l'environnement fermier **pendant la grossesse**

Loss, Bitter et al.

Table I: Environmental and farming characteristics of pregnant women and children in the first year of life by farming status

	Farmer N (%)		Non farmer N (%)		p-value for difference
Population at birth	530	(46.8)	603	(53.2)	
Male	266	(51.4)	294	(51.4)	0.988
Maternal history of asthma	38	(7.2)	61	(10.1)	0.080
Maternal history of hay fever	108	(20.4)	196	(32.5)	<0.001
Maternal farming exposure during pregnancy†					
Contact to stable	464	(89.6)	107	(18.9)	<0.001
Contact to barn	362	(70.0)	65	(11.5)	<0.001
Contact to more than 2 farm animals	208	(39.2)	64	(10.7)	<0.001
Contact to cats and/or dogs	430	(81.3)	233	(38.6)	<0.001
Farm milk consumption	406	(76.6)	98	(16.3)	<0.001
only boiled farm milk	94	(17.8)	27	(4.5)	<0.001
any unboiled farm milk	310	(58.7)	70	(11.6)	
Smoking	46	(8.7)	112	(18.6)	<0.001

La spécificité de l'environnement fermier **pour l'enfant**

Loss, Bitter et al.

Table I: Environmental and farming characteristics of pregnant women and children in the first year of life by farming status

	Farmer N (%)		Non farmer N (%)		p-value for difference
Child's farming exposure during first year of life†‡					
Population at year 1	493	(47.7)	540	(52.3)	
Child living on a farm	486	(98.6)	10	(1.9)	<0.001
Regular visit to farm	487	(99.0)	77	(14.4)	<0.001
Regular stay in stable	332	(71.7)	40	(7.6)	<0.001
Contact to cats and/or dogs	402	(81.5)	188	(34.8)	<0.001
Farm milk consumption	283	(57.8)	51	(9.5)	<0.001
only boiled farm milk	141	(28.8)	27	(5.1)	<0.001
any unboiled farm milk	142	(29.0)	24	(4.5)	
unboiled farm milk after month 10	78	(16.0)	15	(2.8)	<0.001
unboiled farm milk before month 10	60	(12.3)	8	(1.5)	
Early introduced solid food items (food score): 0	51	(10.3)	102	(18.9)	<0.001
1-3	191	(38.7)	214	(39.6)	
4-6	174	(35.3)	157	(29.1)	
7-11	77	(15.6)	67	(12.4)	
Two or more siblings	235	(47.7)	111	(20.6)	<0.001

† Minor discrepancies in percentages due to missings in variables, ‡ Percent of population at year 1

LE LAIT CRU DE FERME

Lait cru de ferme et allergies

TABLE III. Adjusted association§ of reported milk exposure and asthma, atopy, hay fever, and atopic dermatitis (phase II, n = 8334)

Milk exposure reported in phase II	Asthma, aOR (95% CI)		Current asthma, aOR (95% CI)		Atopy,‖ aOR (95% CI)		Hay fever, aOR (95% CI)		Atopic dermatitis, aOR (95% CI)	
Exclusively shop milk	1.00		1.00		1.00		1.00		1.00	
Exclusively farm milk	0.65	0.52-0.81‡	0.64	0.48-0.84†	0.76	0.63-0.92†	0.58	0.44-0.77‡	0.78	0.61-1.00
Only boiled farm milk	1.24	0.82-1.87	1.59	0.98-2.58	0.90	0.60-1.35	1.17	0.68-1.99	1.04	0.54-2.01
Any unboiled farm milk	0.59	0.46-0.74‡	0.55	0.40-0.74‡	0.74	0.61-0.90†	0.51	0.37-0.69‡	0.75	0.59-0.96*

