ORIGINAL ARTICLE

Atopic Dermatitis Phenotypes in Preschool and School-Age Children: A Latent Class Analysis

Galli E[1], Maiello N[2], Cipriani F[3], La Grutta S[4], Fasola S[4], Carello R[1], Caminiti L[5], Licari A[6], Landi M[4,7], Di Mauro D[8], Ricci F[3], Panel of the Italian Society of Pediatric Allergy and Immunology (SIAIP)

[1]Pediatric Allergy Unit, San Pietro Hospital - Fatebenefratelli, Rome, Italy
[2]Dipartimento della Donna, del Bambino e di Chirurgia Generale e Specialistica, Università della Campania Luigi Vanvitelli, Naples, Italy
[3]Pediatric Unit, Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy
[4]Institute for Biomedical Research and Innovation, National Research Council, Palermo, Italy
[5]Department of Pediatrics, Allergy Unit, University of Messina, Messina, Italy
[6]S.C. Pediatria, University of Pavia, Department of Pediatrics, Foundation IRCCS Policlinico San Matteo, Pavia, Italy
[7]National Pediatric Healthcare System, Torino, Italy
[8]Pediatric Clinic of Medicine and Surgery, University of Parma, Parma, Italy

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Abstract

Background: Atopic dermatitis (AD) is the most common chronic inflammatory skin disease in childhood. Few data are available about AD phenotypes and their nationwide distribution.
Methods: We performed a cross-sectional multicenter study involving some of the main Italian pediatric allergy centers from 9 Italian cities. A structured questionnaire was administered to 371 children with AD. Patients were divided in 2 groups: preschool children (aged ≤5 years) and schoolchildren (aged 6-14 years). A latent class analysis was used to detect AD phenotypes and to investigate their association with risk factors and other atopic diseases.
Results: Latent class analysis identified 5 AD phenotypes in preschoolers ("moderate-severe AD, high comorbidity", 8%; "moderate-severe AD, low comorbidity", 35%; "mild AD, low comorbidity", 20%; "mild AD, respiratory comorbidity", 32%; "mild AD, food-induced comorbidity", 5%) and 4 AD phenotypes in schoolchildren ("moderate-severe AD, high comorbidity", 24%; "moderate-severe AD, low comorbidity", 10%; "mild AD, low comorbidity", 16%; "mild AD, respiratory comorbidity", 49%). Parental history of asthma and eczema, early day-care attendance, and exposure to molds were significantly associated with the "moderate-severe AD, high comorbidity" phenotype in preschool children ($P<.05$). The "moderate-severe AD" phenotypes were also associated with the highest burden in terms of medication use and limitations in daily activities.
Conclusions: The detection of different AD phenotypes highlights the need for a stratified approach to the management of this complex disease and for further studies to predict the course of AD and to develop more efficient therapeutic strategies.

Key words: Atopic dermatitis. Epidemiology. Pediatrics. Quality of life. Environment and hygiene hypothesis.

Resumen

Antecedentes: La dermatitis atópica (DA) es la enfermedad crónica cutánea más frecuente en la infancia. Hay pocos datos disponibles sobre los diferentes fenotipos de DA y su distribución geográfica.
Métodos: Se realizó un estudio transversal multicéntrico en nueve de los principales centros italianos de alergia infantil. Se realizó un cuestionario a 371 con DA. Los pacientes fueron divididos en dos grupos: preescolares (<5 años) y escolares (6-14 años). Se empleó un análisis de clases latentes (ACL) para establecer los fenotipos de la DA y su asociación con factores de riesgo y otras enfermedades atópicas.
Resultados: El ACL identificó cinco fenotipos de DA en el grupo preescolar (8% DA moderada-severa con alta comorbilidad, 35% DA moderada-severa con baja comorbilidad, 20% DA leve con baja comorbilidad, 32% DA leve con patología respiratoria asociada, 5% DA leve con alergia alimentaria asociada) y cuatro fenotipos en escolares (24% DA moderada-severa con alta comorbilidad, 10% DA moderada-severa con baja comorbilidad, 16% DA leve con baja comorbilidad, 49% DA leve con patología respiratoria asociada). Los antecedentes familiares de asma y eccema, la asistencia temprana a guardería y la exposición a hongos se asociaron al fenotipo DA moderada-severa con alta comorbilidad en niños preescolares ($p<0,05$). Los fenotipos moderados-severos requerían mayor uso de medicación y tenían mayores limitaciones para su actividad diaria.
Conclusiones: La clasificación de la DA en diferentes fenotipos implica la importancia de un tratamiento estratificado para esta compleja enfermedad así como la necesidad de estudios capaces de predecir el curso de la DA y con ello desarrollar estrategias de tratamiento más eficientes.

Palabras clave: Dermatitis atópica. Epidemiología. Calidad de vida. Hipótesis del entorno y de la higiene.

Introduction

Atopic dermatitis (AD), also known as eczema [1], is a common chronic inflammatory skin disease in childhood, with an estimated prevalence of up to 20% [2].

