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FACULTY OF MEDICINE

DEPARTMENT OF "DERMATOLOGY, VENEREOLOGY AND ALLERGOLOGY"

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**CONTACT ALLERGY
IN ATOPIC DERMATITIS**

ABSTRACT OF A DISSERTATION PAPER

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The dissertation is written on 122 pages, illustrated with 24 tables and 22 figures. The bibliographic reference includes 200 literary sources, 10 of which are in Bulgarian and 190 in English.

The dissertation work was examined, discussed and directed for public defense to an extended departmental council at the Department of "Dermatology, Venereology and Allergology" at Medical University - Pleven.

The public defense of the dissertation work will take place on 2024, at in hall of the auditorium complex at MU – Pleven, in front of a Scientific Jury composed of:

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The materials for the defense of the dissertation are available in the Scientific Department and the website of the Medical University – Pleven - www.mu-pleven.bg.

ABBREVIATIONS USED

AD	-	Atopic dermatitis
AR	-	Allergic rhinitis
BA	-	Bronchial asthma
ACD	-	Allergic contact dermatitis/eczema
BDS	-	Bulgarian Dermatology Society
EH	-	Eczema of the hands
ESS	-	European standard series
DE	-	Dyshidrotic eczema
CA	-	Contact allergy
CD	-	Contact dermatitis
PPD	-	Paraphenylene diamine
FA	-	Formaldehyde
S-1000	-	European standard series
PPD	-	p-Phenylene diamine
IPPD	-	N-Isopropyl-N-phenyl-4-phenylene diamine
MI	-	Methylisothiazolinone
MCI/MI	-	Methylchloroisothiazolinone & Methylisothiazolinone
Lauryl	-	Part of Sesquiterpene lactone mix
Lyrall	-	Hydroxymethyl pentyl cyclohexene carboxaldehyde
MDBGN	-	Methyldibromo-Glutaronitril
2-HEMA	-	2-Hydroxyethyl methacrylate

INTRODUCTION

Atopic dermatitis (AD) is a systemic chronic-relapsing, inflammatory skin disease with a complex pathogenesis. The risk of AD is increased in individuals with primary skin barrier damage due to mutations in the common filaggrin gene, but also in individuals with primary immune dysregulation. It represents the earliest manifestation of the components of the atopic symptom complex, which also includes allergic rhinitis, allergic conjunctivitis, bronchial asthma and atopic characteropathy. Clinically, AD presents with generalized skin dryness, pruritus and dermatitis. The exact cause of the development of AD is still being studied, but it is certainly clear that genetic predisposition and environmental factors are risk factors for its development.

Contact allergy (CA) is an acquired hypersensitivity reaction of the delayed (IV) type caused by direct or systemic contact of an allergen with the skin. After the first encounter with the allergen, a period of sensitization occurs, and upon repeated exposure, allergic contact dermatitis (ACD) develops at the site of contact. The term "allergy" refers to the clinical syndrome, while "hypersensitivity" is a descriptive term for the immunological process. CA is a common problem and affects about 25% of the population in Europe. Despite the many published research material, it remains largely unclear and unpredictable which individual will develop contact allergy and which will not, under the same exposure conditions. ACD is diagnosed by epicutaneous testing, with reporting performed according to International Contact Dermatitis Research Group (ICDRG) criteria. The detection of the allergen is important for both patients and their families due to the high socio-economic importance of the problem, especially in cases of occupational pathology, when more severe forms of ACD lead to temporary incapacity and/or to a change of work environment.

Worldwide, studies are ongoing to answer the question of whether patients with AD have an increased risk of contact sensitization compared to the general population with AD without atopic diathesis. Various factors may influence this relationship, considering the fact that the damaged barrier function of the skin and the dryness, due to the increased TEWL, create the possibility of increased absorption and easy penetration of many irritating substances from the environment, incl. contact allergens (metals, preservatives, cosmetic products, paints, varnishes, fragrances, glues, medicines and others). At the same time, AD and ACD have a comparable clinical presentation, which initially manifests with erythema and papulovesicular exanthema and later with skin xerosis, lichenification and excoriations.

