

# LOWER RISK OF ATOPIC DERMATITIS AMONG INFANTS BORN EXTREMELY PRETERM COMPARED WITH HIGHER GESTATIONAL AGE.

BARBAROT S. <sup>1</sup>, GRAS-LEGUEN C <sup>2</sup>, COLAS H. <sup>2</sup>, GARROT E. <sup>2</sup>, DARMAUN D. <sup>3</sup>, LARROQUE B. <sup>4,5</sup>, ROZE J.C. <sup>2</sup>, ANCEL P.Y. <sup>4,5</sup>

<sup>1</sup> Pediatric Dermatology Unit , Nantes University Hospital, Nantes, France and CEBD Nottingham University, UK

<sup>2</sup> Department of Neonatal Medicine and INSERM CIC 004, Nantes University Hospital

<sup>3</sup> French National Institute for Agricultural Research (INRA), UMR 1280, Nantes University Hospital

<sup>4</sup> INSERM, UMR S953, IFR 69, Epidemiological Research on Perinatal Health and Women's and Children's Health, Paris, France,

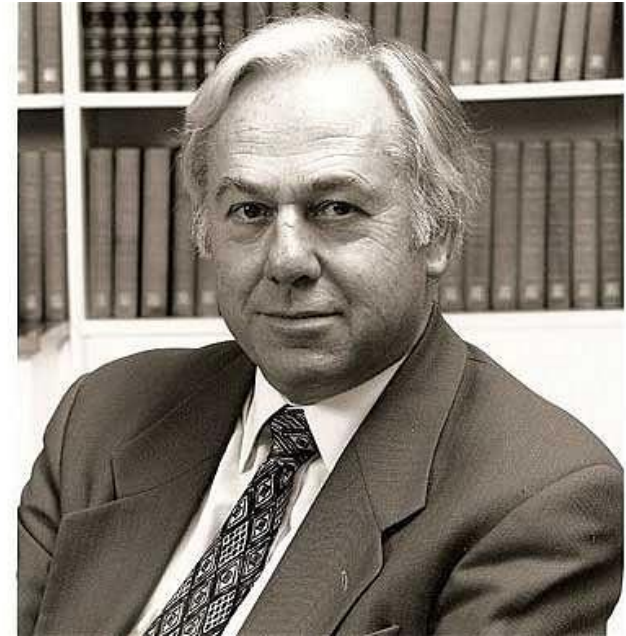


# Developmental Origins of Health and Disease (DOHaD) : The “Barker’s hypothesis”

*“The fetal environment correlates with health later on ”*

Also in the field of atopic diseases...