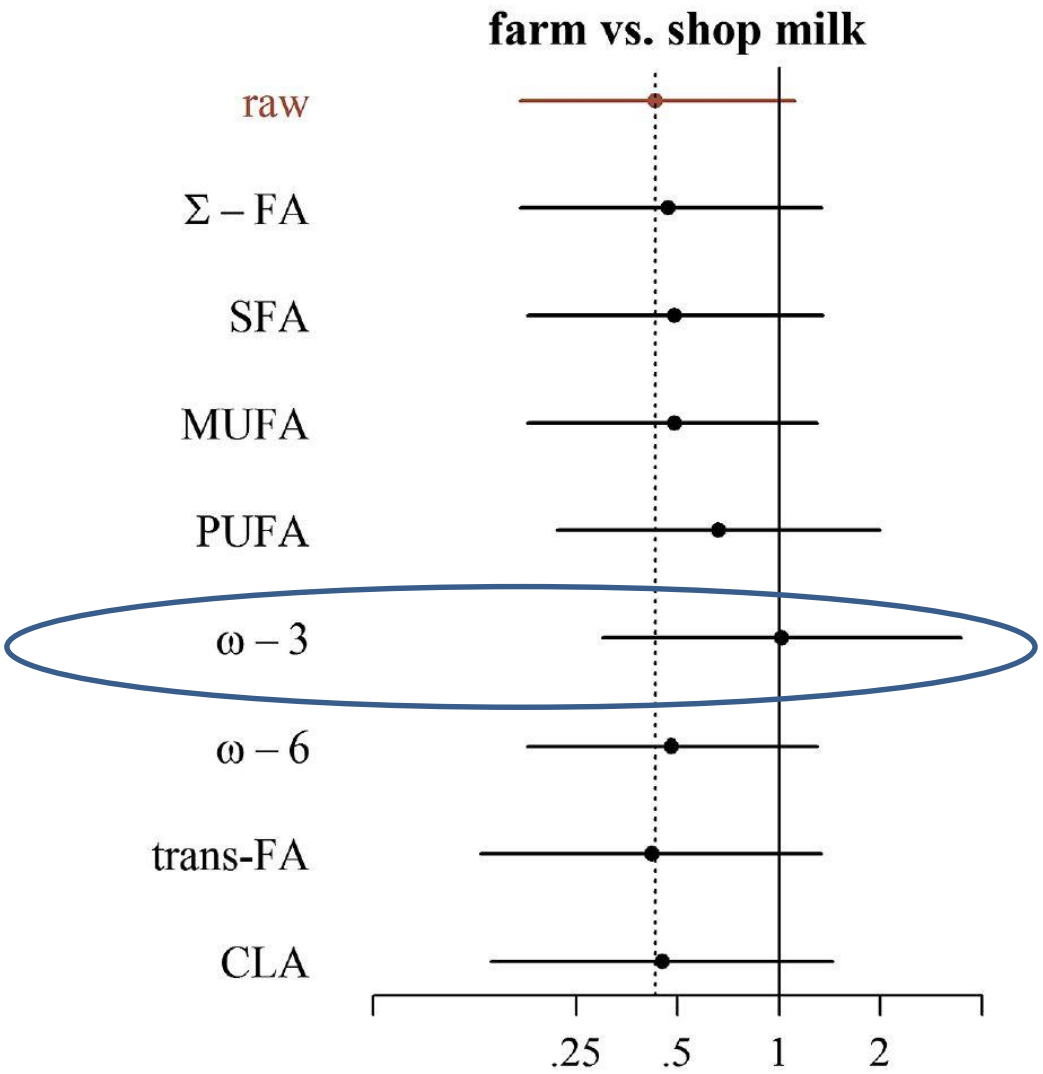
*$P < .05$, †$P < .01$, and ‡$P < .001$.

§aORs with 95% CIs calculated by using weighted logistic regression models adjusted for age, sex, farming status, 2 or more siblings, familial history of asthma or hay fever, breast-feeding, and study center. All models weighted to phase I: n = 34,491.

‖n = 7,606.

→**Effet protecteur de la consommation de lait cru de ferme sur les allergies et l'asthme** par rapport au lait acheté dans le commerce

Loss G, Apprich S, Waser M, Kneifel W, Genuneit J, Büchele G, et al. **The protective effect of farm milk consumption on childhood asthma and atopy: The GABRIELA study.** J Allergy Clin Immunol. 2011 Oct;128(4):766–73.e4.



Brick T, Schober Y, Böcking C, Pekkanen J, Genuneit J, Loss G, et al. **ω-3 fatty acids contribute to the asthma-protective effect of unprocessed cow's milk.** J Allergy Clin Immunol 2016;137:1699–706.e13.

