

Lower risk of atopic dermatitis among infants born extremely preterm compared with higher gestational age

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Summary

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Background It is not yet known whether the risk of developing atopic dermatitis (AD) is influenced by preterm birth. Moreover, AD risk has not been assessed in a large sample of extremely preterm infants (< 29 weeks' gestation).

Objectives To determine whether the risk of AD is influenced by preterm birth.

Methods We investigated the relationship between gestational age (GA) and AD using data from two independent population-based cohorts, including a total of 2329 preterm infants, of whom 479 were born extremely preterm.

Results There was a lower percentage of children with AD in the extremely preterm group compared with those born at a greater GA (Epipage cohort, 2-year outcome: 13.3% for 24–28 weeks, 17.6% for 29–32 weeks, 21.8% for 33–34 weeks, $P = 0.02$; LIFT cohort, 5-year outcome: 11% for 24–28 weeks, 21.5% for 29–32 weeks, 19.6% for 33–34 weeks, $P = 0.11$). After adjusting for confounding variables, a lower GA (< 29 weeks) was significantly associated with decreased risk of AD in the Epipage cohort [adjusted odds ratio (aOR) 0.57, 95% confidence interval (CI) 0.37–0.87; $P = 0.009$] and the LIFT cohort (aOR 0.41, 95% CI 0.18–0.90; $P = 0.03$).

Conclusions Very low GA (< 29 weeks) was associated with a lower risk of AD compared with higher GA (29–34 weeks) and full-term birth.

What's already known about this topic?

- Events occurring in the earliest stages of development can predispose a child to atopic diseases.
- The influence of very low gestational age (GA) on the risk of atopic dermatitis (AD) has not been assessed in a large sample of extremely preterm infants (< 29 weeks' gestation).

What does this study add?

- Very low GA (< 29 weeks) was associated with a lower risk of AD compared with higher GA (29–34 weeks) and full-term birth.

Manifestations of atopic disease include asthma, food allergies, allergic rhinitis and atopic dermatitis (AD). AD, which is also known as atopic eczema, is a chronic itching skin disorder that mainly affects flexural areas. AD is the most prevalent chronic inflammatory condition in children,¹ and has a significant impact on the quality of life of affected individuals and their families.^{2,3} Approximately one in three children with AD devel-

ops asthma or allergic rhinitis. Thus, AD has been regarded as the starting point for the 'allergic march', which is the natural progression towards various atopic disorders in children.^{1,4,5}

It is known that events occurring in the earliest stages of development, or even before birth, can predispose a child to atopic diseases.⁶ Therefore, perinatal conditions for preterm infants, which differ greatly from those of full-term infants,

could influence the evolution of these disorders. In fact, the immune system of preterm infants is not fully developed, affecting the formation of tolerance and sensitization. In addition, extremely preterm infants (< 29 weeks) have a functionally immature skin barrier at birth, which can take more than 4 weeks to develop postnatally.⁷ Moreover, environmental conditions including allergenic exposure, diet and skin/gut microflora vary substantially between premature and full-term infants.

So far, the propensity of preterm infants to develop AD has been a matter of debate. Few reports have been published, and they have yielded conflicting results.^{8–18} In addition, the influence of very low gestational age (GA) on the risk of AD has not been assessed in a large cohort of patients. Therefore, the aim of this study was to examine how GA influenced the risk of AD in two independent cohorts of preterm infants.

Patients and methods

Study population and data sources

Data were obtained from two independent sources, the Epipage¹⁹ and Loire Infant Follow-up Team (LIFT) cohorts studies.²⁰ Epipage was a prospective, population-based cohort