The complex pathogenesis of AD and its interactions with environmental factors account for its multifaceted course and frequent association with allergic sensitization and other atopic diseases, such as food allergy, allergic rhinitis, and asthma [3,4].

Coexistence of multiple allergic diseases has been widely observed in epidemiological studies [5-7] and in clinical practice [8]. AD and food allergy coexist in 35%-40% of children, especially in those with early-onset and more severe and persistent disease [9]. Previous population-based studies identified individual and environmental risk factors, such as urban residence and exposure to molds, which have been associated with a higher prevalence of AD in Italian children and adolescents, thus providing important insights for prevention and interventions [10,11]. The issue of allergy-related comorbidities and their interrelationships were recently investigated at the population level, with different comorbidity clusters being identified at 4 and 8 years of age [3]. Few data are available about AD phenotypes, mainly because of immunological and clinical differences between non–IgE-associated and IgE-associated forms [8,12,13].

In a recent study of 572 children with AD under 3 years of age, Seo et al [14] applied cluster analysis, which identified 4 clusters of AD and demonstrated the heterogeneity of this disease, even in early childhood. Age at onset, age at diagnosis, white blood cell count, eosinophil count, C-reactive protein, and serum total IgE level were the strongest predictors of cluster assignment [14]. Three AD phenotypes ("AD with low sensitization", "AD with multiple sensitizations", "AD with family history of asthma") were identified through cluster analysis in infants aged less than 1 year, based on a mix of demographic and clinical characteristics. Multiple sensitization and family history have been found to be associated with a higher risk of developing asthma during childhood [15].

In their recent birth cohort study of 1038 children (PASTURE study), Roduit et al [16] identified 4 AD subtypes through an innovative latent class analysis (LCA), which was based on the onset and the course of symptoms until 6 years of age [16]. Of note, children with early onset (within 2 years of age) and persistent symptoms proved to be more at risk of developing asthma and food allergy at 6 years of age [16].

While previous studies that phenotype AD highlight the importance of a comprehensive evaluation including asthma, allergic rhinitis, and food allergy, most were limited to young children and were aimed at predicting onset of allergic disease later in life [17]. Cross-sectional AD phenotyping based on both clinical manifestations and comorbidities in various age groups needs to be performed to offer new perspectives in the interpretation of the disease and its proper management.

The present study aimed to detect different AD phenotypes in preschool and school-age children, based on both clinical manifestations of AD and the presence of coexisting respiratory and food allergies. We also aimed to assess the relationship between the classes detected and host and environmental risk factors.

Methods

Study Design and Population

We performed a multicenter, cross-sectional study involving some of the main Italian pediatric allergy centers and other general pediatric centers located in 9 Italian cities (Bologna, Messina, Napoli, Palermo, Parma, Pavia, Roma, Salerno, and Torino).

Pediatric patients who were referred for the first time to one of the aforementioned centers were consecutively enrolled from January 2015 to January 2016.

The inclusion criteria were age ≤14 years and a diagnosis of eczema based on the Hanifin and Rajka criteria [18]. The exclusion criteria were presence of other forms of dermatitis, presence of other conditions (congenital, acquired, or chronic) that may have affected the course of atopic dermatitis, and lack of signed informed consent.

The study was approved by the Ethics Committee of the coordinating center, San Camillo Forlanini Hospital (protocol 2011/CE Lazio 1, Roma, Italy), and by the Ethics Committees of all the other participating hospitals. The signed informed consent of at least 1 parent/caregiver was obtained for each participant at enrolment.

Clinical Assessments

Clinical characteristics, including the evaluation of atopic status and severity of eczema, were assessed by well-trained physicians. Atopy was defined as at least 1 positive reaction to the 7 aeroallergens used for skin prick testing (*Dermatophagoides* mix, grass pollen mix, *Parietaria judaica*, olive, dog and cat dander, and *Alternaria alternata*) (ALK-Abelló) and/or the presence of physician-based diagnosis of food allergy. Severity of AD was defined according to the SCORAD index as "mild" if ≤25 and as "moderate/severe" otherwise [19].

Structured Questionnaire

A structured questionnaire was administered to patients' parents or caregivers. It included items on sociodemographic characteristics and individual and environmental factors over the previous 6 months (symptoms and exacerbations of AD, use of medications for AD, activity limitations due to AD, and the presence of comorbidities).

The sociodemographic characteristics included gender, age, height and weight (from which body mass index [BMI]-for-age z-scores were derived based on WHO reference values), and parental education (<8 or ≥8 years of education for at least 1 parent between mother and father). Age was categorized into 2 groups: preschool children (≤5 years) and school-age children (age range 6-14 years), since such categorization is known to be clinically relevant for associated diseases (eg, allergic asthma) [20].