Taux d'AG Oméga 3 contenu dans le lait consommé

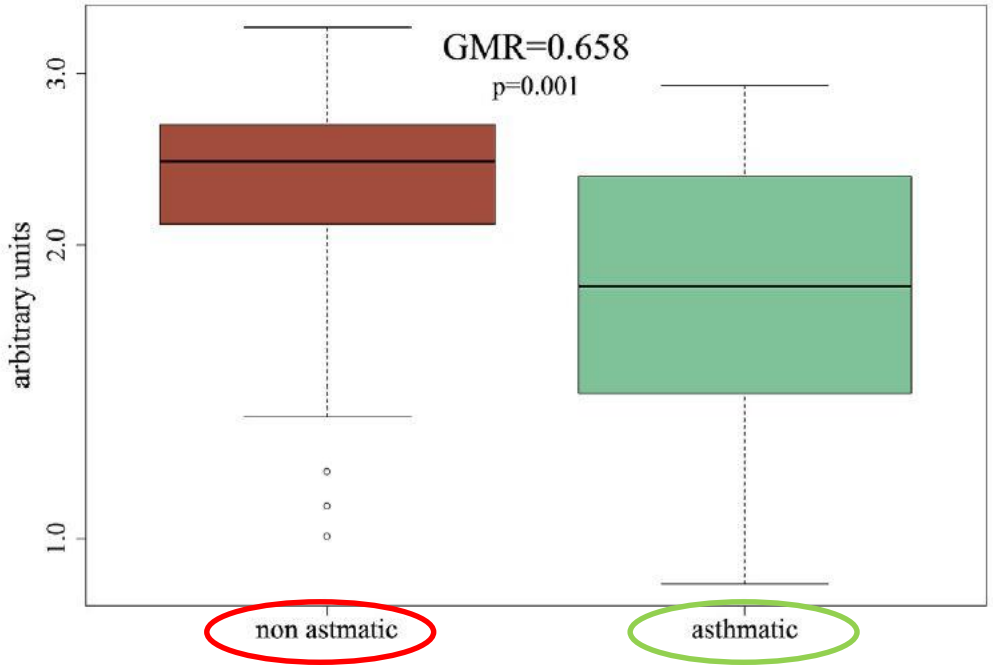
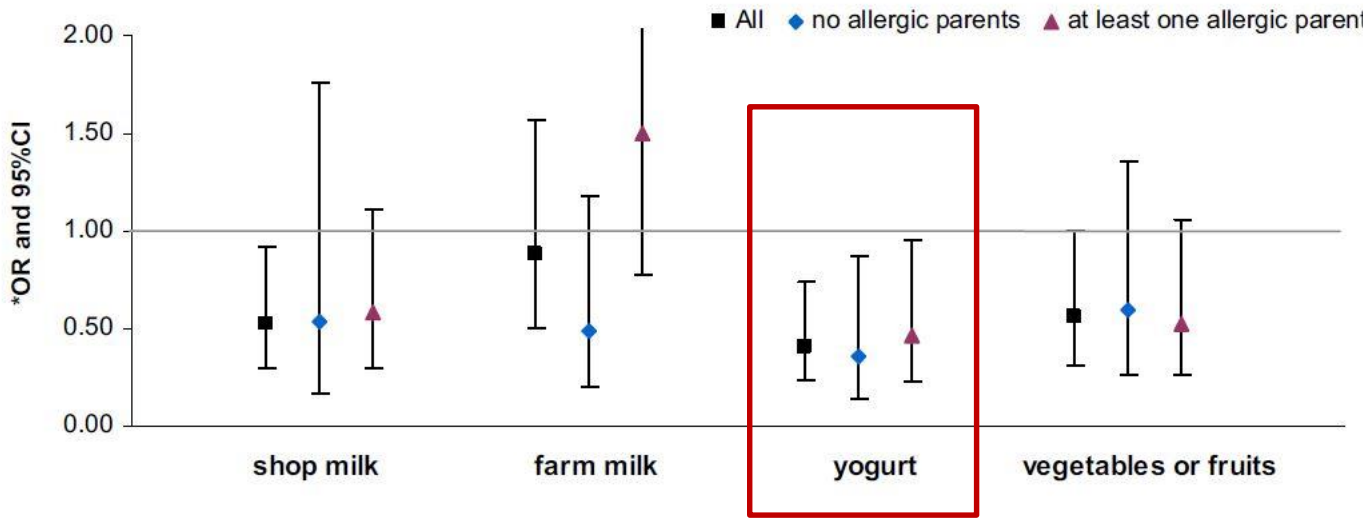


FIG 4. ω-3 PUFA levels (log-transformed) in milk samples consumed by asthmatic and nonasthmatic children and geometric mean ratio *(GMR)*. The GMR was calculated because of log-normal distribution of ω-3 levels.

Brick T, Schober Y, Böcking C, Pekkanen J, Genuneit J, Loss G, et al. **ω-3 fatty acids contribute to the asthma-protective effect of unprocessed cow's milk.** J Allergy Clin Immunol 2016;137:1699–706.e13.