study including infants born at 22–32 completed weeks of gestation in nine French regions in 1997, as well as infants born at 33–34 weeks between April and October 1997.^{19,21} Due to the high number of births at 33–34 weeks, recruitment of these moderately premature infants was stopped after only 2 months.¹⁹ Ultimately, 427 of these moderately preterm infants (33–34 weeks of GA), along with all eligible infants who were born at 22–32 weeks of GA and were alive at discharge, were recruited from the Epipage cohort for this study ($n = 2886$) (Fig. 1). Of the 2886 infants recruited, 224 were not enrolled in the study (follow-up was not proposed for 77, and refused by parents for 147), 434 did not respond to the questionnaire, and 21 had died before the follow-up. Therefore, a total of 2207 preterm infants were included in the follow-up study at 2 years. Furthermore, a full-term reference group from the Epipage cohort was included at birth in the same regions (one in every four births at 39–40 weeks over 1 week in 1997 – the date varied according to region – 667 children) and with the same follow-up (Fig. 1). This full-term reference group was used only for comparison with preterm infants from the Epipage cohort.

LIFT was an open, regional, prospective, population-based study conducted in Western France. From the LIFT cohort, our study included all eligible infants born before 35

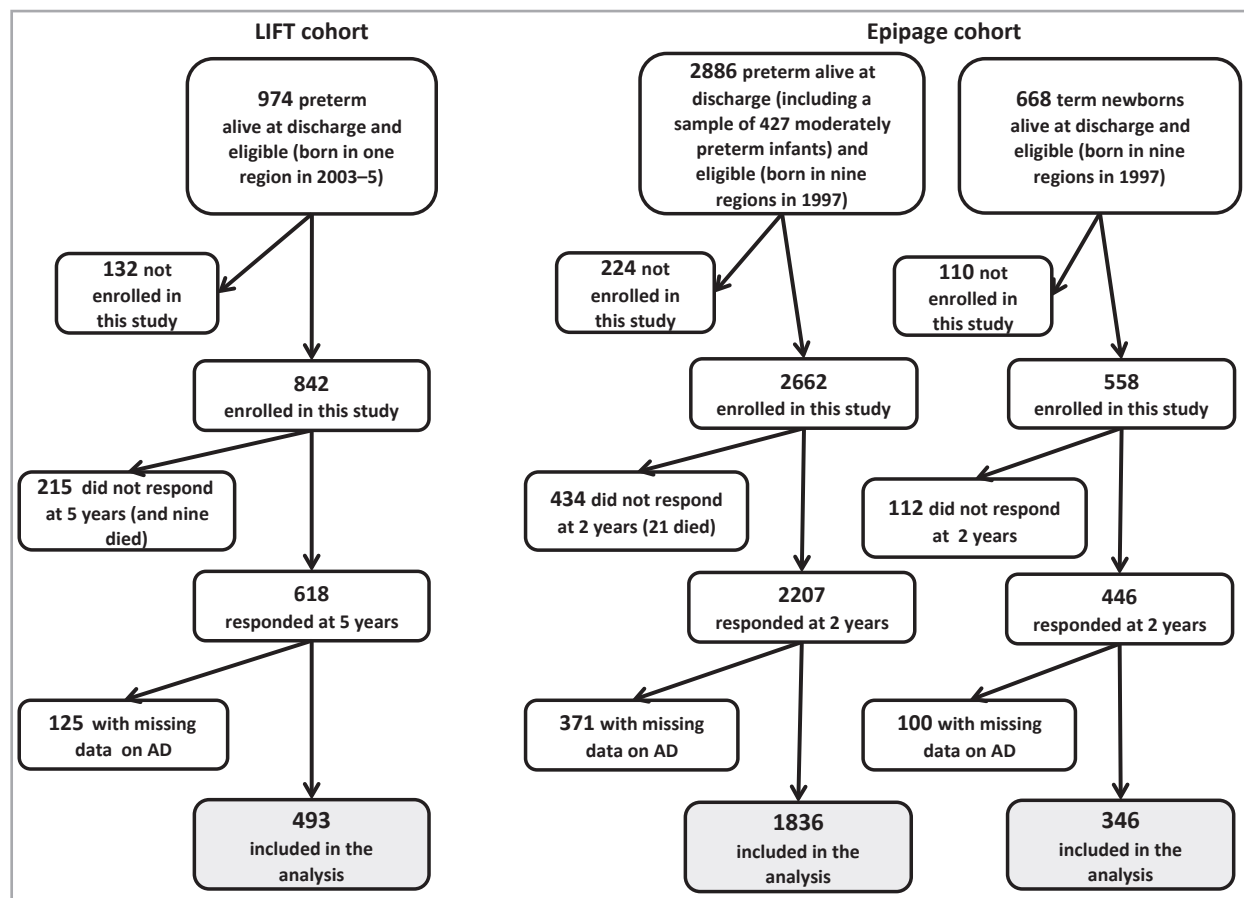


Fig 1. Flow chart of the infants analysed from the LIFT and Epipage cohorts.