For more than 40 years, research has continued on the role of AD as a risk factor for the development of type IV sensitization with subsequent ACD, and the results are controversially discussed. According to some authors, in individuals with AD, contact sensitization is increased, according to others, there is convincing evidence in favor of reduced contact sensitization in populations with AD. There are also many epidemiological studies on the prevalence of CA in patients with AD compared to those without AD, showing mixed results.

These facts, as well as the detailed analysis of the available literature, motivated us to conduct our own research on the prevalence of CA in individuals with atopy data, which is pioneering for the country.

II. PURPOSE OF SCIENTIFIC DEVELOPMENT

Investigate the frequency of contact allergy among individuals with evidence of atopy, determine the features of the clinical course of allergic contact dermatitis in atopics, and compare the results with data on sensitization in the general population

TASKS are set for implementation:

1. Analyze contact allergy in epicutaneously tested persons in Pleven and Ruse regions for the period 2009-2022, dividing patients by gender, age, professional occupation and determining the type of contact dermatitis based on localization of pathological skin changes.
2. Track the frequency of individuals with clinical and anamnestic data on atopy among the studied population, with atopics being distributed by gender, age, professional occupation and to determine the type of contact dermatitis based on the localization of the pathological skin changes.
3. Analyze the frequency of allergens, the cause of allergic contact dermatitis, by determining the top 5 allergens for the region, as well as for the subpopulation of people with atopic diathesis.
4. Investigate and compare the frequency of contact allergy in the studied population and that in patients with atopic diathesis.
5. Investigate and compare the incidence of contact allergy in patients with atopic dermatitis and compare it with that in individuals without atopic dermatitis.
6. Characterize the features of the clinical course of ACD in persons with AD and determine the cross-linked reactions of the allergens from the applied series for epicutaneous testing.

III. MATERIAL AND METHODS

III.1. CLINICAL MATERIAL:

- In the period 2009-2022, with the European standard series S-1000, 455 persons were epicutaneously tested, 224 (49%) of which had a total of 445 positive reactions. All of them sought help from a dermatologist due to specific complaints during the national campaigns of the Bulgarian Dermatology Society for the diagnosis and prevention of allergodermatoses in Bulgaria.
- From the examined, 189 individuals (41.7%) of both sexes with a history of atopy were selected, on average age 37.71 ± 16.55 years, men were 46 (24.3%) and women were 143 (75.7%). (**fig.1**)