LE YAOURT

Yaourt et allergies



Roduit C, Frei R, Loss G, Büchele G, Weber J, Depner M, et al. **Development of atopic dermatitis according to age of onset and association with early-life exposures.** J Allergy Clin Immunol. 2012 Jul;130(1):130–6.e5

Introduction de yaourt <u>avant l'âge d'1an</u> :

→ diminution du risque d'asthme et d'allergie alimentaire à l'âge de 6 ans (OR_a=0,40)

Roduit C, Frei R, Depner M, Schaub B, Loss G, Genuneit J, et al. **Increased food diversity in the first year of life is inversely associated with allergic diseases.** J Allergy Clin Immunol. 2014 Apr;133(4):1056–64.

Yaourt et taux de Butyrate

Butyrate	GMR	95% CI		P value
Food introduced within 1st year:				
Farm milk: yes vs no	1.02	0.88	1.19	0.747
Cow's milk: yes vs no	1.04	0.90	1.20	0.569
Yogurt: yes vs no	**1.20**	**1.00**	**1.44**	**0.045**
Fish: yes vs no	**1.21**	**1.05**	**1.40**	**0.010**
Nuts: yes vs no	0.92	0.78	1.10	0.364
Vegetables or fruits (in first 6 mo): yes vs no	**1.18**	**1.02**	**1.35**	**0.025**
Butter: yes vs no	0.94	0.81	1.10	0.456
Margarine: yes vs no	0.95	0.82	1.10	0.514
Chocolate: yes vs no	0.99	0.86	1.14	0.895
Egg: yes vs no	0.96	0.82	1.00	0.554
Cereals (in first 9 mo): yes vs no	0.88	0.76	1.03	0.107
Meat (in first 9 mo): yes vs no	1.13	0.96	1.32	0.136

Taux de butyrate
dans les selles à l'âge d'1 an

Roduit C, Frei R, Ferstl R, et al. **High levels of Butyrate and Propionate in early life are associated with protection against atopy.** Allergy 2018

Taux de Butyrate et allergies

	Butyrate <95P (<26.88 µmol/g)		Butyrate ≥95P (≥26.88 µmol/g)	
	n	%	n	%
Asthma up to 6 yrs	32/262	12.2	1/15	6.7
Allergic rhinitis up to 6 yrs	27/252	9.7	0/15	0.0
Food allergy up to 6 yrs	32/275	11.6	1/15	6.7
Atopic dermatitis up to 6 yrs	135/284	47.5	5/16	31.3
Inhalant sensitization at 6yrs	107/261	41.0	3/15	20.0
Food sensitization at 6yrs	100/261	38.3	2/15	13.3
Any sensitization at 6yrs	147/261	56.3	4/15	26.7

Roduit C, Frei R, Ferstl R, et al. **High levels of Butyrate and Propionate in early life are associated with protection against atopy.** Allergy 2018

LE FROMAGE

Consommation de fromage à l'âge de 18 mois

TABLE 3 Associations between cheese consumption (yes/no) at 18 mo and allergic diseases and atopic sensitization at 6 yr

	Model 1			Model 2			Model 3			Model 4		
	n	OR	95% CI	n	OR	95% CI	n	OR	95% CI	n	OR	95% CI
Atopic dermatitis[a]	258/839	0.51	0.29-0.90	258/839	0.51	0.29-0.90	241/820	0.63	0.34-1.17	93/674	0.61	0.26-1.45
Doctor-diagnosed food allergy[b]	68/843	0.32	0.15-0.71	68/843	0.32	0.14-0.69	48/823	0.65	0.21-1.96	33/697	0.38	0.12-1.24
Allergic rhinitis[c]	64/870	0.51	0.22-1.19	64/870	0.50	0.22-1.18	59/856	0.95	0.32-2.84	47/725	0.76	0.25-2.34
Asthma[d]	73/837	0.61	0.27-1.40	73/837	0.61	0.27-1.4	65/822	1.11	0.38-3.27	54/701	0.51	0.19-1.32
Sensitization to food allergens (cut off 3.5 KU/L) at 6 yrs[e]	5/707	0.50	0.21-1.19	48/698	0.65	0.25-1.71	46/692	0.83	0.29-2.36	38/582	0.84	0.27-2.65
Sensitization to inhalant allergens (cut off 3.5 KU/L) at 6 yrs[f]	109/704	0.59	0.29-1.23	105/695	0.74	0.34-1.6	104/689	0.87	0.37-2.03	80/579	0.75	0.3-1.88

For all diseases, the modeled probability is the probability to observe the disease.
Boldface values are significant ($P < 0.05$).
Model 1: adjustment for centre, farmer, and parental atopy plus other variables as described below.
Model 2: model 1 + additional adjustment for raw milk consumption at 12 mo.
Model 3: model 1 + exclusion of infants with doctor-diagnosed FA at 1 yr.
Model 4: model 1 + exclusion of infants with AD at 18 mo.

