

Atopic Dermatitis in Israeli Adolescents from 1998 to 2013: Trends in Time and Association with Migraine

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Abstract

Background: Recent data have shown an increasing occurrence of atopic dermatitis (AD) in children and adolescents, as well as in adults. Most of the epidemiologic research on AD is limited to pediatric and youth populations and is based on self-reported questionnaires.

Methods: A nationwide, population-based, cross-sectional retrospective study of adolescents with AD was performed to estimate its prevalence, trends, and association with demographic factors and comorbidities. The study included all Israeli teens going through medical evaluation as part of the assessment before being conscripted into the military from 1998 to 2013.

Results: A total of 1,187,757 adolescents were included in the study population, with an overall prevalence of AD of 0.64% in boys and 0.9% in girls. Over the study period, the prevalence of AD steadily increased, especially in the mild disease group. A greater risk of AD was found in subjects with high predicted socioeconomic status (male: odds ratio [OR] 1.14 [95% confidence interval {CI} 1.11, 1.16]; female: OR 1.08, [95% CI 1.05, 1.10]) and Israeli-born subjects (male: OR 1.34 [95% CI 1.21, 1.48]; female: OR 1.12 [95% CI 1.01, 1.23]). Allergic conditions such as asthma, conjunctivitis, and contact dermatitis were more prevalent in subjects with AD. There was a significantly higher prevalence of migraine in patients with AD (male: OR 1.35 [95% CI 1.18, 1.54]; female: OR 1.51 [95% CI 1.30, 1.74]).

Conclusion: This large cross-sectional study demonstrates the increasing prevalence of AD in adolescents and its relation to other allergic diseases and

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migraine. It is hoped that greater awareness of the distinctive epidemiologic characteristics of this population will lead to better recognition and management of the disease and its comorbidities.

Atopic dermatitis (AD) is a common chronic inflammatory skin disorder with increasing prevalence in recent decades (1). There are remarkable differences in prevalence rates of AD around the world, with a point prevalence of less than 2% in Iran and approximately 22% in Sweden in children 6–7 years old and less than 2% in China and greater than 20% in Morocco for children 13–14 years old (2).

AD usually begins during childhood, with a total of 85% of all cases of AD emerging before 5 years of age. The disease was thought to disappear after its early occurrence, according to the findings of spontaneous remission in more than 70% of atopic children before adolescence (3), but new findings suggest that most children with AD continue to report symptoms and use medications into the third decade of life (4), with low rates of remission—less than 50% in some countries (5).

Although adolescents are susceptible to AD, epidemiologic data in this population are sparse. Over the years, few studies have focused on adolescents with AD. In Germany, a prospective study (6) of 2,857 adolescents reported an incidence of 1.7%, identifying several risk factors for the development of AD in this age group. A cross-sectional study in Denmark (7) comprising 1,501 adolescents reported a lifetime prevalence of 17% for boys and 25.7% for girls.

We conducted a large cross-sectional study of 17-year-olds with a physician-based diagnosis of AD over 16 years. We aimed to evaluate the prevalence and temporal trends of AD in Israel from 1998 to 2013. We also sought to characterize the population of adolescents with AD, along with its known comorbidities such as allergic diseases and migraine.

METHODS

As a part of the military preconscription assessment, most Israeli civilians undergo a routine medical evaluation and fitness-for-service (FFS) classification at a specified age. The result of this process is one or more FFS classification numerical codes indicative of a medical diagnosis or similar diagnoses grouped according to pathogenesis and functional status stored in the candidate's personal and medical record. From the conscripts' medical records, we retrieved demographic details (sex, FFS code with date and age

at FFS determination, region of birth, predicted socioeconomic status [SES], and body mass index [BMI]). The Israeli Defense Force institutional review board approved the study and subjects' anonymity was strictly preserved.

Study Population

The study population included all Israeli teenagers who underwent medical evaluation by the Israeli Defense Force as part of the preconscription assessment from 1998 to 2013. We excluded individuals younger than 16 years and older than 21 years at the time of their medical evaluation. The presence of AD was determined according to the corresponding numerical code described above, assigned based on the findings of a board-certified dermatologist.

Definition of Variables and Comorbidities

SES was predicted according to the place of residence, which is coded on a scale from 1 to 10 based on the Israeli Central Bureau of Statistics. This scoring system stratifies all municipalities into 10 ranks, taking into account variables that might affect SES. Region of birth was categorized into six geographic areas: former USSR countries, Asia (non-USSR), Africa (excluding South Africa and Ethiopia), Western (comprised of non-USSR Europe, North and South America, South Africa, Australia and New Zealand), Ethiopia, and Israel. Comorbidities were diagnosed as specified in Table 1.