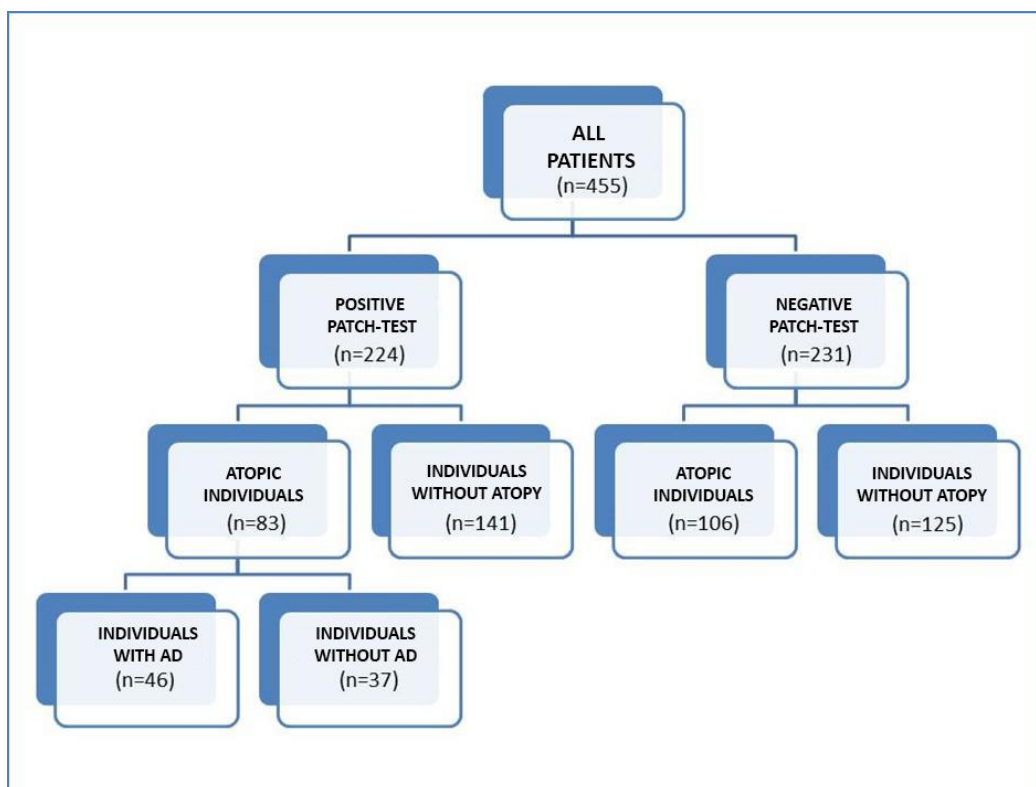


Figure 1: Distribution of clinical material of CA database and definition of subpopulations

III.2. METHODS:

III.2.1. Epidemiological analysis - for the purposes of the analysis, a registration form valid throughout the country was prepared for the needs of the annual campaigns of the "Dermatoallergology" section of the BDS "Diagnosis and prevention of allergic skin diseases". The form is filled out by the doctor and consists of a passport data, anamnestic data, topography of rashes in 23 body areas, occupation of the patient, contact with possible irritants, hobbies of the patient and results of allergy testing. **(Application 1)**

- Epidemiological study to determine the frequency of allergic reactions among 455 randomly selected individuals who actively sought a dermatologist's consultation, stratified by sex, age, occupation, diagnostic group, and location of rash. For the purposes of the study, the examined persons were divided into two age ranges - up to 40 years and 40 and over. The professional environment is defined in the following categories: non-working (retired, students, unemployed, maternity, housewives), working in an office (IT-specialists, employees and associates, financiers, economists, cashiers, managers, etc.), medical (doctors , dentists, nurses, laboratory assistants), aesthetics (manicurists, hairdressers, beauticians) and others (teachers, artists, military professions, car mechanics, tailors, employed in agriculture, in contact with paints and varnishes, etc.).
- Cross-sectional analysis for frequency of allergens, cause of contact allergy among positive individuals:
 - In 224 individuals to determine the frequency of positive reactions to various sensitizers from ESS after epicutaneous testing with S -1000 in order to determine the top allergens for the Pleven-Ruse region.

- In 189 individuals with clinical and/or anamnestic evidence of atopic diathesis, the frequency of sensitization to S -1000 allergens, the cause of contact allergy among 83 positive subjects.
- In 46 individuals with an AD clinic for the presence of contact allergy and the frequency of sensitization to allergens from S -1000.
- Comparative analysis of positive results from epicutaneous testing:
 - Comparative analysis of the positive CA results obtained in the general population for the Pleven Ruse region and those in individuals with data on atopy and assessment of the risk for the appearance of ACD in the group of atopics.
 - Comparative analysis of the results of the epicutaneous testing between the individuals in the two subgroups - with and without AD clinic, to determine the frequency of positive reactions to a given allergen and assess the risk for the appearance of ACD in the subgroups.

III.2.2. Clinical-morphological analysis

The clinical and morphological characteristics of allergic contact dermatitis (ACD/eczema) is studied in individuals with different degrees of skin involvement, and the analysis is also based on the accompanying documentation. The results are interpreted according to the clinical picture, and the patients are grouped into the different subtypes of ACD according to the clinical morphology of the lesions

- History related to data on subjective sensations, toxicity or hypersensitivity to foods, drugs, detergents or other chemical irritants. Personal or family history of atopic dermatitis or other manifestations of atopy, presence of comorbidities, current therapy, past illnesses, etc.
- Dermatological status with determining the nature of the skin inflammation and, based on the location of the exanthema, diagnosis of dermatitis and classification into diagnostic groups - without complaints (healthy); with atopy (with or without atopic dermatitis and personal and family data on atopic diathesis); with allergic dermatoses (ACD/eczema, urticaria, photodermatoses); with other skin diseases (psoriasis, seborrheic dermatitis, rosacea, etc.)