- Intestinal microbiote colonisation
- Skin barrier function

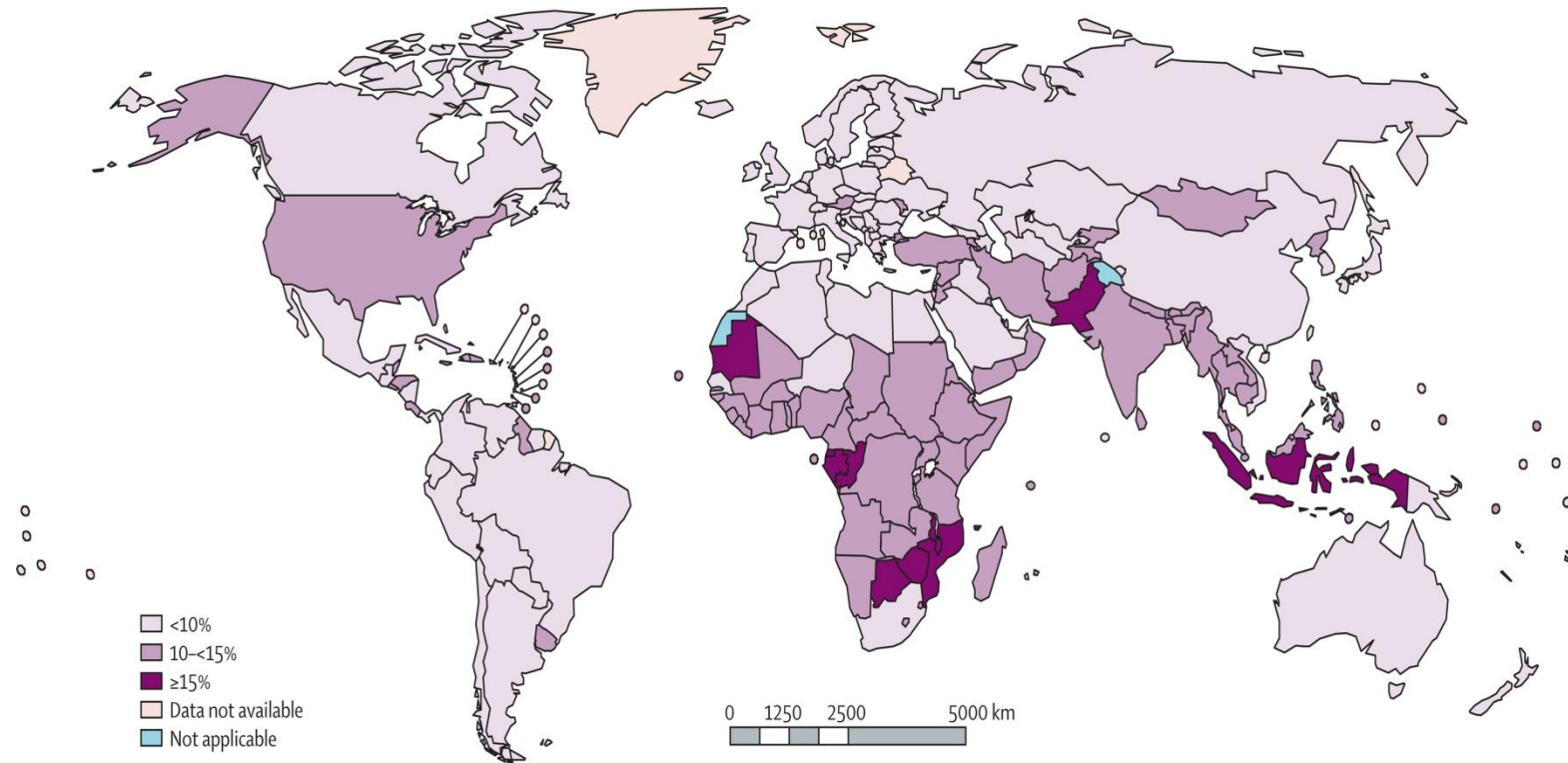


Pr David Barker (1938-2013)

Barker DJ, Thornburg KL. The obstetric origins of health for a lifetime. Clin Obstet Gynecol. 2013.  
Gillman MW. Developmental origins of health and disease. N Engl J Med 2005  
Flohr C. Br J Dermatol. 2013

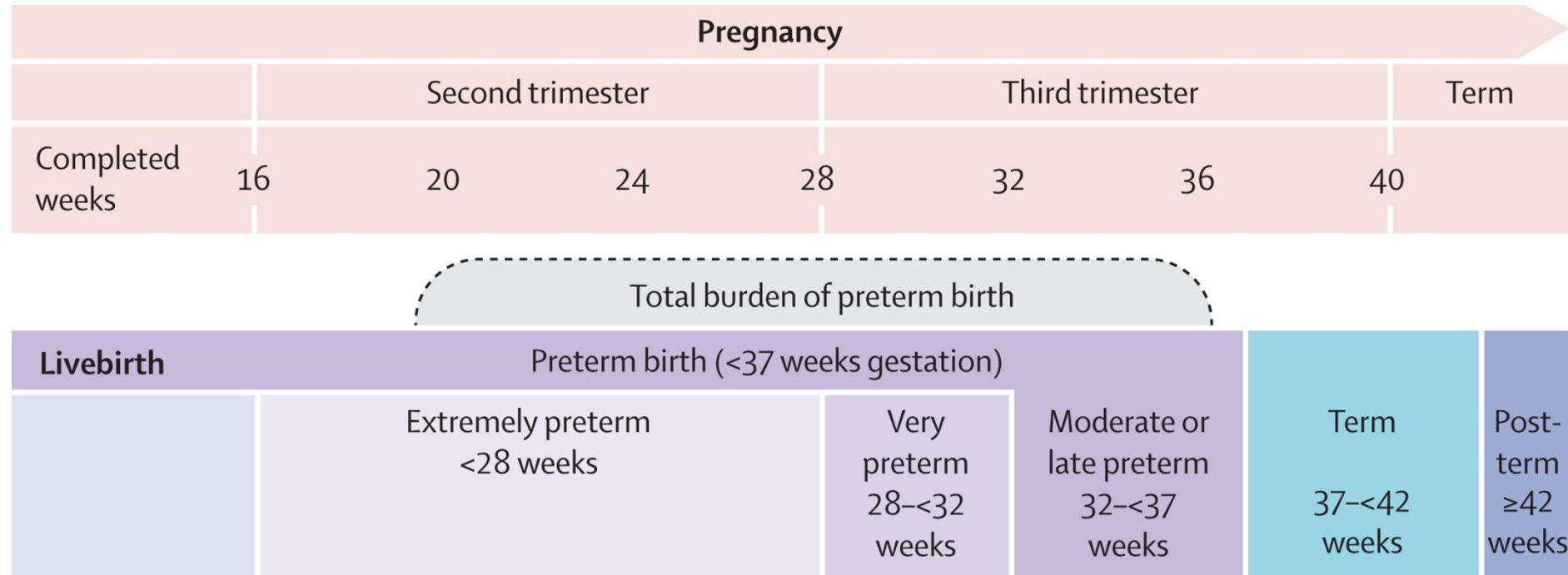
# Prematurity: the issue

- Prevalence ranges from **5% to 18%** (increasing since 1990).
- Prematurity is the leading cause of newborn death
- **Long term complications** are common in premature infants
- Predictors



