

ORIGINAL ARTICLE

Adult eczema in Italy: prevalence and associations with environmental factors

G. Pesce,^{1,*} A. Marcon,¹ A. Carosso,² L. Antonicelli,³ L. Cazzoletti,¹ M. Ferrari,⁴ A.G. Fois,⁵ P. Marchetti,¹ M. Olivieri,⁶ P. Pirina,⁵ G. Pocetta,⁷ R. Tassinari,⁸ G. Verlato,¹ S. Villani,⁹ R. de Marco¹

¹Unit of Epidemiology and Medical Statistics, Department of Public Health and Community Medicine, University of Verona, Verona, Italy

²Unit of Respiratory Medicine and Allergology, CPA-ASL TO-2, Turin, Italy

³Department of Internal Medicine, Immuno-Allergic and Respiratory Diseases, Ospedali Riuniti di Ancona, Ancona, Italy

⁴Section of Internal Medicine, University of Verona, Verona, Italy

⁵Institute of Respiratory Diseases, University of Sassari, Sassari, Italy

⁶Unit of Occupational Medicine, AO Istituti Ospedalieri di Verona, Verona, Italy

⁷Department of Experimental Medicine, University of Perugia, Perugia, Italy

⁸Department of Public Health and Pediatrics, University of Turin, Turin, Italy

⁹Department of Public Health, Experimental and Forensic Medicine, University of Pavia, Pavia, Italy

*Correspondence: G. Pesce. E-mail: giancarlo.pesce@univr.it

Abstract

Background Studies on the prevalence of eczema and atopic dermatitis (AD), and on the factors associated with these diseases, have been mostly performed in children, whereas studies on adult populations are lacking.

Objectives To determine the prevalence of eczema and AD in the Italian adult population, and to investigate risk factors associated with the disease.

Methods A postal screening questionnaire was administered to 18 357 randomly selected subjects aged 20–44 years in the Gene–Environment Interaction in Respiratory Diseases study, which involved seven centres distributed across northern, central and southern Italy. The questionnaire included items on the occurrence of doctor-diagnosed eczema, asthma and hay fever, socio-demographic characteristics and environmental exposures.

Results In all, 10 464 (57.0%) subjects responded to the questionnaire. The prevalence of current eczema was 8.1% (95% CI: 7.6–8.7%), while the prevalence of eczema with asthma and/or hay fever (EAH), which was adopted as proxy of AD, was 3.4% (95% CI: 3.1–3.8%). About 60% of the subjects with current eczema reported the onset of the disease in adulthood. In multi-variable models, the prevalence of eczema was significantly associated with female sex, older age, living close to industrial plants, high levels of heavy traffic near home and living in central-southern Italy.

Conclusions Eczema and EAH are highly prevalent in Italian young adults, especially in women. Our results suggest that adult onset is not unusual, and that environmental factors may influence the occurrence of eczema and EAH.

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Conflict of interest

The authors declare that they have no conflicts of interest

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Introduction

Atopic dermatitis (AD), a.k.a. atopic eczema, is an inflammatory disease, characterized by epidermal dryness and itchiness, that causes typical relapsing lesions. AD is often considered a disease typical of childhood, and it is regarded as infrequent in adulthood.¹ While most published research on AD has been

performed in children, very few studies investigated the epidemiology of the disease in adults, showing that AD is not uncommon in grown-up subjects.^{2–5}

AD considerably impacts the quality of life of patients. The irritating, uncomfortable and unlikeable plaques can cause severe distress and sleepless nights,^{6,7} influencing the personal,

social and occupational life.^{8–11} Despite the high prevalence and socioeconomic costs,¹² AD still has a uncertain aetiology. The increasing trend in the prevalence of AD both in children¹³ and adults¹⁴ suggests that genetic and immunologic predisposition can be triggered by environmental factors, which seem to play a critical role in the manifestation of the disease.

This report from a multi-centre study aimed at determining the prevalence adult eczema and AD in Italy, and at studying the socio-demographic and environmental factors associated with the disease.