Based on the topographic characteristics of the exanthema in the positive individuals, the dermatitis is classified as: No dermatitis (healthy and with other dermatoses); Atopic dermatitis (AD); ACD on the upper limbs; ACD on the lower limbs; ACD on the face; ACD on the body.

III.2.3. Allergological method - epicutaneous testing (patch-testing)

Epicutaneous testing for the diagnosis of contact allergy is performed by means of patch-tests according to the ESCD (European Society of Contact Dermatitis) and ICDRG (International Contact Dermatitis Research Group) testing guidelines. The European standard and extended S-1000 series with 30 and 36 allergens (EEC, European Baseline) were applied (**Appendix 2**) Results are reported at 48 hours, 72 hours, and 7 days and interpreted according to ICDRG criteria. (**fig.2**)






Extreme positive (+++)	Strong positive (++)	Weak positive (+)	Irritant (IR)	Doubtful (?)
				
Coalescing vesicles, bullous reaction	Erythema, papules, infiltration, discrete vesicles	Erythema, infiltration, discrete papules	Discrete, patchy, follicular, or homogenous erythema with no infiltration	Faint macular or homogenous erythema with no infiltration

Figure 2: Scale for reporting the results of epicutaneous testing

III.2.4. Socio-demographic tool - MOAHLFA Index presents the so-called PAFS (population-adjusted frequency of sensitization). Developed and implemented by the German Information Network of Departments of Dermatology (IVDK, <http://www.ivdk.org>) for the needs of population and multicenter studies and defines trends in age-sex and clinical characteristics related to contact allergy followed over the years. Contains 7 factors (**Table 1**)

Table 1: MOAHLFA index

M	Male
O	Occupational Dermatitis
A	Atopic Dermatitis
H	Hand Dermatitis
L	Leg Dermatitis
F	Face Dermatitis
A	age above 40 years

III.2.5. Photo documentation

Canon PowerShot A310 digital camera was used, automatic mode, use of macro mode for the close-focus shots and comparable illumination and distance of the objects. The photos taken have a resolution of 1600 x 1200 pixels and file sizes between 340 and 670 KB.

III. 2.6. Statistical methods

The collected information was entered and processed with the IBM statistical package SPSS Statistics 23.0.0. $p < 0.05$ was chosen as the level of significance at which the null hypothesis is rejected. Some survey data were processed with the Statgraphics statistical computer program package Plus for Windows and EXCEL. The results are described through tables, graphs and numerical values (percentages, coefficients, average values, standard deviation, etc.). Description of qualitative and quantitative variables, variation and correlation analysis, parametric and non-parametric methods for hypothesis testing were used.

III. 2.7. Ethical aspects

Conducting the studies is in accordance with the national and international requirements for conducting clinical studies, including the preservation of the anonymity of the participants and the non-disclosure of personal information. Before the start of the study, each participant received written information and signed an informed consent form.

IV. RESULTS OF OWN RESEARCH

IV.1. Results of a retrospective clinical-epidemiological analysis to determine the prevalence of contact hypersensitivity in Pleven and Ruse regions.

For the specified period during the annual campaigns of the dermatoallergology section of the Bulgarian Dermatology Society "Diagnosis and Prevention of Allergic Skin Pathology", 455 people were covered. All have sought help from a dermatologist due to specific complaints. They were tested epicutaneously with the European standard series S-1000, and 224 (49.23%) of them had at least 1 positive reaction, with a total of 445 positive reactions. The mean age of positive individuals was 39.3 ± 14.69 years. The youngest patient is a 6-year-old boy and the oldest is a 78-year-old man.

Among the 224 positive persons, there were 49 (21.9%) men with an average age of 41.10 ± 16.82 years, and 175 (78.1%) women with an average age of 38.76 ± 14.04 years. The distribution by gender in the age groups "under 40" and "over 40" is shown in figure 3. **(fig.3)** Professional employment is determined both for the general population (455) and for the positive individuals (224), with 5 professional groups being distinguished - unemployed (including students, women on maternity leave, domestic helpers and pensioners), working in an office (IT - specialists, technical assistants, lawyers, financiers), health care workers, employed in aesthetic practice (hairdressers, manicurists, beauticians, cosmetics consultants) and diverse professions (including teachers, engineers, artists, athletes, material production and rural workers farm etc.)