# Prematurity

## Gestational age $\leq 37$ weeks



# Why look at eczema risk in preterm infants?

- Preterm birth is a frequent condition
- Preterm infants have
  - a **very special perinatal environment** compared to full-terms (skin care, diet, drugs, use of incubators...)
  - an immature immune system
  - a specific gut microbiota (low diversity)
  - a **functionally immature skin barrier**



# Skin barrier function in preterm neonates

Stratum corneum immaturity before 29 weeks

inverse correlation  
TEWL / gestational age

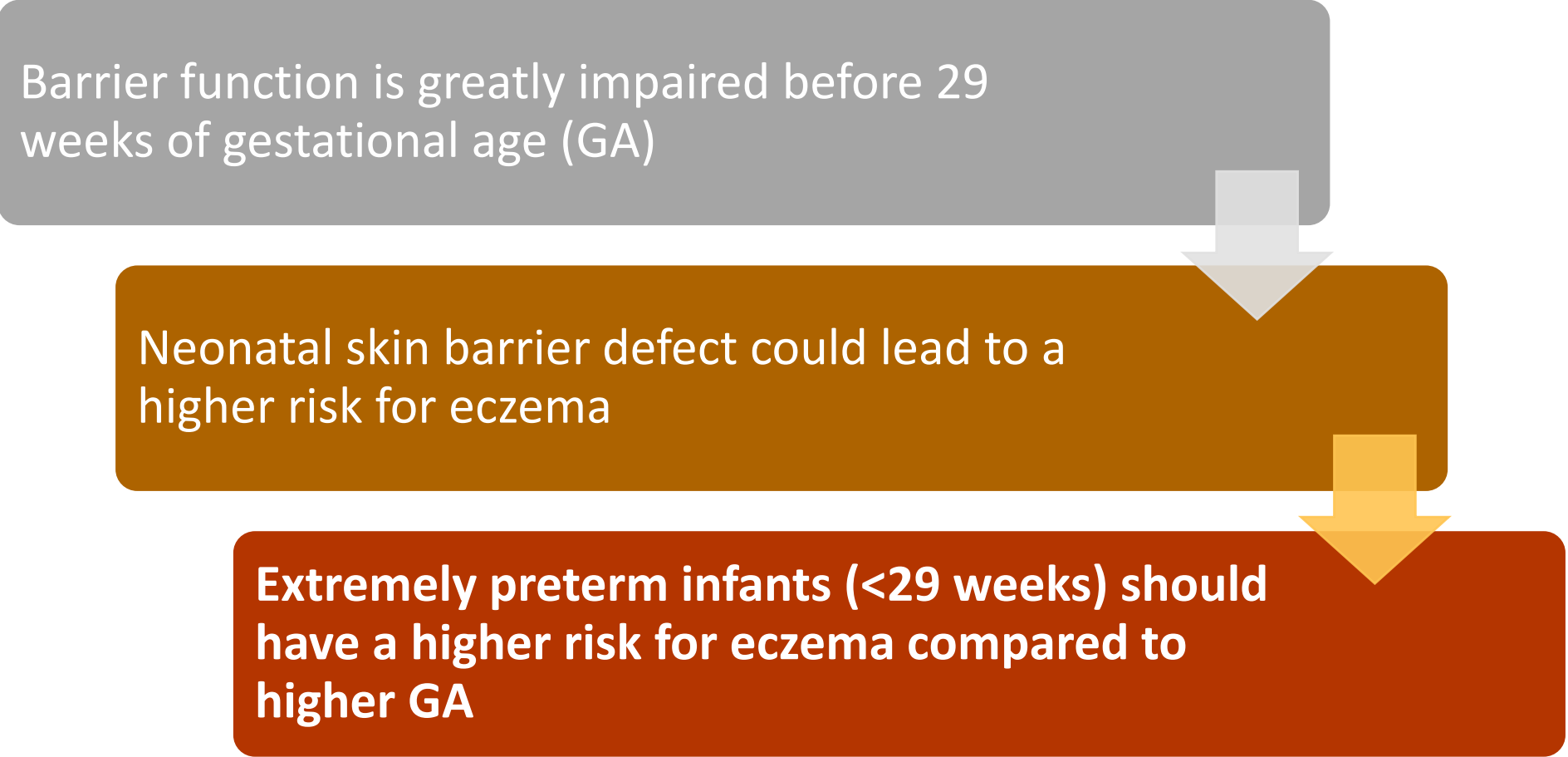
Number of layers of cornified  
cells is lower in epidermis

Functionally immature skin barrier at birth  
Progressive maturation after birth (4 weeks ?)