Methods

Study design and participants

The Gene–Environment Interactions in Respiratory Diseases (GEIRD) project is an ongoing two-stage multi-centre study, aiming at investigating allergic and respiratory conditions in the Italian adult population.¹⁵ As part of GEIRD stage-1, a cross-sectional screening questionnaire was administered between 2005 and 2010 to 18 357 subjects aged 20–44, which were randomly selected from 7 Italian centres: three from northern Italy (Verona, Turin and Pavia), two from central Italy (Ancona and Terni) and two from southern Italy (Sassari and Salerno) (Fig. 1). The GEIRD screening questionnaire (available on www.geird.org) is a modified version of the European Community Respiratory Health Survey (ECRHS) questionnaire,¹⁶ and includes questions on the occurrence of allergic diseases, socio-demographic characteristics and environmental exposures. The questionnaire was mailed up to three times in the case of non-response, and a

final phone interview was carried out to reach the remaining non-responders. All participants were informed about all aspects of the research project and consented to complete and return the questionnaire. Approval to conduct the study was granted from the local ethical committee in each participating centre.

History of eczema, asthma and hay fever

A subject was considered to have:

- 1 *Current asthma*: in case of affirmative answer to the questions ‘Have you ever had asthma?’ and ‘Was this confirmed by a doctor?’, plus he/she reported asthma attacks or use of medicines for asthma in the previous 12 months;
- 2 *Current hay fever*: in case of affirmative answer to both the questions: ‘Do you have nasal allergies including hay fever?’, and ‘Do you still have these nose problems?’.
- 3 *Current eczema*: in case of affirmative answer to the questions ‘Have you ever had atopic dermatitis or eczema, confirmed by a doctor?’, and ‘Do you still have these problems?’

A composite binary variable for eczema with concurrent asthma and/or hay fever (EAH) was also created and considered as proxy of AD.² Childhood and adulthood onset eczema were defined according to reported age at disease onset <18 and ≥18 years, respectively.¹⁷

Covariates and potential confounders

The following covariates were collected from the questionnaire and considered:

- 1 Socio-demographic factors: sex, age (20–29; 30–39; 40–44), school education level (university degree; high school diploma; or lower education otherwise) as a proxy of socio-economical status, and occupation (clerk; manager; unemployed; housewife; self-employed; workman; student).
- 2 Environmental determinants: current smoking habits (non-smoker; smoker; ex smoker), self-reported level of heavy traffic near home (‘high’ if trucks constantly passed near home; ‘moderate’ if trucks frequently passed near home; ‘low’ if trucks never or seldom passed near home), proximity to industrial plants, residential area (inner city; suburb of a city; village or rural area) and geo-climatic area (Sub-continental in the three northern centres; Mediterranean, in the 4 centres from central and southern Italy, Table 1).¹⁸

The season when the questionnaire was completed and the type of contact (mail/phone) were considered as potential confounders. Moreover, as the centres had different final response rates, the centre-specific cumulative percentile rank of response was also included as potential confounder.¹⁹

Statistical analyses

All the statistical analyses were performed with STATA 13.1 (Stata Corp LP, College Station, TX, USA), and a 5% significance level was adopted. Multi-variable logistic regression models were used to evaluate the adjusted associations of the above-

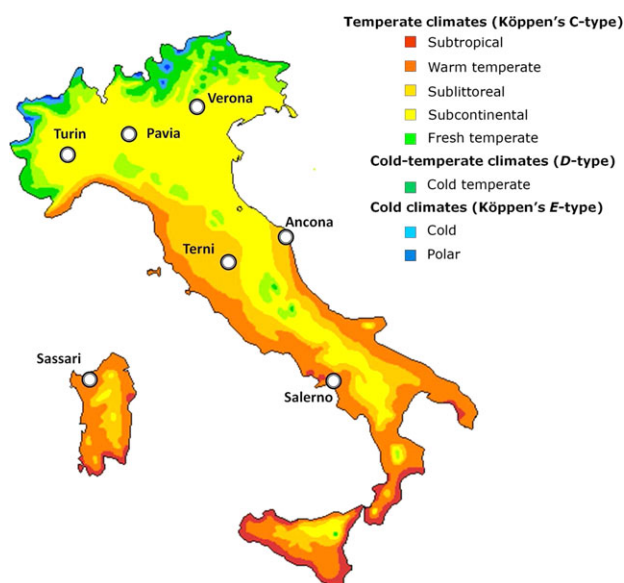


Figure 1 Centres participating in Gene–Environment Interaction in Respiratory Diseases survey, according to climatic regions.