Individual factors included self-reported breastfeeding (exclusive breastfeeding for ≥3 months) and parental history of eczema, asthma, and rhinitis. Environmental factors included daycare attendance before the third year of life, current exposure to traffic (moderate/high vs absent/low traffic intensity in the area of residence), early exposure to pets

(during the first year of life), current exposure to pets (dog/cat), maternal smoking during pregnancy, early exposure to passive smoke (during the first year of life), current exposure to passive smoke (mother/father), early exposure to molds (during the first year of life), and current exposure to molds (self-reported mold odor or visible mold) in the child's bedroom.

The number of self-reported AD exacerbations in the previous 6 months was categorized as ≤3 or >3. Moreover, the questionnaire included self-reported information about the presence of itching in the absence of lesions and night awakenings due to AD (>0 per week) during the previous 6 months. Self-reported medication in the previous 6 months included topical corticosteroids and/or calcineurin inhibitors, topical antibiotics, antifungals, and oral antihistamines. Self-reported activity limitations in the previous 6 months included negative influence (moderate/heavy vs none/slight) of AD in sport, school attendance, sleep quality, recreation, and social relations.

Self-reported AD comorbidities in the previous 6 months were grouped into the following macro-categories: lower respiratory comorbidities (wheezing, asthma, or exercise-

Table 1. Sociodemographic Characteristics of Children, Individual and Environmental Factors, Clinical Evaluation of Atopic Dermatitis, and Comorbidities By Age Group[a]

	Preschool Children n=206 (55%)	Schoolchildren n=165 (45%)	*P* Value[b]	Overall n=371 (100%)
Males	123 (60%)	88 (53%)	.246	211 (57%)
Age, y	3.16 (1.72)	9.44 (2.35)	<.001	5.95 (3.72)
Body mass index, z-score for age	0.64 (1.52)	0.55 (1.35)	.578	0.6 (1.44)
Parental history of eczema	48 (23%)	40 (24%)	.902	88 (24%)
Parental history of asthma	54 (26%)	35 (21%)	.274	89 (24%)
Parental history of rhinitis	74 (36%)	70 (42%)	.238	144 (39%)
Exclusive breastfeeding ≥3 mo	139 (67%)	110 (67%)	.912	249 (67%)
Parental education ≥8 y	185 (95%)	139 (87%)	.020	324 (92%)
Daycare attendance before third year of life	112 (54%)	76 (46%)	.118	188 (51%)
Current exposure to moderate/high traffic	104 (51%)	76 (46%)	.402	180 (49%)
Cat or dog exposure, first year of life	34 (17%)	27 (16%)	1.000	61 (16%)
Current cat or dog exposure	33 (16%)	39 (24%)	.085	72 (19%)
Maternal smoking in pregnancy	10 (5%)	16 (10%)	.100	26 (7%)
Passive smoke exposure, first year of life	62 (30%)	59 (36%)	.266	121 (33%)
Current passive smoke exposure	67 (33%)	67 (41%)	.128	134 (36%)
Mold exposure, first year of life	60 (29%)	51 (31%)	.733	111 (30%)
Current mold exposure	43 (21%)	34 (21%)	1.000	77 (21%)
Atopy, No. (%)	107 (52%)	121 (73%)	<.001	228 (61%)
Severity of atopic dermatitis			.059	
Mild (SCORAD <25)	131 (64%)	101 (61%)	.667	232 (62%)
Moderate (SCORAD 25-50)	52 (25%)	55 (33%)	.106	107 (29%)
Severe (SCORAD >50)	23 (11%)	9 (6%)	.063	32 (9%)
>3 exacerbations in the last 6 mo, No. (%)	78 (38%)	69 (42%)	.456	147 (39.6%)
Itch without lesions	108 (52%)	92 (56%)	.531	200 (54%)
Night awakenings	103 (50%)	71 (43%)	.209	174 (47%)
Lower respiratory comorbidities[c]	60 (29%)	65 (39%)	.046	125 (34%)
Uncontrolled wheezing, No. (%)	7 (3%)	21 (13%)	.001	28 (7%)
Upper respiratory comorbidities[d], No. (%)	115 (56%)	136 (82%)	<.001	251 (68%)
Food allergy, No. (%)	49 (24%)	40 (24%)	1.000	89 (24%)
Food-induced comorbidities[e], No. (%)	35 (17%)	39 (24%)	.118	74 (20%)

[a]Data are expressed as mean (SD) for quantitative variables and as No. (%) for categorical variables.
[b]*P* values are from *t* test (quantitative variables) or Fisher exact test (categorical variables). Significant P values are in bold typeface.
[c]Wheezing or asthma.
[d]Allergic rhinitis or conjunctivitis or rhinoconjunctivitis.
[e]Urticaria, angioedema, oral allergic syndrome, or anaphylaxis.

induced bronchoconstriction), upper respiratory comorbidities (allergic rhinitis, conjunctivitis, or rhinoconjunctivitis), and food-induced comorbidities (urticaria, angioedema, oral allergic syndrome, or anaphylaxis due to foods).