# Hypothesis

Barrier function is greatly impaired before 29 weeks of gestational age (GA)



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graph TD; A[Barrier function is greatly impaired before 29 weeks of gestational age (GA)] --> B[Neonatal skin barrier defect could lead to a higher risk for eczema]; B --> C[Extremely preterm infants (<29 weeks) should have a higher risk for eczema compared to higher GA];
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Neonatal skin barrier defect could lead to a higher risk for eczema

**Extremely preterm infants (<29 weeks) should have a higher risk for eczema compared to higher GA**



# What do we already know about this question ?

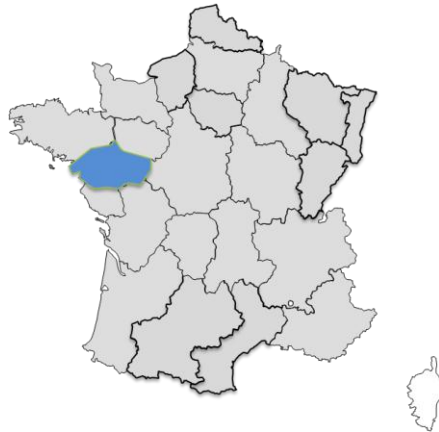
- Previous studies have produced conflicting results
- So far, eczema risk *has not been assessed in a large sample of preterm infants* so that different gestational age categories could be compared to each other
- It is still not yet known whether the risk of developing eczema is influenced by extremely preterm birth



# LIFT cohort

*(Loire Infant follow up Team)*

- Open regional preterm birth cohort
- Infants born <35weeks from january 2003 to dec 2005
- 5-year telephone interview

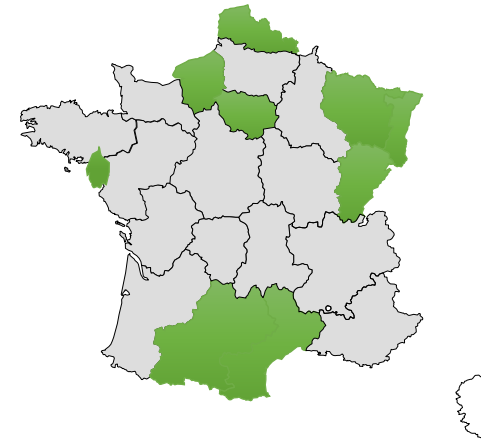


Roze JC et al. Arch Pediatr 2007

# EIPAGE cohort

*(Etude Epidemiologique des Petites Ages Gestationnels)*

- Multicentric preterm birth cohort
- Infants born < 35 weeks in 1997 followed until 5 years
- A full term group as a reference
- 2-year written questionnaire