Table 1 Geo-climatic characteristics of the GEIRD centres

GEIRD centre	Latitude North	Mean temperature (°C)	Temperature range (°C)	Degree day (HDD)	Climatic classification
Sub-continental area					
Verona	45°26'	12.7	21.7	2617	E
Pavia	45°11'	12.6	22.5	2623	E
Torino	45°04'	12.0	20.4	2468	E
Mediterranean area					
Ancona	43°37'	13.6	17.3	1688	D
Terni	42°34'	15.5	19.2	1650	D
Sassari	40°43'	16.1	16.2	1185	C
Salerno	40°41'	18.2	15.7	994	C

The meteorological data from each centre were obtained using the data collected in the period 1981–2010 from the reference weather stations of the Italian Air Force Meteorological Service. The annual mean temperature is defined as the mean of the daily temperature mean values, and the temperature range is defined as the difference between the average temperature of the hottest and the coldest month. The centre-specific values of HDD and their climatic classification were obtained by the Italian National Agency for Energy (ENEA) (http://efficienzaenergetica.acs.enea.it/doc/dpr412-93_allA_tabel-lagradigiorno.pdf). According to the Italian law n.412/1993, HDD is defined as the annual summation of the difference between the conventional base indoor temperature (i.e. 20°C) and daily outdoor temperature measured in the days with mean temperature lower than 12°C.

HDD, heating degree day.

Table 2 Response rate and prevalence of Eczema and EAH in the centres participating in the GEIRD study

GEIRD centre	Eligible subjects <i>n</i>	Response rate %	Subjects included* <i>n</i>	Eczema % (95% CI)	EAH % (95% CI)
Sub-continental area					
Verona	7393	53.0	3818	7.4 (6.6–8.2)	2.8 (2.3–3.3)
Pavia	2579	67.7	1716	8.3 (7.0–9.6)	2.7 (2.0–3.5)
Torino	2605	37.1	944	8.4 (6.6–10.1)	3.9 (2.7–5.2)
Torino	2208	54.6	1158	5.4 (4.1–6.7)	2.0 (1.2–3.8)
Mediterranean area					
Ancona	10 965	59.7	6265	8.5 (7.8–9.2)	3.8 (3.4–4.3)
Ancona	2811	59.1	1744	8.4 (7.1–9.7)	3.8 (2.9–4.7)
Terni	3015	61.9	1616	8.1 (6.7–9.4)	2.8 (2.0–3.7)
Sassari	2347	53.0	1205	9.7 (8.0–11.4)	4.8 (3.6–6.0)
Salerno	2792	63.6	1700	8.3 (7.0–9.6)	4.1 (3.1–5.0)
Total	18 357	57.0	10 083	8.1 (7.6–8.7)	3.4 (3.1–3.8)

EAH: current eczema with overlapping asthma and/or rhinitis. *Subjects with missing data on the occurrence of eczema, asthma or hay fever were excluded from the analyses.

mentioned variables with eczema and EAH, adjusting for potential confounders. Because the questionnaire administered from centre of Ancona missed the information on 'proximity to industrial plants' and 'residential area', the subjects recruited in this centre ($n = 1744$) were excluded from the multi-variable analyses.

Results

Response rates and prevalence across centres

Of 18 357 eligible subjects, 10 464 subjects responded to the GEIRD screening questionnaire (response rate: 57%) (Table 2). In all, 10 083 subjects with complete information on eczema, asthma and hay fever occurrence were included in the study. A total of 1492 subjects (14.8%, 95% CI: 14.1–15.5) reported that

they had suffered from eczema at some time in the past, and 819 (8.1%, 95% CI: 7.6–8.7) reported that they were currently suffering from the disease. In particular, 347 subjects (3.4%, 95% CI: 3.1–3.8) had EAH, defined as current eczema with concurrent asthma and/or hay fever (Fig. 2). The prevalence of subjects with current eczema and EAH was minimum in Turin (5.4% and 2.0%, respectively) and maximum in Sassari (9.7% and 4.8%, respectively).