completed weeks of GA between January 2003 and December 2005, hospitalized at Nantes University Hospital, and alive at discharge ($n = 974$) (Fig. 1). Of the 974 recruited, 132 were not enrolled in the study (follow-up was not proposed or was refused by parents), 215 did not respond at 5 years, and nine died before 5 years. Finally, 618 infants were included in the follow-up study at 5 years.

Each cohort was registered with the French clinical research data protection authority, the Commission Nationale de l'Informatique et des Libertés, and approved by the local ethics committees. For the Epipage cohort, parents were informed of the study in the maternity or neonatal unit, and verbal consent was provided at the time of study enrolment. For the LIFT cohort, written consent was obtained from parents at the time of study enrolment.

Atopic dermatitis assessment

LIFT cohort data were collected at 5 years through standardized telephone interviews administered to parents between December 2010 and February 2011. Presence of AD was defined as a positive answer to the question, 'Has a doctor ever told you that your child had atopic eczema?' The interview also included questions on family allergy history (mother, father and/or siblings). For the Epipage cohort, a questionnaire was mailed to parents after 2 years, and AD was assessed by the same question via parental disclosure of physician-diagnosed eczema. In both cohorts, responders were defined as infants enrolled in the follow-up study with known AD status at 5 years (LIFT) or 2 years of age (Epipage). Nonresponders were defined as infants not enrolled in the follow-up study and infants without data on AD diagnosis. Ultimately, AD data were available for 1836 preterm and 346 full-term infants at 2 years of age (Epipage cohort) and 493 preterm infants at 5 years of age (LIFT cohort) (Fig. 1).

Perinatal factors

For both cohorts, basic data were collected in maternity and neonatal wards. These included the level of maternal education (in the Epipage cohort), GA, the infant's sex and birthweight, plurality, use of systemic antibiotics, antenatal administration of corticosteroids, breastfeeding at discharge and family history of allergies (mother, father and/or siblings). The birthweight z -score was calculated using the least mean square method.²² This score expresses the difference between an individual child's weight and the average weight of comparable children, born at the same GA in the reference population.

Statistical analysis

We first analysed the number of infants with and without AD at 2 years of age in the Epipage cohort and at 5 years of age in the LIFT cohort, according to GA at birth. We analysed the data from these cohorts independently, without pooling data between the two cohorts. In the Epipage cohort, we

used a sample of full-term infants for comparison with the preterm group. Secondly, the crude association between AD and pregnancy and characteristics of preterm infants was analysed. Finally, the association between GA and AD was studied after adjusting for potential confounders, including birthweight z -score, sex, Caesarean section, age, use of systemic antibiotics during the neonatal period, family allergy history and level of maternal education. Logistic regressions were performed for univariate and multivariate analyses. Crude and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were determined, and two-sided tests were used in all cases. Missing data were excluded from the analysis. All analyses were performed with SPSS v.15.0 (IBM, Armonk, NY, U.S.A.).

Results

Characteristics of the study population

Comparing the characteristics of responders and nonresponders from the two preterm cohorts, we found no significant differences in the duration of assisted ventilation and birthweight z -scores. However, responders were slightly more likely than nonresponders to have a lower GA, be delivered by Caesarean section, and be treated with intravenous antibiotics during the neonatal period ($P < 0.05$, data not shown). In the Epipage cohort, nonresponding mothers of preterm infants had a higher maternal education level than responders (45% vs. 37%, $P < 0.01$; data not shown).