Disease Categories

The criteria for cutaneous disease categories were established in 1997, primarily to identify conscripts' medical fitness for combat duty. A board-certified dermatologist diagnosed AD based on medical history and clinical features of itchy eczematous lesions, xerosis, and lichenification of the skin with characteristic distribution, as recommended in previous guidelines (8). In our study, subjects were divided into two groups (mild and moderate to severe disease), according to the criteria in Table 2. Patients with moderate to severe AD are considered unfit for combat.

TABLE 1. Diagnostic Criteria of Comorbidities as Defined According to Fitness-for-Service Classification Numerical Codes

Diagnosis and diagnostic criteria
Asthma
Abnormal pulmonary function test (plethysmography, spirometry, methacholine challenge test)
Diagnosis requires a consultation with board-certified pulmonologist
Rhinitis
Allergic or vasomotor rhinitis
Recurrent complaints of rhinorrhea and postnasal drip
Supported by positive allergy tests to specific allergens
Diagnosis requires consultation with board-certified otorhinolaryngologist or allergy specialist
Conjunctivitis
Allergic or chronic blepharoconjunctivitis
Diagnosis requires consultation with board-certified ophthalmologist
Contact dermatitis
Irritant or allergic contact dermatitis
Characteristic rash after exposure to suspected substance, with appropriate location and interval
Supported by positive patch tests for suspected substance or clinical improvement after cessation of that exposure
Diagnosis requires consultation with board-certified dermatologist
Migraine
Episodes of characteristic headache for migraine lasting at least 6 hours at least once a month
Diagnosis requires consultation with board-certified neurologist

TABLE 2. Classification of Atopic Dermatitis According to Severity

Mild	Moderate to severe
Remission for at least 1 year	Frequent disease exacerbations
Rare disease exacerbations	Large to extensive skin involvement with functional impairment
Involvement of minimal skin area	Systemic treatment for long periods
Sporadic topical treatment with good response	Partial or no response to ongoing or recurrent treatment

TABLE 3. Anthropometric Variables of the Study Population ($N = 1,187,757$)

Variable	Boys		Girls	
	Study population ($n = 694,412$)	AD population ($n = 4,472$)	Study population ($n = 493,345$)	AD population ($n = 4,367$)
Body mass index, kg/m^2 , mean $\pm$ SD	22.2 $\pm$ 4.0	22.6 $\pm$ 4.0	21.9 $\pm$ 3.8	22.2 $\pm$ 3.9
Predicted socioeconomic status, mean $\pm$ SD (1-10 scale)	5.7 $\pm$ 1.7	6.3 $\pm$ 1.6	6.1 $\pm$ 1.6	6.3 $\pm$ 1.5
Age, mean $\pm$ SD	17.4 $\pm$ 0.6	17.3 $\pm$ 0.5	17.2 $\pm$ 0.5	17.2 $\pm$ 0.4
Region of birth, n (%)				
Israel	562,733 (81.1)	3,807 (85.1)	399,797 (81.1)	3,562 (81.6)
Western Europe, America, Australia	28,236 (4.1)	183 (4.1)	18,180 (3.7)	182 (4.2)
Eastern Europe	87,228 (12.6)	462 (10.3)	66,240 (13.4)	593 (13.6)
Africa (other than Ethiopia)	464 (0.1)	1 (0.0)	221 (0.0)	1 (0.0)
Ethiopia	13,074 (1.9)	14 (0.3)	7,633 (1.5)	20 (0.5)
Asia	2,073 (3)	4 (0.1)	962 (0.2)	8 (0.2)

AD, atopic dermatitis, SD, standard deviation.

Statistical Analysis

All data were summarized and displayed as mean $\pm$ standard deviation for continuous variables and number (percentage) of patients in each group for categorical variables. Two conditional multivariate logistic regression analyses (one for boys, one for girls) were conducted to examine the prevalence of AD adjusted for age, region of birth, predicted SES, and comorbidities. All analyses were performed using SPSS version 21.0 (IBM Armonk, NY, USA).

RESULTS

Subject Characteristics

The study included 1,187,757 (694,412 male, 493,345 female) apparently healthy predrafted teenagers listed as fit for combat duty. The mean subject age was 17.4 ± 0.6 years for boys and 17.2 ± 0.5 years for girls. Of this cohort, 8,839 (0.7%) examinees were diagnosed with AD based on assignment of the corresponding numerical code. Anthropometric variables of the study population are listed in Table 3.