Age at the onset in subjects with current disease

Figure 3 represents the age at the onset of the disease in the subjects with current eczema and EAH, stratified by age group. Nearly 60% of the subjects in their twenties reported that they had symptoms for the first time when they were children (<18 years). This percentage decreased to 35% and 25% in

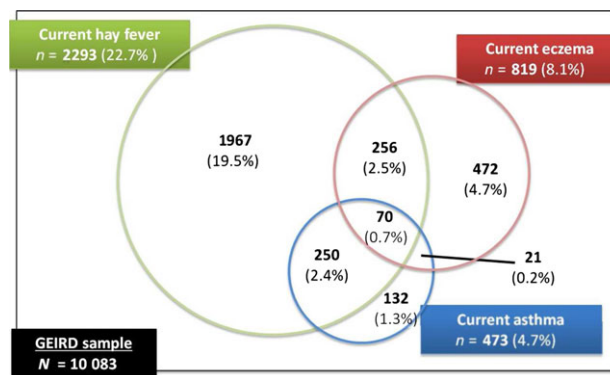


Figure 2 Distribution of current eczema, hay fever and asthma in the GEIRD sample.

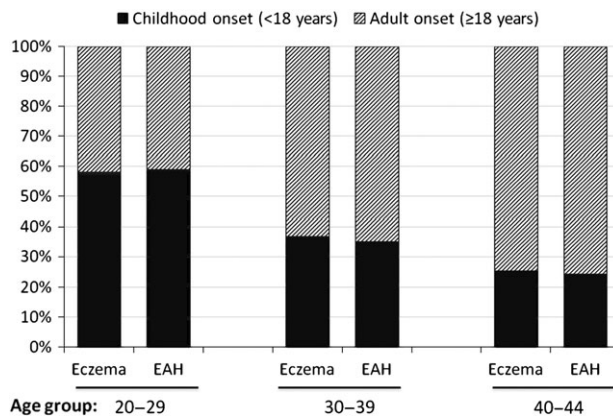


Figure 3 Proportion of childhood and adult onset eczema and EAH in subjects with current disease, stratified by age group.

subjects in their thirties and forties, respectively. Overall, only 40% of adults with eczema or EAH reported that they had their first symptom before the age of 18. There was no significant difference in the age at onset between subjects with eczema and subjects with EAH.

Associations of socio-demographic factors and environmental determinants with adult eczema

The prevalence of eczema and EAH across strata of socio-demographic and environmental variables is shown in Table 3. The prevalence of both eczema and EAH was lower in men and in subjects in their twenties compared to women and to older subjects. Unemployed subjects had the highest prevalence of eczema and EAH (9.9% and 4.1%, respectively), while students the lowest (6.9% and 2.2%, respectively).

Subjects who lived in proximity to roads trafficked by trucks or to industrial plants had a higher prevalence of eczema and EAH compared to subjects living farther away. Finally, centres

from central/southern Italy had a higher prevalence of eczema and EAH with respect to centres from northern Italy.

After adjusting for all covariates and potential confounders (Table 4), the risk of having eczema and EAH was 57% and 86%, respectively, significantly higher in women than men ($P < 0.001$). Compared to older subjects, adults in their twenties had nearly 30% lower risk of having eczema ($P < 0.01$). Occupation was no longer associated with eczema in multi-variate analysis. Subjects living in proximity of industrial plants had about 40% higher risk of having eczema or EAH ($P = 0.001$ and $P = 0.02$, respectively), and living close to heavy trafficked roads was significantly associated with 30% higher risk of having eczema ($P = 0.02$). The risks of having eczema and EAH were, respectively, 24% ($P = 0.01$) and 56% ($P = 0.001$) higher in subjects living in cities with Mediterranean climate than in those living in cities with sub-continental climates in northern Italy.

Discussion

Eczema represents a group of diseases with similar clinical characteristics, and there is not a clinical standard for the definition of the disease.¹ Similarly to the approach used by Silverberg and Hanifin,² two definitions were used in this study, which captured different subsets of the eczema/AD disease spectrum. Our definition of *eczema*, which was based on self-reported doctor diagnosed 'eczema or atopic dermatitis', might have resulted in an overestimation of the true prevalence of AD by including other eczematous skin disorders, such as irritant and/or allergic contact dermatitis. In contrast, the composite definition of *EAH*, based on the concurrent presence of eczema and asthma or hay fever, is likely to be more specific in identifying the clinical cases of extrinsic AD, but might underestimate the real prevalence of AD since many patients develop AD without having other allergic disorders.² Both of these definitions are accepted and have been used in previous epidemiological studies.²⁰ In the present study, we assumed the definition of EAH as proxy indicator of AD.²

The main findings of the study were as follows:

- 1 In Italian subjects aged 20–44 years, the prevalence rates of current eczema and current EAH were 8.1% and 3.4%, respectively, and most of the subjects reported an adult onset of disease;
- 2 The prevalence of eczema and EAH is significantly higher in centres of central and southern Italy compared to those in northern Italy;
- 3 Living in air polluted areas, such as in proximity of heavy trafficked roads or industrial plants, is associated with significantly increased risk of eczema and EAH.