The demographic and clinical characteristics of all included preterm and term infants are shown in Table 1. In the LIFT cohort, 493 preterm infants were included in the analysis: 88 were born at 24–28 weeks (18%), 237 at 29–32 weeks (48%) and 168 at 33–34 weeks (34%). In the Epipage cohort, 1836 preterm infants were included in the analysis: 391 were born at 24–28 weeks (21%), 1202 at 29–32 weeks (65%) and 243 at 33–34 weeks (13%). In the full-term reference group, 346 infants were included.

Gestational age and prevalence of atopic dermatitis in infants

With regard to the relationship between GA and later development of AD, the percentage of children with AD in the extremely preterm group (< 29 weeks) was significantly lower than in those born at a greater GA in the Epipage cohort, and tended to be lower in the LIFT cohort (Table 2). Using the 33–34 week category as a reference, we found that lower GA (< 29 weeks) was associated with decreased risk of AD in the Epipage (OR 0.55, 95% CI 0.36–0.84; $P = 0.01$) and LIFT cohorts (OR 0.52, 95% CI 0.24–1.12; $P = 0.09$) (Table 3). Moreover, there were no significant differences observed with regard to AD between the > 29 week GA subgroups: 29–32, 33–34 and 39–40 weeks (term) in the Epipage cohort, $P = 0.12$ and $P = 0.72$; and 29–32 and 33–34 weeks in the LIFT cohort, $P = 0.21$.

Table 1 Demographic and clinical characteristics of preterm and term infants from the LIFT and Epipage cohorts

Characteristics	LIFT cohort Preterm, N = 493	Epipage cohort Preterm, N = 1836	Term, N = 346
Infant characteristics, n (%)			
Male	279 (56.6)	953 (51.9)	181 (52.3)
Gestational age at birth			
24–28 weeks	88 (17.8)	391 (21.3)	–
29–32 weeks	237 (48.1)	1202 (65.5)	–
33–34 weeks	168 (34.1)	243 (13.2)	–
Birthweight, z-score ^a			
< –2	20 (4.1)	53 (2.9)	3 (0.9)
–2 to –1	104 (21.1)	309 (16.9)	44 (12.7)
–1 to 0	202 (41.0)	817 (44.7)	160 (46.2)
0 to 2	163 (33.1)	641 (35.1)	137 (39.6)
> 2	4 (0.8)	7 (0.4)	2 (0.6)
Pregnancy characteristics			
Caesarean section	335 (68.0)	1021 (55.6)	27 (7.8)
Prenatal treatment with corticosteroids ^b	355 (72.0)	1338 (74.0)	–
Prenatal treatment with antibiotics ^c	99 (20.1)	337 (20.1)	–
Multiple pregnancy	208 (42.2)	598 (32.6)	4 (1.2)
Neonatal hospitalization characteristics			
Respiratory distress syndrome ^d	243 (49.3)	704 (38.8)	–
Assisted ventilation > 10 days	58 (11.8)	200 (10.9)	–
Antibiotic treatment during the neonatal period ^e	403 (81.7)	1081 (67.2)	–
Other characteristics			
Breastfeeding ^f	151 (30.6)	413 (23.6)	172 (49.7)
Family history of allergies	182 (36.9)	840 (45.8)	184 (53.2)
Number of siblings > 0 ^g	237 (48.1)	702 (43.3)	199 (57.5)

Information available for ^a1827, ^b1809, ^c1676, ^d1815, ^e1609, ^f1748 and ^g1622 of the 1836 preterm infants in the Epipage cohort.