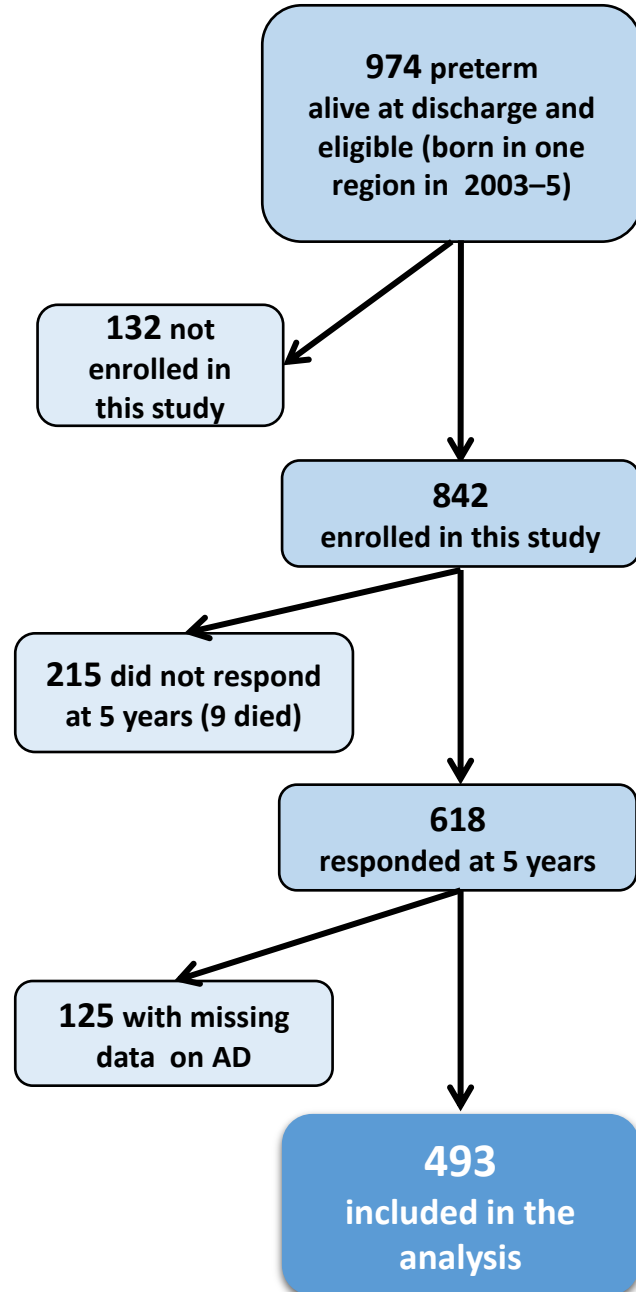


Larroque B et al. Arch Dis Child Fetal Neonatal 2004

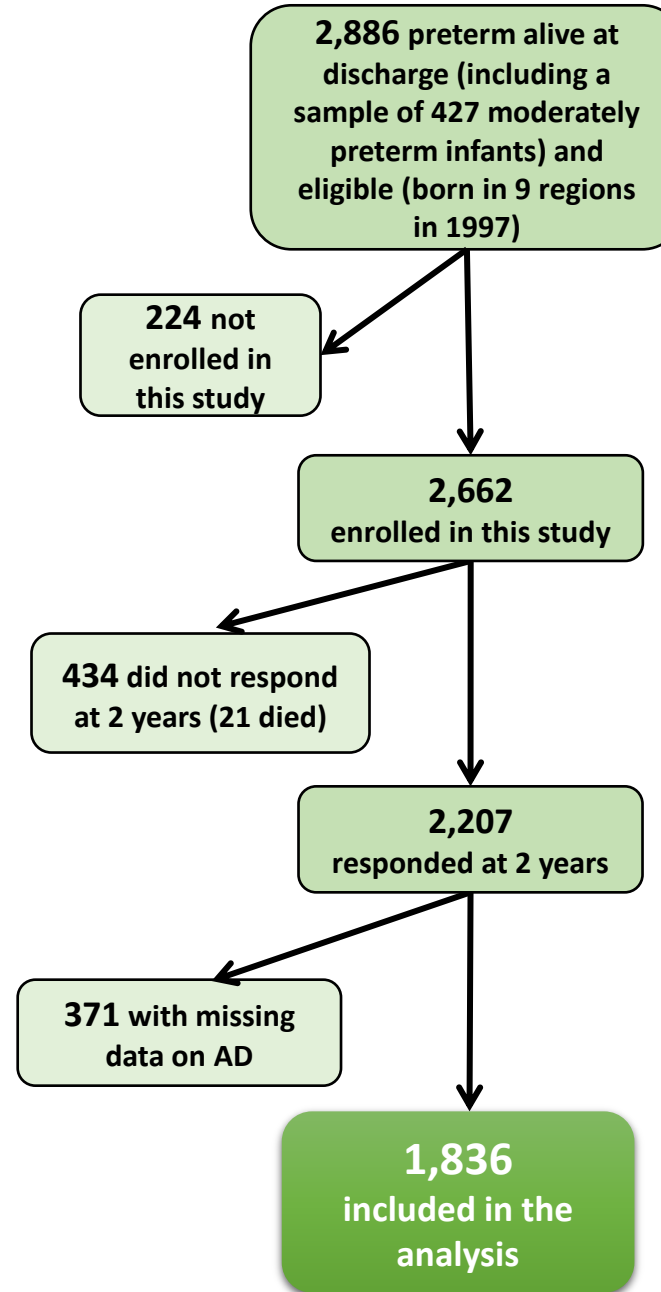
# Outcome variable

LIFT			EPIPAGE		
<i>questionnaire</i>	<i>outcome</i>	<i>age</i>	<i>questionnaire</i>	<i>outcome</i>	<i>age</i>
Parental telephone interview	positive answer to the question: <i>"Has a doctor ever told you that your child had atopic eczema?"</i>	5 years	Parental questionnaire sent by mail	Same question as in LIFT	2 years

## LIFT cohort



## EPIPAGE cohort



# Potential confounders collected in both cohorts

## Neonates

- Gender
- Birth weight
- Gestational age

## Pregnancy

- Multiple pregnancy
- Number of siblings > 0
- Caesarean section
- Prenatal treatment with antibiotics
- Prenatal treatment with steroids