Eczema and AD are common in adults

In this national multi-centre population-based study, we found a 8.1% prevalence of eczema and 3.4% prevalence of EAH in Italian young adults. These results are consistent with recent

Table 3 Prevalence (with 95% confidence interval) of eczema and EAH across strata of socio-demographic and environmental variables

Variable	n	Eczema		EAH	
		Prevalence	95% CI	Prevalence	95% CI
Socio-demographic factors					
Gender					
Male	4788	6.5	5.8–7.2	2.7	2.2–3.2
Female	5290	9.6	8.8–10.4	4.1	3.6–4.7
Age					
20–29	2850	6.7	5.7–7.6	2.9	2.3–3.5
30–39	4399	8.8	8.0–9.6	3.6	3.1–4.2
40+	2855	8.5	7.5–9.5	3.7	3.0–4.4
Schooling					
Lower education	1920	8.3	7.0–9.5	3.3	2.5–4.1
High school	5409	7.9	7.1–8.6	3.4	3.0–3.9
University	2700	8.6	7.6–9.7	3.6	2.9–4.3
Occupation					
Clerk	4052	8.4	7.5–9.2	3.9	3.3–4.5
Manager	537	7.8	5.5–10.1	3.0	1.5–4.4
Unemployed	677	9.9	7.6–12.2	4.1	2.6–5.6
Housewife	709	9.4	7.3–11.6	2.7	1.4–3.9
Self-employed	1527	8.6	7.2–10.0	3.7	2.7–4.6
Workman	1428	6.4	5.2–7.7	3.0	2.1–3.9
Student	1108	6.9	5.4–8.4	2.2	1.3–3.0
Environmental exposures					
Smoking habits					
Non-smoker	5616	7.7	7.0–8.4	3.3	2.9–3.7
Smoker	2732	8.3	7.3–9.4	3.6	2.9–4.2
Past smoker	1603	9.4	8.0–10.9	3.7	2.8–4.7
Traffic level near home					
Low	5663	7.4	6.7–8.1	3.1	2.6–3.5
Moderate	2615	8.4	7.3–9.4	3.4	2.7–4.1
High	1698	10.0	8.6–11.4	4.5	3.5–5.5
Proximity to industrial plants					
No	6472	7.6	7.0–8.2	3.1	2.7–3.5
Yes	1647	10.0	8.6–11.5	4.4	3.4–5.4
Residential area					
City centre	3217	8.3	7.3–9.2	3.5	2.8–4.1
Suburbs	3999	8.0	7.2–8.8	3.3	2.7–3.9
Countryside	1040	7.5	5.9–9.1	3.4	2.3–4.5
Geo-climatic area					
Sub-continental	3818	7.4	6.6–8.3	2.8	2.3–3.3
Mediterranean	6265	8.5	7.8–9.2	3.8	3.4–4.3

EAH: current eczema with overlapping asthma and/or rhinitis.

reports from other large population-based surveys conducted in Europe and in the United States.^{2–5} A US study, which used the 2010 National Health Interview Survey (NHIS) data, reported a 12-month prevalence of adult eczema of 10.2% and 3.2% prevalence of EAH.² Another study from the ECRHS reported that the 12-month prevalence of eczema and AD in 11 European countries was approximately 7.1% and 2.4%, respectively, in the

27–56 years age group, with great variation between and within countries.³

There are no Italian population-based studies in young adults to directly compare our study with. We are aware of only a prior survey that assessed the prevalence of skin disorders in a representative sample of the Italian adult population, aged 45 and older, which reported a lifetime prevalence of AD of 4.7%.²¹

Table 4 Adjusted estimates of association of socio-demographic and environmental factors with prevalence of eczema and EAH