AD Prevalence and Trends

The overall prevalence of AD was 0.64% in boys and 0.9% in girls, rising steadily over the study period (Fig. 1A). Between 1998 and 2013, the prevalence of AD rose from 0.26% in boys and 0.5% in girls to 1.0% and 1.36%, respectively. When divided into disease categories according to severity, mild disease was more prevalent in both sexes (0.5% for boys, 0.7% for girls) than moderate to severe disease (0.1% for boys, 0.19% for girls), with a gradual increase in the prevalence of mild disease over the study period (Fig. 1B).

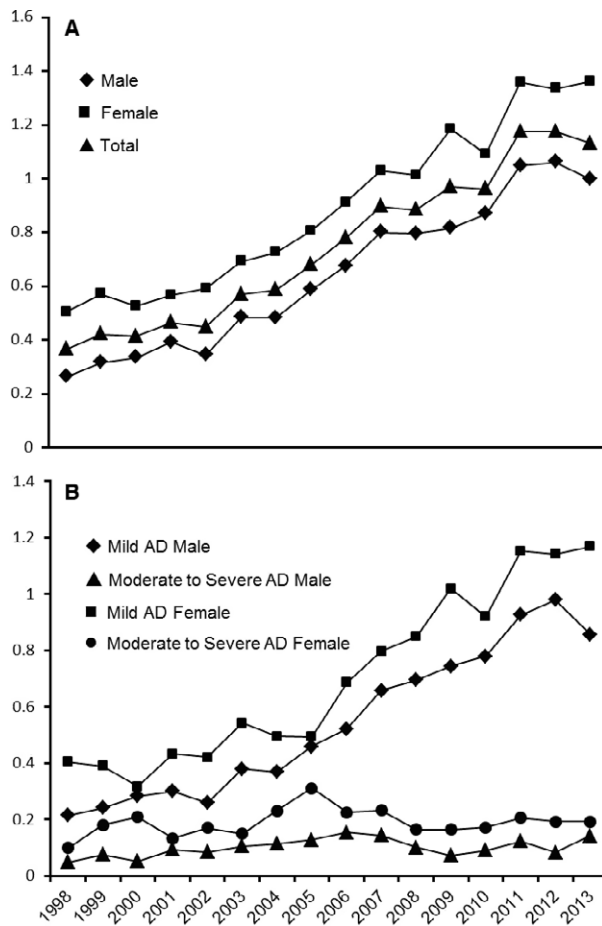


Figure 1. (A) Percentage of adolescents with atopic dermatitis and (B) according to severity during each year of the study ($n = 8,839$).

AD and Association with Possible Risk Factors

The associations between various variables, including age, predicted SES, region of birth, and other diseases, and AD are described in Table 4. Statistically

significantly greater odds of the presence of AD for both sexes was noted for high predicted SES and for subjects born in Israel. An association was found with other allergic conditions, such as asthma, rhinitis, conjunctivitis, and contact dermatitis. AD was also associated with migraine in boys and girls.

DISCUSSION

The average prevalence of AD was 0.64% in boys and 0.9% in girls, with an approximate tripling over the course of the 16-year study period. The previously reported overall prevalence of AD in Israeli adolescents was 0.5% in boys and 0.7% in girls using the same population and diagnostic criteria used in our study but limited to 1998 to 2008 (9). Our study highlights the current trend of the growing prevalence of AD in Israeli adolescents.

The International Study of Asthma and Allergies in Childhood (ISAAC) (2,10) provides valuable data on the prevalence and trends of AD using a questionnaire survey administered to close to 2 million children in 106 countries. After a mean 7-year follow-up of the ISAAC population, a mixed pattern was found in adolescents. A decrease in prevalence was reported in some previously high-prevalence countries in the developed world (e.g., UK, New Zealand), whereas the prevalence in developing countries had increased. Such disparity of trends points to the likely consequence of environmental risk factors in the development of AD (11).