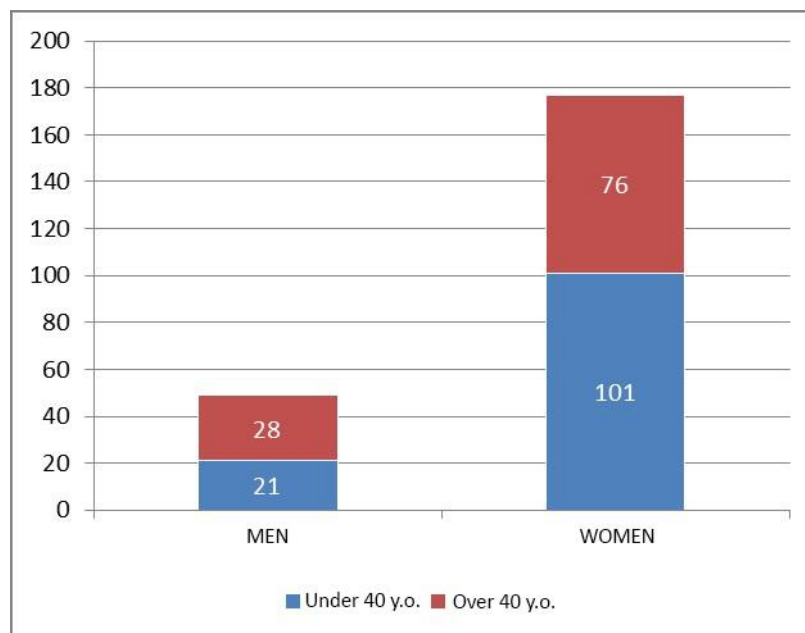


Figure 3: Distribution of 224 positive patients by gender and age group

In the general population, the largest number of those tested in the heterogeneous professions (163, 36%), followed by the group of the unemployed (110, 24%), office workers (103, 23%), health care (48, 10%) and aestheticians (31.7%). **(Table 2)**

Table 2: Professional status of 455 tested persons for the period 2009 – 2022.