Variable, n (%)	Eczema		EAH	
	Adjusted OR† (95% CI)	P-value	Adjusted OR† (95% CI)	P-value
Socio-demographic factors				
Gender				
Male	1	–	1	–
Female	1.57 (1.31–1.89)	<0.001	1.86 (1.40–2.45)	<0.001
Age				
20–29	0.71 (0.56–0.91)	0.007	0.79 (0.55–1.13)	0.192
30–39	1	–	1	–
40–44	0.97 (0.80–1.18)	0.740	0.98 (0.73–1.31)	0.873
Schooling				
Lower education	1	–	1	–
High school	0.91 (0.72–1.14)	0.407	1.00 (0.70–1.43)	0.998
University	0.86 (0.66–1.13)	0.283	0.84 (0.56–1.28)	0.428
Occupation				
Clerk	1	–	1	–
Manager	1.12 (0.76–1.65)	0.558	1.01 (0.56–1.82)	0.985
Unemployed	1.31 (0.95–1.81)	0.097	1.20 (0.75–1.92)	0.453
Housewife	1.03 (0.75–1.41)	0.850	0.63 (0.37–1.07)	0.087
Self-employed	1.22 (0.95–1.57)	0.114	1.13 (0.78–1.64)	0.533
Workman	0.83 (0.61–1.13)	0.233	0.90 (0.58–1.41)	0.653
Student	1.31 (0.94–1.83)	0.115	0.75 (0.43–1.29)	0.298
Environmental exposures				
Smoking habits				
Non-smoker	1	–	1	–
Smoker	1.16 (0.96–1.41)	0.126	1.10 (0.82–1.47)	0.537
Past smoker	1.25 (0.99–1.56)	0.057	1.02 (0.71–1.45)	0.934
Traffic level near home				
Low	1	–	1	–
Moderate	1.08 (0.89–1.32)	0.427	0.97 (0.71–1.31)	0.817
High	1.29 (1.04–1.61)	0.021	1.24 (0.89–1.73)	0.195
Proximity to industrial plants				
No	1	–	1	–
Yes	1.38 (1.13–1.69)	0.001	1.41 (1.05–1.90)	0.023
Residential area				
City centre	1	0.807	1	–
Suburbs	0.98 (0.81–1.18)	0.616	0.99 (0.74–1.31)	0.917
Countryside	0.93 (0.70–1.24)	0.126	1.05 (0.69–1.60)	0.833
Geo-climatic area				
Sub-continental	1	–	1	–
Mediterranean	1.24 (1.05–1.48)	0.013	1.56 (1.20–2.03)	0.001

†Adjusted for all the variables included in the table plus season of response, centre-specific cumulative percentile rank of response and type of survey (postal waves/telephone).

OR, odds ratio.

Statistically significant associations are shown in bold.

Subjects with adult eczema report prevalently an adult onset of the disease

Eczema is conventionally regarded as a disease of childhood, developing in the first years of life and commonly remitting by

the adolescence. If this was true, it would be reasonable to expect a large difference in the prevalence of current eczema between adults and children. However, a recent survey reported a 1-year prevalence of eczema of 10.1% and 7.7% in Italian children aged

6–7 and 13–14, respectively,¹³ which is similar to the prevalence that we found in adults (8.1%). This result is quite in agreement with the literature. When comparing the results of large epidemiological surveys carried out in children and in adults within the same country, the 12-months prevalence of eczema is similar in the adolescent and adult populations. In the United States, for example, the reported prevalence of current eczema was 10.7% in children and 10.2% in adults.¹⁸ The same parallel can be done in Europe by comparing the results of the ISAAC study in children and the ECRHS study in adults.^{3,13}

Another finding is that more than half of the subjects with eczema and EAH reported an adult onset (≥ 18 years) of the disease. The prevalence of subjects with adult onset is about 40% in the 20–29 years age group, and it raises to over 70% in the subjects aged 40–44. These data are consistent with a prior US epidemiologic study report,²² and suggest that eczema in adults is mostly represented by new adult onset disease rather than the comeback or the persistence of childhood disease. However, given the self-reported design of the study, which makes it potentially prone to recall bias, these results might be influenced by the fact that the memory of childhood eczema might vanish with increasing age. Prospective cohort studies examining the age at onset are needed to understand the connection between childhood and adult eczema.