Asthma (or wheezing) was defined as a parent's report of a physician-based diagnosis and at least 1 of the following: (*1*) use of medications or hospital admissions for asthma in the previous 6 months; and (*2*) asthma or wheeze after physical exercise, or attacks of dyspnea with wheeze, or dry cough/chest tightness with wheeze in the previous 6 months.

Control of asthma (or wheezing) was assessed according to the GINA guidelines [20].

Rhinoconjunctivitis was defined as a parent's report of symptoms (itchy, runny, or blocked nose without a cold and red itchy eyes) or a physician-based diagnosis of allergic rhinitis.

Food allergy was defined as a parent's report of a physician-based diagnosis of food allergy, as well as the occurrence of allergic symptoms associated with food (urticaria, angioedema, oral allergy syndrome, or anaphylaxis) with evidence of food-specific sensitization by skin test or detection of food-specific IgE. Urticaria, angioedema, oral allergy syndrome, and anaphylaxis associated with food ingestion reported by parents not satisfying the abovementioned definition of food allergy were also considered separately as food-induced comorbidities.

Statistical Analysis

All the statistical analyses were performed in R 3.3.2 and were stratified by age group, ie, preschool children (≤5 years) and school-age children (6-14 years). Sociodemographic characteristics and individual and environmental factors were compared between the 2 age groups using the *t* test (quantitative variables) or Fisher exact test (categorical variables). Statistical significance was set at $P<.05$.

LCA was used to detect eczema phenotypes (*R* package *poLCA*) in the 2 age groups. The variables used for phenotyping referred both to clinical manifestations of eczema and to the presence of comorbidities, as follows: atopy, severity of AD, AD exacerbations (previous 6 months), itching in the absence of lesions (previous 6 months), night awakenings due to AD (previous 6 months), lower respiratory comorbidities (previous 6 months), upper respiratory comorbidities (previous 6 months), and food-induced comorbidities (previous 6 months). The Akaike Information Criterion (AIC) was used to define the number of classes with the best fit to the data, with the smallest AIC representing the optimal model. Posterior probabilities of class membership were computed for each child, who was assigned to the class associated with the highest probability [21].

Labels were assigned to the classes detected according to the distributions of the phenotyping variables, which were compared graphically. The distributions of the sociodemographic characteristics and host and environmental factors were also compared between the classes detected using analysis of variance (quantitative variables) or the Fisher exact test (categorical variables). Statistical significance was set at $P<.05$. Disease burden was described graphically by plotting the proportion of each variable in each class, with a color scale spanning from white (proportion of 0%) to red (proportion of 100%) (R function *levelplot*, package *lattice*).

Results

Descriptive Statistics

The study population comprised 371 children (57% boys). The mean (SD) age of patients was 5.95 (3.72) years at enrolment; 206/371 (55%) were preschool children, and 165/371 (45%) were schoolchildren. Sociodemographic characteristics and individual and environmental factors by age group are summarized in Table 1.

The percentage of mothers or fathers with ≥8 years of education was significantly higher in preschool children (95% vs 87%, $P=.02$). A parental history of eczema, asthma, and rhinitis was reported, respectively, in 88 (24%), 89 (24%), and 144 (39%) children, with no significant differences between the age groups. A total of 249 children (67%) were exclusively breastfed for ≥3 months, 188 children (51%) attended daycare before the third year of life, 180 children (49%) lived in an area with moderate or high traffic, and 72 children (19%) were currently exposed to pets (cat or dog) (16% in the first year of life). No significant differences were observed by age group.

Current exposure to passive smoke (mother or father) was reported in 134 children (36%), while 121 children (33%) were exposed during the first year of life (no significant differences by age group). Maternal smoking in pregnancy was reported in 26 children (7%) (no significant differences by age group). Current exposure to molds in the child's bedroom was observed in 77 cases (21%), while exposure in the first year of life was reported in 111 (30%) (no significant differences by age group).

The 2 age groups were similar in terms of severity of AD, even if a slightly higher percentage of severe AD was observed in younger children (11% vs 6%, $P=.063$) (Table 1). Atopy was more frequent in schoolchildren than in preschool children (73% vs 52%, $P<.001$), as was the prevalence of lower respiratory comorbidities (39% vs 29%, $P=.046$), upper respiratory comorbidities (82% vs 56%, $P<.001$), and uncontrolled wheezing (13% vs 3%, $P=.001$) (Table 1).

Latent Class Analysis in Preschool and School-age Children

Based on the AIC (the smallest representing the optimal model), LCA identified 5 AD phenotypes in preschool children (2-class AIC, 2047.97; 3-class AIC, 2034.50; 4-class AIC, 2021.17; 5-class AIC, 2013.34; 6-class AIC, 2020.56) (Figure 1) and 4 AD phenotypes in schoolchildren (2-class AIC, 1561.46; 3-class AIC, 1559.70; 4-class AIC, 1547.21; 5-class AIC, 1559.37; 6-class AIC, 1565.60) (Figure 2). The percentage distributions of the phenotyping variables for each of the identified classes in the 2 age groups are shown in detail in the supplementary material (Tables S1 and S2).