77% des enfants qui n'avaient jamais mangé de fromage n'étaient pas en éviction des PLV

Nicklaus S, Divaret-Chauveau A, Chardon M-L, et al. ; Pasture Study Group. **The protective effect of cheese consumption at 18 months on allergic diseases in the first 6 years**. *Allergy. 2018;00:1–11.*

Diversité de Fromage à l'âge de 18 mois

TABLE 4 Associations between cheese diversity score at 18 mo and allergic diseases and atopic sensitization at 6 yr

	Model 1			Model 2			Model 3			Model 4		
	n	OR	95% CI	n	OR	95% CI	n	OR	95% CI	n	OR	95% CI
Atopic dermatitis[a]	245/788	0.64	0.48-0.85	245/788	0.64	0.48-0.85	229/770	0.7	0.51-0.91	92/635	0.68	0.44-1.04
Doctor-diagnosed food allergy[b]	62/790	0.55	0.33-0.92	62/790	0.54	0.32-0.91	43/771	0.68	0.37-1.24	31/655	0.86	0.42-1.74
Allergic rhinitis[c]	60/818	0.93	0.56-1.54	60/818	0.93	0.56-1.53	55/804	1.17	0.70-1.94	44/682	1.26	0.72-2.21
Asthma[d]	67/786	0.96	0.61-1.5	67/786	0.96	0.61-1.51	59/771	1.13	0.72-1.79	50/659	0.82	0.48-1.40
Sensitization to food allergens (cut off 3.5KU/l) at 6 yrs[e]	48/667	0.75	0.44-1.29	46/658	0.83	0.48-1.44	44/652	0.91	0.53-1.57	37/549	0.85	0.46-1.57
Sensitization to inhalant allergens (cut off 3.5KU/l) at 6 yrs[f]	103/664	0.9	0.61-1.31	99/655	0.95	0.65-1.40	98/649	1.03	0.70-1.51	76/546	0.97	0.62-1.51

Boldface values are significant ($P < 0.05$).
Model 1: adjustment for centre, farmer, and parental atopy plus other variables as described below.
Model 2: model 1 + adjustment for raw milk consumption at 12 mo.
Model 3: model 1 + exclusion of infants with doctor-diagnosed FA at 1 yr.
Model 4: model 1 + exclusion of infants with AD at 18 mo.

Nicklaus S, Divaret-Chauveau A, Chardon M-L, et al. ; Pasture Study Group. **The protective effect of cheese consumption at 18 months on allergic diseases in the first 6 years**. *Allergy. 2018;00:1–11.*

PRÊT POUR L'INTERVENTIONNEL ?

Essai clinique : MARTHA study

LMU KLINIKUM DER UNIVERSITÄT MÜNCHEN

Dr. von Haunersches Kinderspital

- Etude interventionnelle randomisée avec consommation dès l'âge de 6 mois et pendant 2,5 ans :
  - Lait UHT
  - Lait de ferme traité de façon minimale mais sûre au plan microbiologique
- Impact sur l'asthme et les allergies → suivi jusqu'à l'âge de 5 ans
- Déjà 833 familles inclues !
- https://www.martha-studie.de/english-version/

Le groupe d'étude PASTURE :

Pekkanen J, Karvonen A, Roponen M, Hyvärinen A, Kirjavaien P, Remes S (Finlande);
Dalphin JC, Kaulek V, Laurent L, Dalphin ML, Vuitton D (France);
von Mutius E, Ege M, Depner M, Schmausser-Hechfellner E, Schaub B, Genuneit J, Illi S, Kabesch M, Renz H (Allemagne); Braun-Fahrländer C, Lauener R, Roduit C, Frei R (Suisse); Riedler J (Autriche); Doekes G (Pays-Bas)

Hommage au Pr Jean-Charles Dalphin

Juin 1956 – Octobre 2019

- Professeur en pneumologie et allergologie
- Investigateur principal de l'étude PASTURE en France
- Environnement fermier et maladies respiratoires

MERCI POUR VOTRE ATTENTION

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