In relation to the recent variations in the global prevalence of AD, Israel is uniquely positioned; its population is composed of diverse ethnic groups and since its establishment it has undergone rapid urbanization. The complex interaction between genetic and environmental factors in the pathogenesis of AD is well known, among them urbanization, better

TABLE 4. Risk Factors for Atopic Dermatitis in Adolescents

Variable	Male ($n = 4,472$)*		Female ($n = 4,367$)*		Total ($n = 8,839$)	
	OR (95% CI)	p-Value	OR (95% CI)	p-Value	OR (95% CI)	p-Value
Predicted SES	1.14 (1.11–1.16)	<0.001	1.08 (1.05–1.11)	<0.001	1.15 (1.11–1.19)	<0.001
Age	0.99 (0.92–1.06)	0.74	0.92 (0.84–1.01)	0.08	0.98 (0.96–1.01)	0.06
Birth region Israel	1.34 (1.21–1.48)	<0.001	1.12 (1.01–1.23)	0.02	1.17 (1.11–1.24)	<0.001
Migraine	1.35 (1.18–1.55)	<0.001	1.51 (1.31–1.74)	<0.001	2.06 (1.89–2.24)	<0.001
Asthma	3.14 (2.89–3.42)	<0.001	3.46 (3.15–3.81)	<0.001	6.79 (6.44–7.17)	<0.001
Rhinitis	4.14 (3.82–4.48)	<0.001	3.80 (3.47–4.16)	<0.001	6.21 (5.93–6.50)	<0.001
Conjunctivitis	2.57 (2.12–3.12)	<0.001	3.26 (2.54–4.20)	<0.001	9.81 (8.53–11.28)	<0.001
Contact dermatitis	7.38 (5.46–9.96)	<0.001	4.15 (3.17–5.44)	<0.001	8.24 (6.86–9.62)	<0.001

CI, confidence interval; OR, odds ratio.

*The covariates were adjusted for age, region of birth, predicted socioeconomic status (SES) and comorbidities (migraine, asthma, rhinitis, conjunctivitis, contact dermatitis).

personal hygiene, and exposure to various cosmetic and industrial antigens (e.g., fragrances, preservatives, air pollutants), each contributing to AD's growing prevalence (12). Nevertheless, we found an association between AD and high-predicted SES and with Israeli-born subjects, as previously described (9). The years 1990 and 1991 saw a major influx into Israel of thousands of immigrants from the former Soviet Union and Ethiopia, with subsequent years reflecting a drastic decline in immigration (derived from the Israel Central Bureau of Statistics). As such, Israel's increasing prevalence of AD from 1998 to 2013 cannot be attributed to waves of immigration, although children of immigrants from underdeveloped countries tend to adopt the prevalence features of their developed birth country (13). This finding may indicate a higher risk of AD in Israeli-born subjects constantly exposed to urbanization.

There is a recognized association between AD and other atopic diseases, such as allergic rhinitis and asthma, with their sequential development termed the "atopic march" (14). Moreover, other allergic diseases such as food allergy (15), allergic keratoconjunctivitis (16), and urticaria (17) have been found to be associated with AD. We found an association between AD in adolescence and contact dermatitis and with atopic diseases such as asthma, rhinitis, and conjunctivitis, similar to presentation in children.

A significant association was also found between AD and migraine for both sexes. This relationship was previously described in some smaller studies in children that showed 18.2% of individuals with migraine also have atopic disease (18). In addition, a case-control study in children with and without migraine demonstrated a higher risk of AD and other atopic diseases (19). Furthermore, several reports found a greater prevalence of headache and migraine in children with atopic disorders than their peers without atopic disorders (20), and a recent cross-sectional study of a large pediatric population demonstrated that children with eczema have higher odds (1.52) of having headaches (21). Our study revealed a statistical association between AD and migraine in adolescents, consistent with the association previously found in children. This association suggests a pathophysiological link between migraine and AD (22).

There are some limitations to our study. Information on the severity of comorbidities was lacking in our database, and therefore we could not correlate it with the severity of AD. In addition, irritant dermatitis and allergic contact dermatitis were grouped under the same FFS code in this database, although their pathogenesis is different. This is why

more specific data were not available regarding the association between subtypes of contact dermatitis and AD. A dermatologist made the diagnosis of AD, which required active disease at the time of examination. Thus the diagnoses may have underestimated the actual prevalence of AD because of its chronic nature of remission and exacerbation. Moreover, the AD severity classification used for the current study was based on clinical findings retrieved from our database rather than derived from a validated classification system. The SES is a predicted rather than an absolute variable, tied to place of residence. In addition, our study, which reports on the point prevalence of AD in 17-year-olds, does not distinguish between residual pediatric AD and onset of new AD in adolescence.