AD Phenotypes in Preschool-age Children

According to the distribution of the phenotyping variables (Figure 1), the classes detected for preschool children were labelled as follows: Class 1 (n=16, 8%), "moderate-severe AD, high comorbidity"; Class 2 (n=73, 35%), "moderate-severe AD, low comorbidity"; Class 3 (n=42, 20%), "mild AD, low

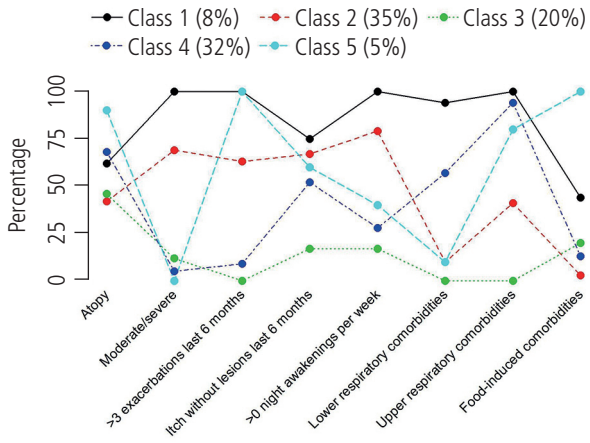

Figure 1. Clinical manifestations and comorbidities of dermatitis for the phenotypes detected using latent class analysis in preschool children. Class 1, "moderate-severe, comorbid AD"; Class 2, "moderate-severe, low comorbid AD"; Class 3, "mild, low comorbid AD"; Class 4, "mild AD, respiratory comorbidity"; Class 5, "mild AD, food-induced comorbidity".

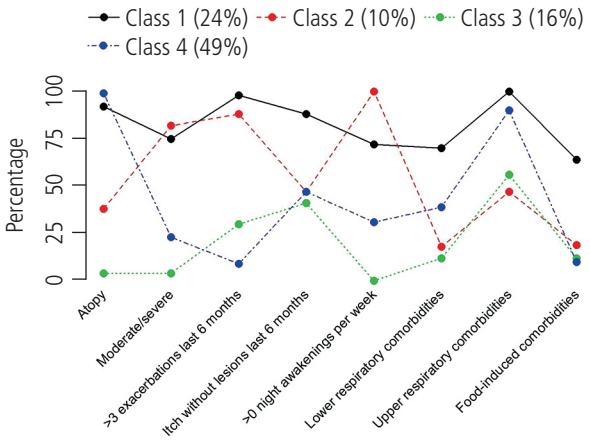

Figure 2. Clinical manifestations and comorbidities of dermatitis for the phenotypes detected using latent class analysis in schoolchildren. Class 1, "moderate-severe, comorbid AD"; Class 2, "moderate-severe, low comorbid AD"; Class 3, "mild, low comorbid AD"; Class 4, "mild AD, respiratory comorbidity.

comorbidity"; Class 4 (n=65, 32%), "mild AD, respiratory comorbidity"; Class 5 (n=10, 5%), "mild AD, food-induced comorbidity".

Concerning the 2 classes with moderate-severe AD (Classes 1 and 2), the first included the more severe forms: AD was always moderate/severe (100% in Class 1 vs 69% in Class 2), children had always had >3 exacerbations in the previous 6 months (100% in Class 1 vs 63% in Class 2) and night awakenings (100% in Class 1 vs 79% in Class 2). The most apparent difference between the 2 mild comorbid classes (Class 4 and 5) was the presence of frequent AD exacerbations in all the children with food-induced comorbidities (100% in Class 5 vs 9% in Class 4). Atopy was present in more than 40% of children in all classes (Table S1).

AD Phenotypes in Schoolchildren

According to the different distributions of the phenotyping variables (Figure 2), the labels attributed to the classes detected for schoolchildren were as follows: Class 1 (n=40, 24%), "moderate-severe AD, high comorbidity"; Class 2 (n=17, 10%), "moderate-severe AD, low comorbidity"; Class 3 (n=27, 16%), "mild AD, low comorbidity"; Class 4 (n=81, 49%), "mild AD, respiratory comorbidity". In contrast with preschool children, the mild AD phenotype with food-induced comorbidities was not detected in schoolchildren; such comorbidities were frequently observed only in the moderate-severe comorbid phenotype (Class 1).

Overall, phenotypes 1 to 4 in schoolchildren were comparable to those in preschool children. However, the moderate-severe comorbid phenotype (Class 1) was more frequent in schoolchildren (24%) than in preschool children (8%). Moreover, the "mild, low comorbid AD" phenotype (Class 3) was substantially nonatopic (only 4% atopic), but more frequently associated with itch in the absence of lesions (41%) and upper respiratory comorbidities (56%) in schoolchildren.