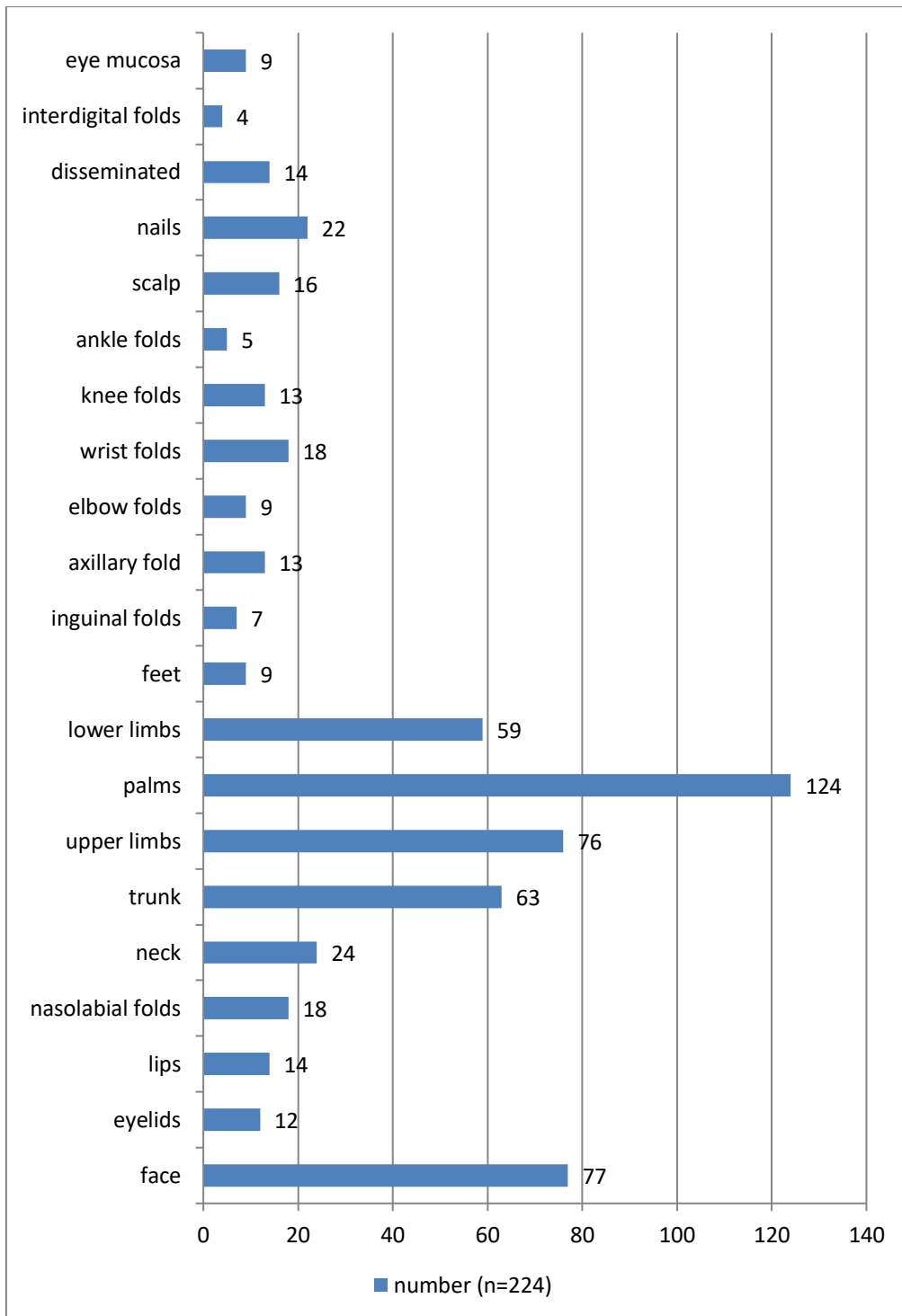
2009 – 2022	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2021	2022
PROFESSIONS (n=455)	59	31	30	23	28	39	35	47	35	29	42	18	39
non-working	24	6	7	3	8	8	7	7	4	6	7	6	17
office workers	12	9	8	9	3	10	10	13	7	6	10	3	3
medicine	10	3	0	1	4	2	2	7	2	1	5	3	8
aesthetics	0	0	3	4	3	0	0	7	10	3	1	0	0
others	13	13	12	6	10	19	16	13	12	13	19	6	11
TOTAL	59	31	30	23	28	39	35	47	35	29	42	18	39

In the group of persons with positive reactions, the frequency of CA is the highest in the general professional group (30%), followed by the group of office workers (25%), non-workers (23%), estheticians (11%) and doctors (11%). (**Table 3**)

Table 3: Professional status of 224 positive persons for the period 2009 – 2022.

2009 - 2022	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2021	2022
POSITIVE (n=224)	22	10	15	19	7	25	17	25	27	6	23	10	16
non-working	9	2	6	4	3	5	4	4	2	1	3	2	6
office	5	5	4	6	0	7	6	6	5	1	7	2	2
medicine	4	1	0	1	1	2	1	5	2	0	4	2	1
aesthetics	0	0	2	4	2	0	0	5	9	2	1	0	0
others	4	2	3	4	1	11	6	5	9	4	8	4	7
TOTAL	22	10	15	19	7	25	17	25	27	8	23	10	16

In order to determine the trend in the development of contact allergy in the region, the professional status of the 224 positive individuals was analyzed, in which the topography of the rash syndrome was determined, the type of dermatitis was determined, and the MOAHLFA index was calculated. In positive patients, the most frequent localization of the rash was the palms (124 times, 55.3%), the face (77 times, 34.4%), the upper limbs (76 times, 33.9%), the torso (63 times, 28.1%), the lower extremities (59 times, 26.3%), making the diagnosis "hand eczema" the most common, followed by facial dermatitis, with 14 (6.25%) cases of disseminated exanthema and those with atopic dermatitis were 46 (20.5%). (**fig. 4 and table 4**)



* the sum of pathological changes is greater than 224 due to the fact that in one patient there is more than one anatomic area affected by dermatitis

Figure 4: Topography of rash syndrome in patients with CA (n=224)