Risk of atopic dermatitis in relation to gestational age and infant characteristics

Among preterm infants, we next considered other characteristics with regard to the relationship between AD and GA (Table 3). We observed that a family history of allergies was associated with a higher risk of AD in both cohorts. Moreover, a high level of maternal education was associated with an increased risk of AD in the Epipage cohort; however, this information was not available for the LIFT cohort. In addition, very low birthweight (z-score < –2) was associated with a lower risk of AD in the Epipage cohort, but not in the LIFT cohort. The risk of AD was also linked to the duration of assisted ventilation during the neonatal period in the LIFT cohort, while it was not associated with AD in the Epipage

Table 2 Prevalence of atopic dermatitis according to gestational age in the LIFT and Epipage cohorts^a

Gestational age	LIFT cohort, N = 493		p-value ^b	Epipage cohort, N = 2182 ^c		p-value ^b
	n/N	%		n/N	%	
24–28 weeks	10/88	11	0.11	52/391	13.3	0.02
29–32 weeks	51/237	21.5		212/1202	17.6	
33–34 weeks	33/168	19.6		53/243	21.8	
39–40 weeks	–	–		71/346	20.5	

^aBased on a parental report of physician-diagnosed atopic dermatitis within the first 5 years (LIFT cohort) or 2 years of life (Epipage cohort). ^bPearson χ^2 -test. ^cIncludes 1836 infants born preterm and 346 infants born at full term.

cohort. We also determined that breastfeeding at discharge and use of intravenous antibiotics during the neonatal period were not associated with a significant risk of AD in either cohort. Furthermore, using the 33–34 week category as a reference, we found that by adjusting for birthweight z-score and/or family allergy history (in addition to high level of maternal education in the Epipage cohort), lower GA (< 29 weeks) was significantly associated with decreased risk of AD in the LIFT [adjusted OR (aOR) 0.41, 95% CI 0.18–0.90; P = 0.03] and Epipage cohorts (aOR 0.57, 95% CI 0.37–0.87; P = 0.009) (Table 4). However, adjustments for sex, Caesarean section, use of systemic antibiotics during the neonatal period and age did not yield effects on the results for either cohort (data not shown).

Discussion

In the present study, we found that very low GA (< 29 weeks) was associated with a reduced risk of AD compared with later preterm (29–34 weeks) and term GA by analysing two independent cohorts of premature infants. Conversely, a family history of allergies and/or a high level of maternal education were identified as predictors of increased risk of AD. Interestingly, no associations were observed between AD risk and smaller family size or perinatal factors (Caesarean section, breastfeeding, or neonatal treatment with intravenous antibiotics). Moreover, our observed 5-year cumulative incidence of AD for infants born at full term was 21%, which is in accordance with recent European epidemiological data.²³

In addition, we did not find an association between asthma outcome at 2 years and GA in the Epipage cohort (data not shown; data not available for the LIFT cohort). Although preterm infants are generally considered to be at risk for asthma,^{24,25} data regarding this condition should be interpreted with caution in very preterm cohorts. Indeed,

Table 3 Characteristics of preterm infants and odds ratios (ORs) for atopic dermatitis^a

Characteristics	LIFT cohort, N = 493			Epipage cohort, N = 1836		
	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		
Birthweight, z-score ^b						
< -2	1.3	0.39–1.53	0.70	0.29	0.09–0.96	0.04
-2 to -1	0.98	0.51–1.91	0.96	0.97	0.67–1.39	0.85
-1 to 0	1.44	0.85–2.45	0.17	1.13	0.86–1.47	0.40
0 to 2	1			1		
Pregnancy characteristics						
Caesarean section	0.95	0.59–1.53	0.83	1.13	0.88–1.44	0.34
Prenatal treatment with corticosteroids ^c	1.34	0.79–2.27	0.27	0.95	0.72–1.25	0.72
Prenatal treatment with antibiotics ^d	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 ^e	0.79	0.59–1.05	0.10	0.97	0.86–1.10	0.66
Other characteristics						
Breastfeeding ^f	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 ^g	0.82	0.52–1.28	0.38	1.02	0.98–1.06	0.40

CI, confidence interval; NA, not available. ^aBased on a parental report of physician-diagnosed atopic dermatitis within the first 5 years (LIFT cohort) or 2 years of life (Epipage cohort). Information available for ^b1827, ^c1809, ^d1676, ^e1609, ^f1748 and ^g1622 of the 1836 preterm infants in the Epipage cohort.