Geo-climatic and environmental factors are associated with adult eczema

Previous research showed that climate factors influence the prevalence of childhood eczema in US.²³ Our analyses highlighted a regional variability in the prevalence of eczema within Italy. In fact, the risk of having eczema and EAH was, respectively, 24% and 56% higher in central/southern Italy, which has a milder, Mediterranean climate, with respect to northern Italy, which has sub-continental climate.¹⁹ These differences in the prevalence of eczema could be ascribed by variations of climate itself and of its intrinsic components (e.g. mean annual temperature, atmospheric temperature range, UV light exposure, outdoor humidity, precipitations, characteristics and length of the pollen season), as well as to other differences that are closely correlated with geo-climatic variations, such as different lifestyle, time spent outdoors and diet.

Given the boot shape of the Italian peninsula, most of the principal towns in southern Italy lie on the coast. Accordingly, 3 out of 7 centres that participated to the study, all in central/southern Italy, are coastal cities. The proximity to sea not only directly contributes to the climate (e.g. humidity, precipitations, outdoor temperature range) but it also modifies population's life-styles and behaviours, which might in turn influence the risk of developing eczema.

Living close to heavy traffic was another independent risk factor for eczema and EAH. Some earlier studies have shown a similar positive association in children^{24,25} and in adults.^{4,26}

In experimental studies, diesel exhaust particles have been reported to modulate the immune response towards IgE production and to concur in the onset of allergic inflammation by activating macrophages and other mucosal cell types and by affecting the production of cytokines and chemokines.²⁷ Moreover, exposure to NO₂ has been shown to damage the skin barrier function and increase trans-epidermal water loss.²⁸ Heavy traffic exposure may therefore worsen the skin and immunological function, facilitating the development and the relapse of eczema.

Further emphasizing the role of pollution in the occurrence of eczema, our results showed that living in proximity to industrial plants significantly increases the risk of eczema and EAH of about 40%. This is consistent with the results from two studies carried out in Turkey and Sweden, which recently reported that occupational exposure to chemical fumes is associated with an increased risk of eczema.^{5,29} Taken together, these data suggest that environmental air pollution may affect the susceptibility to eczema, and agree with many epidemiological studies that showed an increasing trend in the prevalence of eczema and AD, especially in developing countries that are undergoing rapid urbanization and industrialization.³⁰

Strengths and limits of the study

The strength of this study includes being a large-scale, population-based study, and controlling for confounding socio-demographic and environmental factors. The use of a standardized methodology enabled the direct comparison of disease prevalence across the centres. We acknowledge that the moderate response rate of 57% is a limitation of this study. However, it is consistent with those obtained by other recent epidemiological surveys in randomly selected subjects from the general population.⁵ In the analysis, we have tried to account for differential response rates in participating centres by including percentile rank of response in multi-variable models.

Since eczema is commonly thought as a disease of childhood, most of the questionnaires are specifically designed to identify the skin lesions in children. In adults, however, eczema has a more assorted distribution, for example with frequent hand and head-neck involvement.⁸ To partially overcome these problems, our definitions of eczema and AD were based on self-reported doctor diagnosis rather than on symptoms. These definitions, however, have not been validated in previous studies and they might be prone to recall and to diagnostic bias.

The study also suffers of the limits of the cross-sectional design and, consequently, the associations of the variables with eczema must be interpreted cautiously. Finally, this study was based on a short screening questionnaire developed to investigate mainly respiratory diseases. As a consequence, it lacks of more detailed information on the anatomical location of skin lesions, which would have been useful to differentiate among possible eczema phenotypes.

Conclusions

Eczema and EAH are highly prevalent in Italian adults, especially in women, and most of the investigated subjects reported an adult onset. The associations of eczema with proximity to heavy-trafficked roads and industrial plants suggest a link between environmental air pollution and the disease. Geo-climatic variations seem also to influence the occurrence of eczema in adults.

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GPe and AM conceived the study and planned the statistical analyses. GPe performed the statistical analyses, wrote the first draft of the manuscript and contributed to the survey design and data collection. AM, AC, LA, LC, MF, AGF, PM, MO, PP, GPo, RT, GV, SV, RdM critically reviewed the manuscript for important intellectual content.

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