Sociodemographic Characteristics and Individual and Environmental Factors by Class

Table 2 summarizes the distribution of the variables listed in Table 1 by class in preschool children. Increasing age was observed in the mild comorbid phenotypes (Classes 4 and 5). Higher proportions of children with a parental history of eczema and asthma were observed in Class 1 ("moderate-severe AD, high comorbidity") and Class 4 ("mild AD, respiratory comorbidity"). Daycare attendance before the third year of life was more frequent in Class 1 ("moderate-severe AD, high comorbidity") and less frequent in Class 3 ("mild AD, low comorbidity"). Exposure to molds in the first year of life was more frequent in Class 1 ("moderate-severe AD, high comorbidity") than in the other classes. No significant associations were observed in schoolchildren (Table 3).

AD Phenotype Burden

Figure 3 represents the disease burden by AD phenotypes in the 2 age groups. In both preschool children and schoolchildren, medication use and limitations in daily activities in the previous 6 months were more frequent in the moderate-severe AD phenotypes (Classes 1 and 2), particularly in Class 1. In preschool children, the burden in terms of medication use was higher and quite similar in Class 1 ("moderate-severe AD, high comorbidity") and in Class 5 ("mild AD, food-induced comorbidity"): oral antihistamines were used, respectively, in 94% and 70% of patients and topical corticosteroids in 88% and 90% of patients in the previous 6 months, although while the need for topical antibiotics was recorded in 90% of patients in Class 1, only 30% of patients in Class 5 had used these drugs in the previous 6 months. The disease burden in Class 1 ("moderate-severe AD, high comorbidity") was lower in schoolchildren: the main differences were observed in the use of topical antibiotics and in limitations to daily activities (lighter color intensities) (Figure 3).

Table 2. Sociodemographic Characteristics and Individual and Environmental Factors by Class in Preschool Children[a]

	Class 1[b] n=16 (8%)	Class 2 n=73 (35%)	Class 3 n=42 (20%)	Class 4 n=65 (32%)	Class 5 n=10 (5%)	*P* Value[c]
Males	12 (75%)	37 (51%)	22 (52%)	46 (71%)	6 (60%)	.080
Age, y	2.88 (1.44)	2.86 (1.74)	2.38 (1.7)	4.04 (1.45)	3.35 (1.49)	<.001
Body mass index, z-score for age	0.95 (1.58)	0.42 (1.4)	0.35 (1.09)	0.98 (1.7)	0.47 (2.21)	.169
Parental history of eczema	10 (62%)	14 (19%)	5 (12%)	17 (26%)	2 (20%)	.003
Parental history of asthma	8 (50%)	21 (29%)	3 (7%)	21 (32%)	1 (10%)	.002
Parental history of rhinitis	6 (38%)	20 (27%)	14 (33%)	29 (45%)	5 (50%)	.234
Exclusive breast feeding ≥3 months	11 (69%)	53 (73%)	28 (67%)	40 (62%)	7 (70%)	.742
Parental education ≥8 years	15 (94%)	62 (91%)	36 (95%)	63 (98%)	9 (100%)	.374
Daycare attendance before third year of life	13 (81%)	40 (55%)	13 (31%)	40 (62%)	6 (60%)	.003
Current exposure to moderate/high traffic	12 (75%)	37 (52%)	22 (52%)	31 (48%)	2 (20%)	.100
Cat or dog exposure, first year of life	2 (12%)	12 (16%)	7 (17%)	11 (17%)	2 (20%)	.994
Current cat or dog exposure	2 (12%)	9 (12%)	6 (14%)	14 (22%)	2 (20%)	.626
Maternal smoking in pregnancy	3 (19%)	1 (1%)	2 (5%)	4 (6%)	0 (0%)	.076
Passive smoke exposure, first year of life	6 (38%)	18 (25%)	15 (36%)	21 (32%)	2 (20%)	.609
Current passive smoke exposure	6 (38%)	21 (29%)	14 (33%)	24 (37%)	2 (20%)	.765
Mold exposure, first year of life	10 (62%)	25 (34%)	10 (24%)	14 (22%)	1 (10%)	.012
Current mold exposure	4 (25%)	14 (19%)	5 (12%)	19 (29%)	1 (10%)	.231

[a]Quantitative variables are expressed as mean (SD); categorical variables are expressed as No. (%).
[b]Class 1, "moderate-severe AD, high comorbidity"; Class 2, "moderate-severe AD, low comorbidity"; Class 3, "mild AD, low comorbidity"; Class 4, "mild AD, respiratory comorbidity".
[c]*P* values were calculated using an ANOVA test (quantitative variables) or the Fisher exact test (categorical variables) tests. Significant *P* values are in bold typeface.