Table 4 Association between gestational age at birth and risk of atopic dermatitis^a in preterm infants after adjusting for birthweight (z-score), family allergy history and high level of maternal education

	LIFT cohort, N = 493			Epipage cohort, N = 1836		
	OR	95% CI	P-value	OR	95% CI	P-value
Adjusted for birthweight z-score						
24–28 weeks	0.53	0.25–1.15	0.11	0.54	0.35–0.82	0.004
29–32 weeks	1.16	0.70–1.92	0.57	0.76	0.54–1.07	0.10
33–34 weeks	1			1		
Adjusted for birthweight z-score and family history of allergies						
24–28 weeks	0.41	0.18–0.90	0.03	0.57	0.37–0.87	0.001
29–32 weeks	1.08	0.64–1.81	0.79	0.78	0.55–1.10	0.16
33–34 weeks	1			1		
Adjusted for birthweight z-score, family history of allergies and high level of maternal education						
24–28 weeks	NA			0.57	0.37–0.87	0.009
29–32 weeks	NA			0.78	0.55–1.10	0.16
33–34 weeks	NA			1		

OR, odds ratio; CI, confidence interval; NA, not available. ^aBased on a parental report of diagnosis of atopic dermatitis provided by a physician within the first 5 years (LIFT cohort) or 2 years of life (Epipage cohort).

bronchopulmonary dysplasia (BPD) is highly prevalent in preterm infants. Thus, recurrent respiratory symptoms, such as wheezing and lower respiratory infections, are frequent BPD

manifestations in the first 2 years for this population. Therefore, these symptoms should probably not be interpreted as atopic disease.

A major strength of our study is that it involved two independent cohorts (LIFT and Epipage), and that it fits within the prospective, population-based design of these cohort studies. Additionally, GA in our study was estimated based on the date of the last menstrual period and early ultrasound results, which is the standard method for the majority of pregnant women in France. Therefore, the data collected should be highly reliable and of high quality.²⁶

This study also had some limitations that should be considered when interpreting the results. In the LIFT cohort, lower GA (< 29 weeks) was not significantly associated with decreased risk of AD compared with a greater GA. This result may be due to a lack of power affecting the LIFT cohort, as the number of subjects in the very low GA group was low ($n = 88$). However, after adjusting for confounding variables, a lower GA (< 29 weeks) was significantly associated with decreased risk of AD in both cohorts.

In the Epipage cohort, nonresponding mothers of preterm infants had a higher maternal education level compared with responders. As the maternal education level is a known risk factor for AD,²⁷ this discrepancy could have resulted in an underestimation of the prevalence of AD in responders compared with nonresponders; however, this difference was unlikely to modify our observed relationship between GA and AD risk among responders. Furthermore, the rate of infants lost to follow-up was higher in the groups that showed increased GA (data not shown). However, there is no reason to suspect that patients with AD within these groups would be more likely to be lost to follow-up. Thus, it is not probable that this discrepancy explains the observed association between GA and AD.

A primary concern in the interpretation and comparison of epidemiological studies arises from the use of different definitions for describing patient disease states. With regard to AD, some studies define it as 'reported eczema',^{12,27} while others use the U.K. diagnostic criteria²⁸ or the International Study of Asthma and Allergies in Childhood questionnaire.²⁹ Also, variations in the definition of AD can result in differences in reports regarding estimations of lifetime, last year or point prevalence. Moreover, as the use of parental reporting can result in misclassification of AD cases, we used a parental report of physician-diagnosed atopic eczema as the outcome variable. Also, in questionnaires, we deliberately used 'atopic eczema' (LIFT cohort) or 'eczema' (Epipage cohort) and not 'atopic dermatitis', because this wording of the question had sufficient sensitivity and specificity to provide relevant data on the cumulative incidence of AD, as previously reported.^{30,31} Furthermore, AD was not assessed in exactly the same manner for our two distinct cohorts, as a questionnaire was mailed to parents of the Epipage cohort and a standardized telephone questionnaire was used for the LIFT cohort. Additionally, AD outcome was not assessed at the same age for these cohorts. Although this could explain the difference observed in AD prevalence between the two groups, the same questions were used in each cohort for all infants, regardless of GA. Thus, a nondifferential misclassification of AD could have led to an underestimation of its association with GA. However, we did

not pool the data from the two cohorts in this study, and we examined the association between GA and AD independently for each cohort. Finally, as our study was observational, the possibility of residual confounding cannot be excluded.