## Level of maternal education (only in Epipage)

## Family history of allergy

## Neonatal period

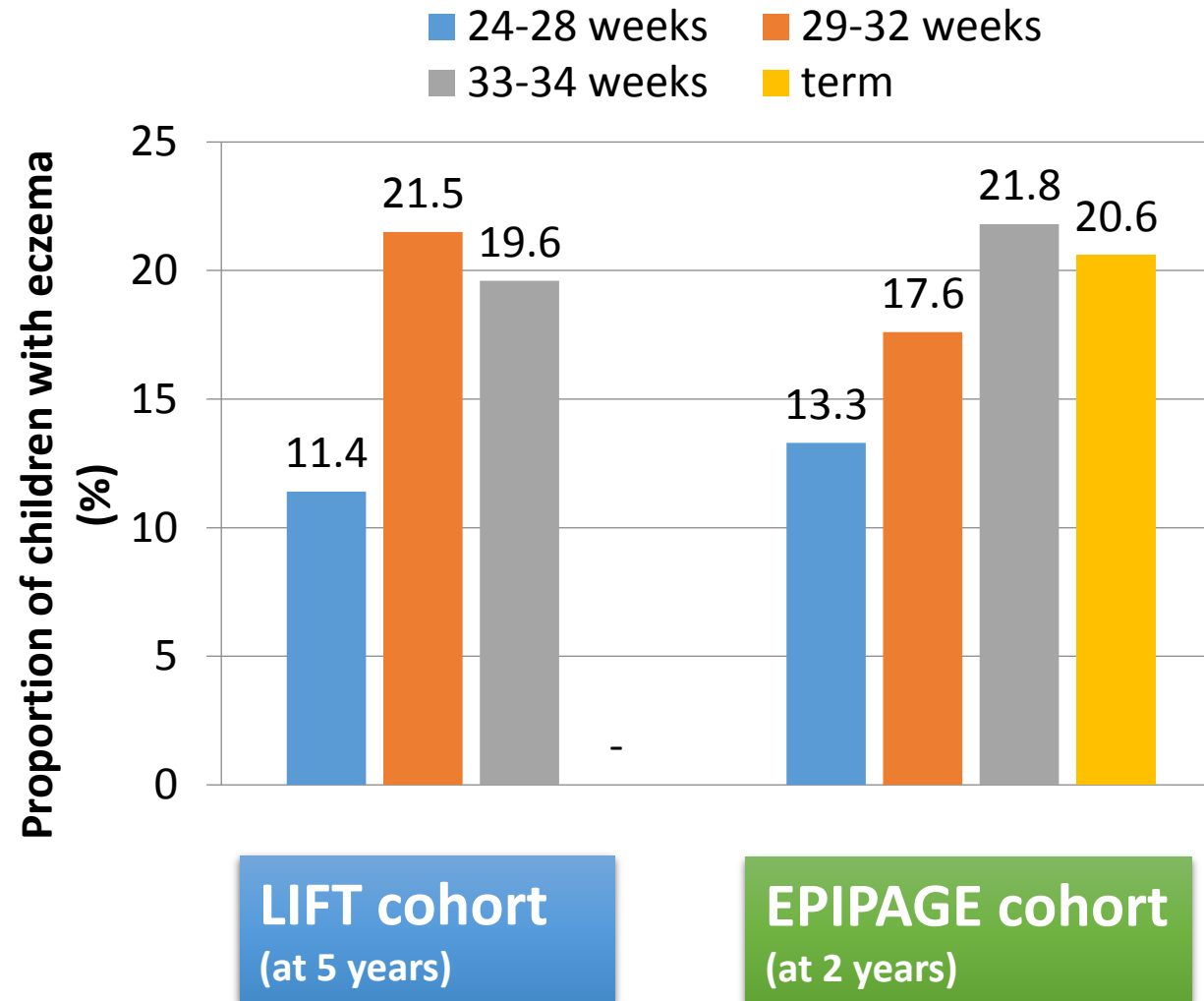
- Use of antibiotics
- Assisted ventilation > 10 days

## Breastfeeding

# Prevalence of eczema according to gestational age

	LIFT cohort (at 5 years)			EIPAGE cohort (at 2 years)		
	(N=493)		p-value	(N=2,181)		p-value
Gestational age	n/N	(%)		n/N	(%)	
24-28 weeks	10/88	(11.4)	0.11	52/391	(13.3)	0.02
29-32 weeks	51/237	(21.5)		212/1,202	(17.6)	
33-34 weeks	33/168	(19.6)		53/243	(21.8)	
Term	-	-		71/345	(20.6)	