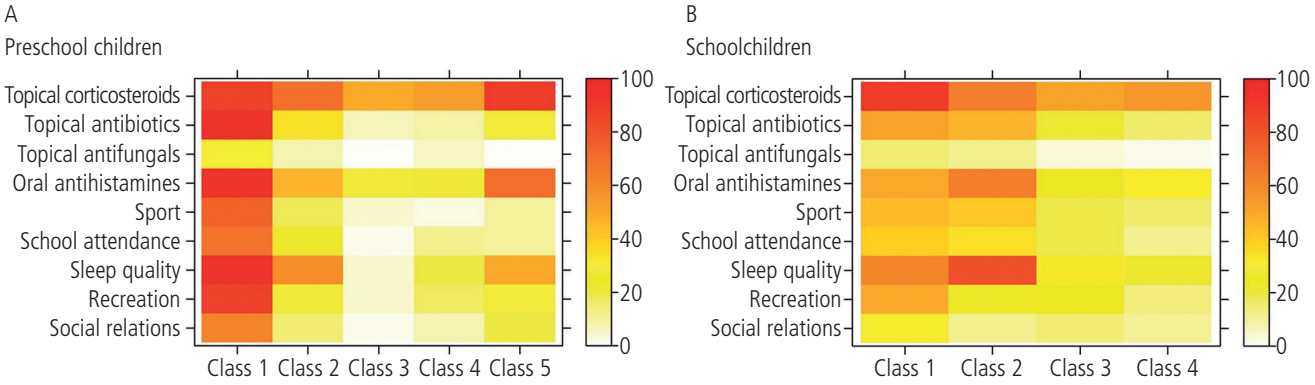

Figure 3. Medication use and activity limitations in the previous 6 months for each phenotype detected through latent class analysis in preschool children (A) and schoolchildren (B). The proportion of each variable in each class is represented with a color scale spanning from white (0%) to red (100%). Class 1, "moderate-severe, comorbid AD"; Class 2, "moderate-severe, low comorbid AD"; Class 3, "mild, low comorbid AD"; Class 4, "mild AD, respiratory comorbidity"; Class 5, "mild AD, food-induced comorbidity".

Discussion

Based on clinical presentation and LCA, the present cross-sectional study identified 5 different AD phenotypes in preschool children and 4 AD phenotypes in schoolchildren. The phenotypes were classified according to the severity of AD (mild or moderate-severe) and the presence of atopic comorbidities. In preschool children, distinct classes characterized by respiratory or food-induced comorbidities were identified, while in schoolchildren the association with atopic comorbidities seemed to be independent of the comorbidity type.

AD is complex owing to both its multifaceted clinical manifestations and disease course, so that it is sometimes

Table 3. Sociodemographic Characteristics and Individual and Environmental Factors by Class in Schoolchildren[a]

	Class 1[b] n=40 (24%)	Class 2 n=17 (10%)	Class 3 n=27 (16%)	Class 4 n=81 (49%)	*P* Value[c]
Males	23 (57%)	9 (53%)	13 (48%)	43 (53%)	.895
Age, years	9.64 (2.19)	9.3 (2.16)	9.07 (2.19)	9.5 (2.53)	.779
Body mass index for age z-score	0.52 (1.01)	0.4 (1.49)	0.64 (1.29)	0.57 (1.49)	.959
Parental history of eczema	16 (40%)	3 (18%)	4 (15%)	17 (21%)	.073
Parental history of asthma	12 (30%)	4 (24%)	3 (11%)	16 (20%)	.298
Parental history of rhinitis	15 (38%)	9 (53%)	10 (37%)	36 (44%)	.659
Exclusive breast feeding ≥3 months	27 (68%)	12 (71%)	16 (59%)	55 (68%)	.857
Parental education ≥8 years	35 (90%)	14 (88%)	22 (81%)	68 (88%)	.764
Daycare attendance before third year of life	23 (57%)	7 (41%)	8 (30%)	38 (47%)	.159
Current exposure to moderate/high traffic	20 (50%)	6 (35%)	15 (56%)	35 (43%)	.534
Cat or dog exposure, first year of life	11 (28%)	3 (18%)	4 (15%)	9 (11%)	.151
Current cat or dog exposure	11 (28%)	4 (24%)	7 (26%)	17 (21%)	.830
Maternal smoking in pregnancy	1 (2%)	1 (6%)	5 (19%)	9 (11%)	.143
Passive smoke exposure, first year of life	13 (32%)	7 (41%)	13 (48%)	26 (32%)	.450
Current passive smoke exposure	16 (40%)	8 (47%)	14 (52%)	29 (36%)	.475
Mold exposure, first year of life	15 (38%)	8 (47%)	6 (22%)	22 (27%)	.232
Current mold exposure	8 (20%)	6 (35%)	4 (15%)	16 (20%)	.446

[a]Quantitative variables are expressed as mean (SD); categorical variables are expressed as No. (%).
[b]Class 1, "moderate-severe AD, high comorbidity"; Class 2, "moderate-severe AD, low comorbidity"; Class 3, "mild AD, low comorbidity"; Class 4, "mild AD, respiratory comorbidity".
[c]*P* values were calculated using an ANOVA test (quantitative variables) or the Fisher exact test (categorical variables) tests.

difficult to ascertain whether we are addressing a single illness or a variety of illnesses that may overlap in time. The knowledge of the clinical phenotype could be useful not only for the management of current symptoms (such as night awakenings and itch) and use of medications, but also for implementing preventive measures to limit the development of comorbidities [22].