AD is a multifactorial disease caused by genetic and environmental factors. Patients with AD have a functionally defective skin barrier, even in nonlesional skin. Recent reports have suggested that the skin barrier plays a key role in maintaining effective protection against AD and other allergic disorders.^{32,33} The well-established association between AD and loss-of-function mutations within the filaggrin gene supports the hypothesis that an intrinsically impaired skin barrier could be a first step in the development of AD.^{32,34} From this perspective, neonatal defects in skin barriers could constitute a pivotal starting point for allergic disorders.

GA also exerts a strong influence on skin barrier function; in infants born at full term, the stratum corneum is developed and ensures efficient protection. Stratum corneum maturation occurs at around 29–37 weeks of GA,⁷ and skin barrier function is regarded as impaired in infants born before 29 weeks. Surprisingly, we found that infants born at a lower GA (< 29 weeks) had a reduced risk of AD compared with infants born preterm at a later GA (29–34 weeks) or at full term.

It is unclear why lower GA would be associated with a decreased risk of AD, but several hypotheses can be proposed. Firstly, continuous stimulation of the immune system by environmental saprophytes via the skin appears to be necessary to induce immune tolerance by activating the regulatory network, including regulatory T cells and dendritic cells.³⁵ Therefore, a functionally impaired skin barrier in very preterm infants could result in early transcutaneous exposure to antigens, leading to the development of tolerance. Secondly, the diversity of intestinal microflora is reduced in very preterm infants and increases progressively,³⁶ and it is unknown whether limited microflora in very preterm infants could influence the acquisition of immune tolerance and lead to reduced risk of AD. Thirdly, increased birthweight and postmaturity have been associated with higher total serum IgE levels, and postmaturity may be associated with a reduced thymus weight, which can alter the balance of T-helper (Th)1 and Th2 cell populations in the thymus in favour of Th2 cells.³⁷ A shorter period of exposure to Th2 cytokines during pregnancy could also bias the fetal immune system towards atopy.³⁸ Interestingly, the results from the Epipage cohort confirm that the risk of AD is diminished in preterm infants with very low birthweights.^{12,17} Fourthly, frequent use of aggressive washing products such as soap could augment the risk of AD in children.³⁹ However, it is unlikely that there were differences in washing and bathing practices during hospitalization or at home in our population. Furthermore, it is unlikely that current methods of routine care during hospitalization led to our observed result, as a recent study found that young adults born prematurely in the 1970s and 1980s with very low birthweight had a lower incidence of atopy.¹⁷ Finally, one explanation for the low rate of AD observed in children born at lower GA could be the higher rate of

mortality noted in preterm infants with AD. However, our results do not support this hypothesis, and infants born before 29 weeks were actually more likely to have a family history of allergies in the LIFT cohort (data not shown).

Previous studies investigating the association between GA and AD have produced conflicting results. Indeed, some studies found that a low GA was associated with reduced risk of AD^{9–11} or atopy,¹⁷ while others reported low GA to be linked to a higher risk of AD⁸ or atopy.¹⁸ Moreover, additional investigations found no significant association between GA and AD at all.^{12–14,17} Direct comparisons between these studies are difficult, due to variation in study designs, AD definitions and study populations. In most of these studies, the number of preterm infants was lower and the mean GA of preterm infants was higher than in our study. To our knowledge, no study has been published on the risk of AD in a large cohort of preterm infants that includes a large number of infants born before 29 weeks of GA.

In conclusion, this large, population-based cohort study revealed that, among preterm infants, there is an association between very low GA (< 29 weeks) and a decreased risk of AD, compared with higher GA (29–34 weeks) and full-term birth. Further studies are needed to confirm these results, and to understand how these findings are influenced by factors such as the environment, nutrition, immune system development and skin barrier function in very preterm infants.

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