The strengths of our study are its very large population and its extensive period of 16 years; both are key features in the estimation of disease prevalence and trends. Furthermore, diagnosis of AD and the noted comorbidities typically do not necessitate specific diagnostic tests and depend on characteristic clinical findings. In our study, all of the diagnoses were physician based and subject to rigorous requirements. It is likely that this diagnostic approach has better reliability and validity than commonly used self-reported questionnaires.

In conclusion, this large, nationwide, cross-sectional Israeli study revealed an increase in AD prevalence in adolescents over a period of 16 years. Epidemiologic characteristics of this population included higher predicted SES, being born in Israel, and an association with other allergic diseases and migraine. Defining the unique risk factors and comorbidities in this population may contribute to the management of AD.

REFERENCES

1. Bieber T. Atopic dermatitis. *N Engl J Med* 2008; 358:1483–1494.
2. Asher MI, Montefort S, Björkstén B et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC phases one and three repeat multicountry cross-sectional surveys. *Lancet* 2006;368:733–743.
3. Kay J, Gawkrödger DJ, Mortimer MJ et al. The prevalence of childhood atopic eczema in a general population. *J Am Acad Dermatol* 1994;30:35–39.
4. Margolis JS, Abuabara K, Bilker W et al. Persistence of mild to moderate atopic dermatitis. *JAMA Dermatol* 2014;150:593–600.
5. Pyun BY. Natural history and risk factors of atopic dermatitis in children. *Allergy Asthma Immunol Res* 2015;7:101–105.

6. Peters AS, Kellberger J, Vogelberg C et al. Prediction of the incidence, recurrence, and persistence of atopic dermatitis in adolescence: a prospective cohort study. *J Allergy Clin Immunol* 2010;126:590–595.
7. Mortz C, Lauritsen J, Bindslev-Jensen C et al. Prevalence of atopic dermatitis, asthma, allergic rhinitis, and hand and contact dermatitis in adolescents. The Odense adolescence cohort study on atopic diseases and dermatitis. *Br J Dermatol* 2001;144:523–532.
8. Eichenfield LF, Tom WL, Chamlin SL et al. Guidelines of care for the management of atopic dermatitis: section 1. Diagnosis and assessment of atopic dermatitis. *J Am Acad Dermatol* 2014;70:338–351.
9. Wohl Y, Wainstein J, Bar-Dayana Y. Atopic dermatitis in Israeli adolescents—a large retrospective cohort study. *Acta Derm Venereol* 2014;94:695–698.
10. Beasley R. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. *Lancet* 1998;351:1225–1232.
11. Flohr C, Mann J. New insights into the epidemiology of childhood atopic dermatitis. *Allergy* 2014;69:3–16.
12. Kim K. Influences of environmental chemicals on atopic dermatitis. *Toxicol Res* 2015;31:89–96.
13. Williams HC, Pembroke AC, Forsdyke H et al. London-born black Caribbean children are at increased risk of atopic dermatitis. *J Am Acad Dermatol* 1995;32:212–217.
14. Spergel JM, Paller AS. Atopic dermatitis and the atopic march. *J Allergy Clin Immunol* 2003;112(Suppl):S118–S127.
15. Worth A, Sheikh A. Food allergy and atopic eczema. *Curr Opin Allergy Clin Immunol* 2010;10:226–230.
16. Chen JJ, Applebaum DS, Sun GS et al. Atopic keratoconjunctivitis: a review. *J Am Acad Dermatol* 2014;70:569–575.
17. Bingeors K, Svensson Å, Isacson D et al. Self-reported lifetime prevalence of atopic dermatitis and co-morbidity with asthma and eczema in adulthood: a population-based cross-sectional survey. *Acta Derm Venereol* 2013;93:438–441.
18. Özge A, Öksüz N, Ayta S et al. Atopic disorders are more common in childhood migraine and correlated headache phenotype. *Pediatr Int* 2014;56:868–872.
19. Munoz-Jareno N, Fernandez-Mayoralas D, Martinez-Cervell C et al. Relationship between migraine and atopy in childhood: a retrospective case-control study. *Rev Neurol* 2011;53:713–720.
20. Mortimer M, Kay J, Gawkrödger D et al. The prevalence of headache and migraine in atopic children: an epidemiological study in general practice. *Headache* 1993;33:427–431.
21. Silverberg JI. Association between childhood eczema and headaches: an analysis of 19 US population-based studies. *J Allergy Clin Immunol* 2016;137:492–499.
22. Mehle ME. Allergy and migraine: is there a connection? *Curr Opin Otolaryngol Head Neck Surg* 2008;16:265–269.