## Prevalence of eczema according to gestational age



# Crude ORs for eczema in preterm infants

	LIFT Cohort				EPIPAGE Cohort			
	N=493				N=1,836			
Characteristics	OR	95% CI		p-value	OR	95% CI		p-value
Infant characteristics								
Male	1.05	(0.66 - 1.64)		0.85	0.80	(0.63 - 1.02)		0.07
Gestational age at birth								
24-28 weeks	0.52	(0.24 - 1.12)		0.09	0.55	(0.36 - 0.84)		0.01
29-32 weeks	1.12	(0.69 - 1.83)		0.65	0.77	(0.55 - 1.08)		0.13
33-34 weeks	1				1			
Birth weight, Z-score								
<-2]	1.3	(0.39 - 1.53)		0.70	0.29	(0.09 - 0.96)		0.04
[-2; -1]	0.98	(0.51 - 1.91)		0.96	0.97	(0.67 - 1.39)		0.85
[-1; 0]	1.44	(0.85 - 2.45)		0.17	1.13	(0.86 - 1.47)		0.40
[0; 2]	1				1			
Pregnancy characteristics								
Cesarean section	0.95	(0.59 - 1.53)		0.83	1.13	(0.88 - 1.44)		0.34
Prenatal treatment with corticosteroids	1.34	(0.79 - 2.27)		0.27	0.95	(0.72 - 1.25)		0.72
Prenatal treatment with antibiotics	0.85	(0.48 - 1.52)		0.59	1.18	(0.87 - 1.60)		0.30
Multiple pregnancy	1.49	(0.94 - 2.32)		0.09	0.96	(0.74 - 1.25)		0.77
High level of maternal education	NA				1.32	(1.04 - 1.69)		0.02
Neonatal hospitalization characteristics								
Assisted ventilation >10 days	0.37	(0.14 - 0.95)		0.04	0.72	(0.47 - 1.11)		0.14
Treatment with antibiotics during the neonatal period	0.79	(0.59 - 1.05)		0.10	0.97	(0.86 - 1.10)		0.66
Others								
Breastfeeding	1.04	(0.66 - 1.64)		0.85	1.46	(1.11 - 1.93)		0.08
Family history of allergies	3.09	(1.94 - 4.91)		0.01	1.91	(1.49 - 2.44)		0.001
Number of siblings >0	0.82	(0.52 - 1.28)		0.38	1.02	(0.98 - 1.06)		0.40



## Adjusted eczema risk in preterm infants

	LIFT cohort				EPIPAGE cohort			
	N=493				N=1,836			
	OR	(IC 95%)		p-value	OR	(IC 95%)		p-value
Adjusted for birthweight (Z-score)								
24-28 w	0.53	(0.25	-	1.15)	0.11	<b>0.54</b>	<b>(0.35 -</b>	<b>0.82) 0.004</b>
29-32 w	1.16	(0.70	-	1.92)	0.57	0.76	(0.54 -	1.07) 0.10
33-34 w.	1				1			
Adjusted for birthweight (Z-score) and family history of allergies								
24-28 w.	<b>0.41</b>	<b>(0.18</b>	<b>-</b>	<b>0.90)</b>	<b>0.03</b>	<b>0.57</b>	<b>(0.37 -</b>	<b>0.87) 0.001</b>
29-32 w.	1.08	(0.64	-	1.81)	0.79	0.78	(0.55 -	1.10) 0.16
33-34 w.	1		-		1		-	
Adjusted for birthweight (Z-score), family history of allergies, level of maternal education,								
24-28 w.	NA				<b>0.57</b>	<b>(0.37 -</b>	<b>0.87) 0.009</b>	
29-32 w.	NA				0.78	(0.55 -	1.10)	0.16
33-34 w.	NA				1			