Table 4: MOAHLFA-index in the study of the general population for 455 tested, of which 224 had CA

<i>parameter</i>	Positive individuals (n=224)	
	number	%
Men	49	21.9%
Occupational dermatitis	22	9.8%
Atopic dermatitis	46	20.5%
Dermatitis of the hands	82	36.6%
Dermatitis of the feet	22	9.8%
Facial dermatitis	33	14.7%
Age over 40 years	102	45.5%

The results of epicutaneous testing showed 445 positive reactions with the highest frequency of positive tests to nickel – 126 (28.3% of all reactions). The top allergens are also cobalt chloride - 81 tests (18.2%), a mix of textile dyes - 29 (6.5%), PPD - 27 reactions (6.06%), potassium dichromate - 25 reactions (5.61 %), Peruvian balsam – 19 times (4.26%), as well as preservatives MI, MCI, MI/MCI, MDBGN – a total of over 30 positive tests. No reported positive reactions to Clioquinol, Mercapto mix, Tixocortol-21-pivalate, 2-Methoxy-6-n-pentyl-4-benzoquinone. (*fig.5*)

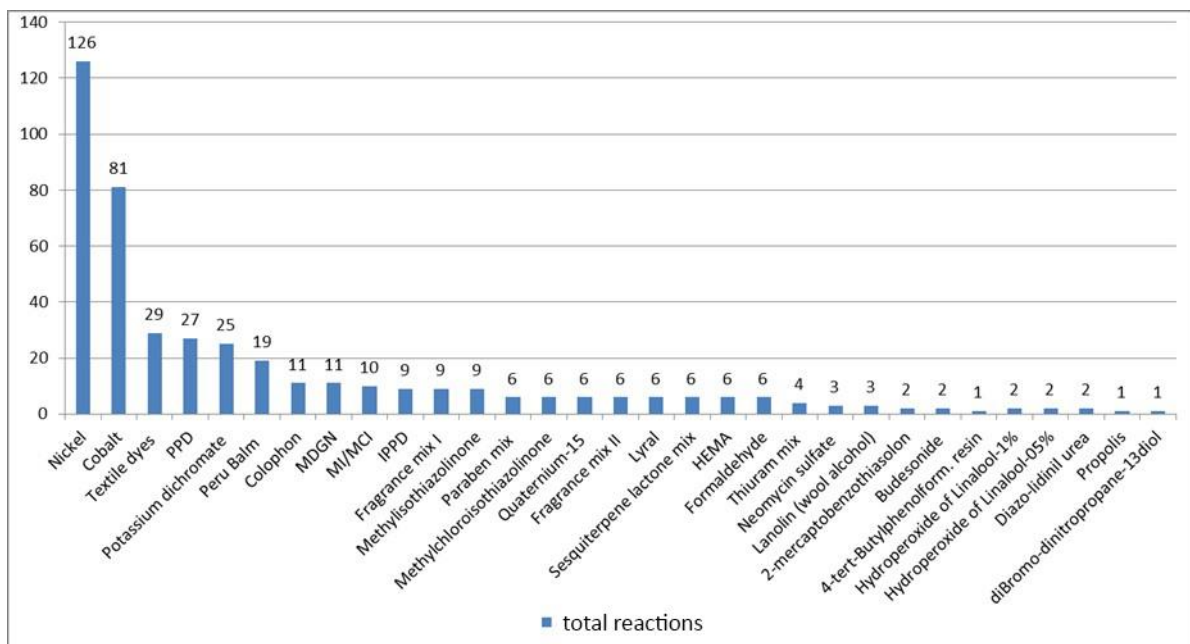


Figure 5: Frequency of allergens, cause of contact allergy in 224 positive subjects after patch testing

In view of the goal of the scientific development and after analysis of the working material, the two subpopulations and the two subgroups of positive individuals were determined by cross-sectional analysis: (*fig. 6*)

- ✚ Subpopulation of individuals with data on atopy (atopic dermatitis, urticaria or rhinoconjunctivitis, bronchial asthma) – 83
 - persons with atopic dermatitis – 46
 - atopics without atopic dermatitis – 37
- ✚ Subpopulation of individuals without data on atopy used as controls – 141

The results of the analysis show that:

- ✚ the frequency of CA in the general population tested epicutaneously is 49% - 224 individuals out of 455 tested, 445 positive reactions, 1.9 reactions per person, with the highest frequency being positive reactions to nickel (126 reactions, 28.6%)
- ✚ the incidence of CA in the subpopulation without data on atopy was 53% - 141 positive out of 266 examined, 265 positive reactions, 1.8 reactions per person
- ✚ the frequency of CA in the subpopulation with atopic pathology was 44% - 83 positive out of 189 atopics examined, 180 positive reactions, 2.2 reactions per person.