The heterogeneity of AD has been demonstrated even in early childhood. Seo et al [14] identified 4 clusters of AD in children aged <3 years by exploring the presence of 11 variables including both clinical and laboratory data [14]. A direct comparison between these phenotypes and our classes is not possible, because we analyzed a population of a different age and because our characterization of phenotypes was based more on clinical features and the presence of comorbidities and less on laboratory data.

In the recent PASTURE study, Roduit et al [16] identified 4 phenotypes of eczema: early transient (9.2%), early persistent (6.5%), late onset (4.8%), and never/infrequent (7.5%). The phenotypes detected in the PASTURE study (longitudinal study) and in our study (cross-sectional) are not directly comparable, since the study design is completely different and we focused on severity and comorbidities of AD, rather than on onset and persistence over time. For example, while asthma and rhinitis were mainly associated with early persistent eczema in the PASTURE study, in our study, such diseases were mainly associated with more severe eczema (Class 1, moderate-severe AD, high comorbidity) or detected as main diseases with comorbid eczema (Class 4, mild AD, respiratory comorbidity). A recent study by Abuabara et al [23] applied the LCA approach to study the course of AD in a cohort of children treated with pimecrolimus (>6 weeks) [23] and identified 2 main phenotypes related to the persistence or disappearance of the disease. Once again, the clinical phenotypes identified by Abuabara et al are not directly comparable with those of our study owing to the longitudinal design and the specific, long-term treatment.

Nevertheless, the various methodological approaches may complement each other in clinical practice: while the longitudinal phenotypes may prove to be more informative when working with children in the first year of life, the cross-sectional information may be more interesting in managing preschoolers and schoolchildren. For example, in preschool children, we observed a higher prevalence of respiratory symptoms among the 2 moderate-severe AD phenotypes (Class 1 and Class 2), thus suggesting the importance of investigating the presence of respiratory signs and symptoms in patients with moderate-severe AD. Furthermore, we observed that the burden in terms of medication use in preschool children is higher in classes with more frequent exacerbations (Class 1 and 5), thus suggesting the need for daily skin care.

The genetic background (in particular parental history of eczema and asthma) seems to have a considerable influence in the preschool group and is associated with the "moderate-severe AD, high comorbidity" phenotype (Class 1), while in the school-age group, this association is no longer found, probably owing to the role of concomitant risk factors in influencing AD phenotype.

In preschool children, exposure to environmental risk factors, in particular mold during the first year of life, was associated with Class 1 ("moderate-severe AD, high comorbidity"); this result is in agreement with previous findings in Italian children in the SIDRIA study [11]. Having attended daycare before the third year of life was associated with the most severe phenotypes (Class 1).

The aforementioned risk factors were also detected in a recent Asian mother-offspring cohort study, in which the authors found that maternal allergic history and attendance at a day-care center increased the odds of developing AD between 6 and 12 months [24].

As expected, limitations to daily activities (sport, school attendance, and recreation) were higher in "moderate-severe" classes (1 and 2), and sleep quality and social relationships were poorer. The level of drug consumption was also higher in these phenotypes, maybe owing to a higher susceptibility to skin infections, especially by *Staphylococcus aureus*. Therefore, disease severity is relevant, since it directly affects therapeutic management [25] and indirectly affects the quality of life of patients and their families.

The main strength of the present study is the cooperation between multiple centers in different regions of Italy, based on the same diagnostic criteria and period of enrolment, and bringing together a large case series to characterize the clinical phenotype of AD patients. The phenotyping approach proposed could therefore represent a starting point for more personalized management and therapy.

The study is also subject to limitations. First, as it was questionnaire-based, some of the self-reported data could not be confirmed. Second, as it was cross-sectional in design, it lacked follow-up data, such as information on possible transitions from one phenotype to another over time. Further follow-up studies are needed to analyze the clinical progress of patients with the phenotypes identified.

In conclusion, we identified 5 different AD phenotypes in preschool children and 4 AD phenotypes in schoolchildren. These were associated with both shared and different risk factors and atopic comorbidities. Our findings highlight the need for a stratified approach to the management of this complex disease.

Further studies exploring the progress of the phenotypes identified may offer valuable information that will enable us to define stratified approaches to predict the future course of AD and to develop more efficient therapeutic strategies.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Elena Galli

Pediatric Allergy Unit, San Pietro Hospital - Fatebenefratelli
Via Cassia, 600 – 00198 Rome (Italy)
E-mail: elenagalli53@gmail.com; galli.elena@fbfrm.it