# Discussion

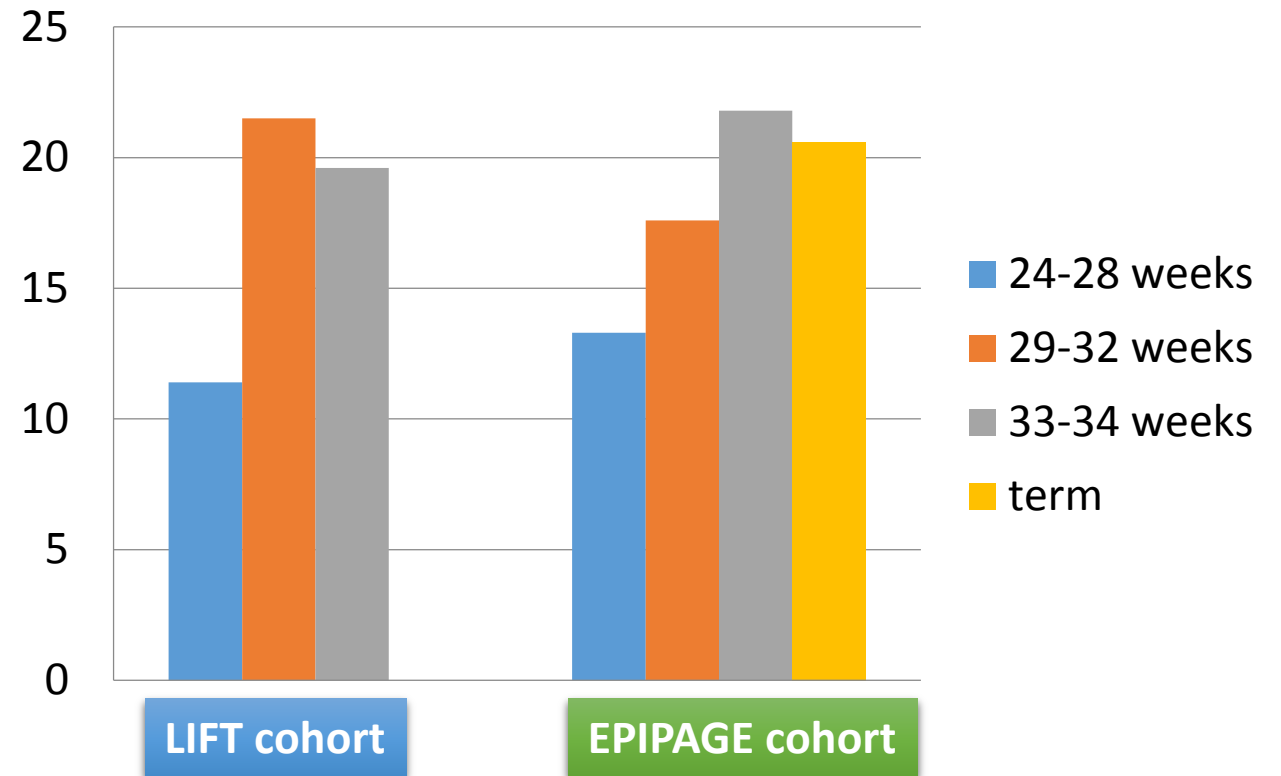
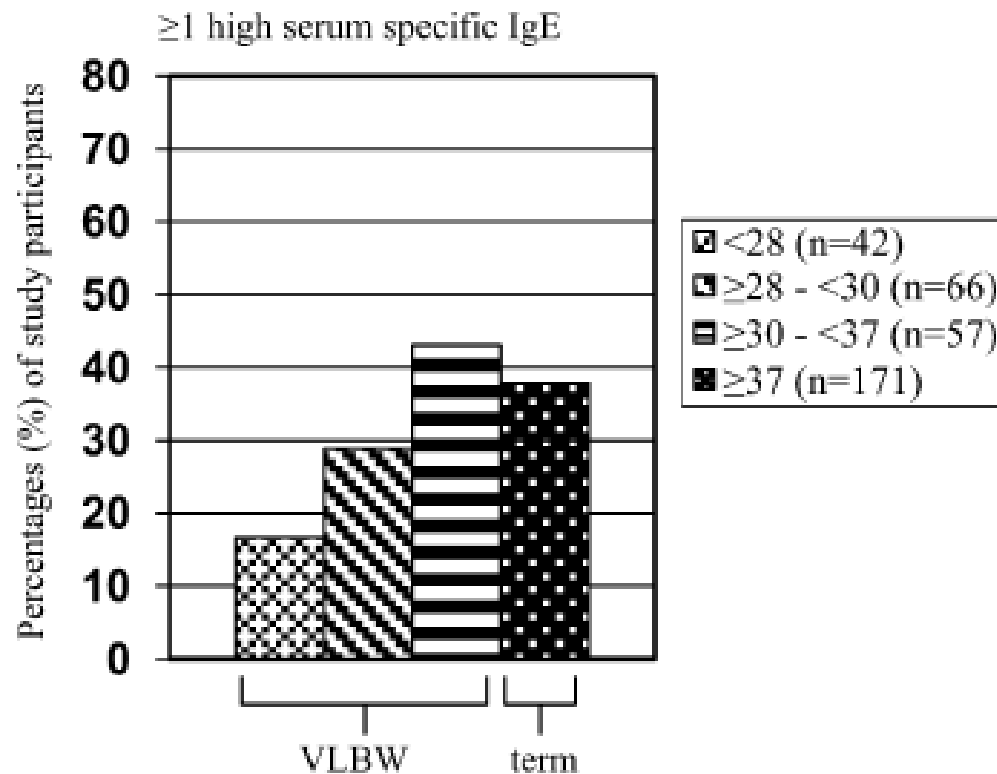
## Strengths

- 2 independent birth cohorts
- Size allowed us to look at eczema risk among preterm infants
- GA assessment very reliable (early ultrasound)

## Weaknesses

- Small size of extremely preterm category in LIFT cohort
- Outcome variable assessed at a different time point in each cohort (non differential bias)
- No data on IgE sensitisation
- No data on *FLG* mutations

# Preterm birth and atopy



# Why eczema risk is reduced in extremely preterm?

## Role of the intestinal microbiota in preterm?

- Unlikely regarding existing evidence
- Van Zwol *A Acta Paediatr* 2010

## Induction of tolerance through a impaired skin barrier?

## Role of skin microbiome in preterm neonates?

- No data

## Role of a shorter exposition to Th2 cytokines during pregnancy in preterms?

Wegmann TG 1993

## Do atopic mothers have longer pregnancies ?

- Atopic mothers were more frequent in the full-term group in EPIPAGE
- Savilahti *Clin Exp Allergy* 2004

## Role of external factors (skin care, incubators...) ?

- Needs further investigation

# Conclusion

- Among preterm infants, there is an association between **extreme preterm birth and a 50% decreased risk for eczema** compared to higher GA (29-34weeks)

An “eczema paradox” in very preterm infants ?

- Further studies are needed to
  - replicate these results in other countries
  - understand how these findings are influenced by *environmental factors, nutrition, immune system development and skin barrier function*
- At least it is good news for these children...





**Nantes**

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