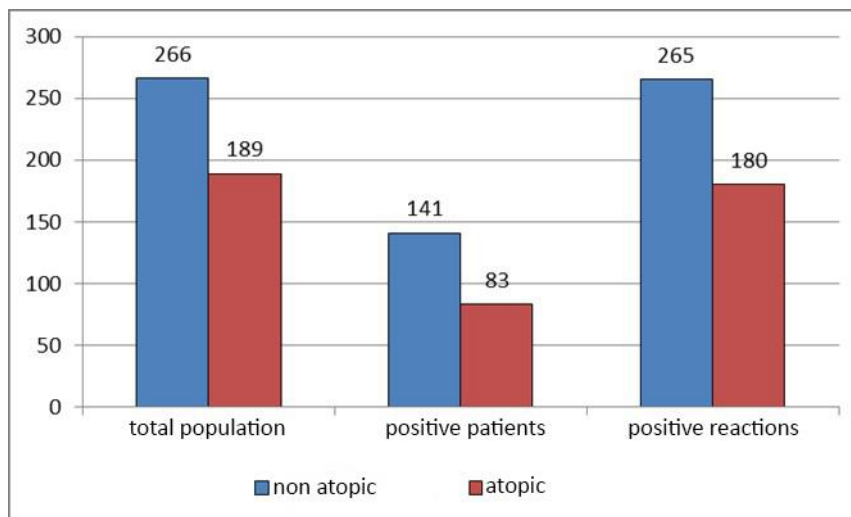


Figure 6: Distribution of the total population according to the results from epicutaneous testing

In order to follow the distribution of atopic individuals in relation to gender and age, people were divided into two age groups - under 40 years and over 40 years. The result with the χ^2 -test showed that, compared to controls, atopics had significant difference in the distribution between men and women under and over 40 years of age – 7.2% for men and 44.6% for women under the age of 40 and 16.9% for men and 30.1% for women over 40 years ($\chi^2=5.019$, $df=1$, $p=0.025$).

In relation to the general epidemiological data for the studied atopic and non-atopic individuals, no statistically significant differences were found in the distribution of individuals in the two subpopulations. (**Table 5**)

Table 5: General epidemiological data for the studied atopic and non-atopic individuals according to the MO(A)HLFA index (AD not included in the table)

subpopulations parameter	With atopy n=83		No atopy n=141		χ^2
	number	%	number	%	r
Men	20	24.1	29	20.6	0.537
Occupational dermatitis	9	10.8	13	9.21	0.601
Dermatitis of the hands	32	40.5	50	35.4	0.458
Dermatitis of the feet	9	10.8	13	9.2	0.383
Facial dermatitis	9	10.8	24	17.0	0.467
Age over 40 years	40	48.2	62	43.9	0.540

Differences between atopics and individuals without data on atopy were sought regarding the most common sensitizers. There is a statistically significant difference in the distribution for the mix of textile dyes ($p < 0.001$) and the preservative methylidibromoglutaronitrile ($p < 0.012$). (**Table 6**)

Table 6: Comparison of the distribution of the most common allergens in subpopulations

subpopulations		With atopy n=83		No atopy n=141		χ^2
Allergens		number	%	number	%	r
1	Nickel	47	56.6	78	55.3	0.714
2	Cobalt	27	32.5	53	37.6	0.562
3	Textile dyes	19	22.9	10	7.1	0.001
4	Potassium dichromate	11	13.2	14	9.9	0.445
5	PPD	9	10.8	18	12.8	0.670
6	MDBGN	8	9.6	3	2.1	0.012
7	Peru Balm	5	6	14	9.9	0.311
8	MI/MCI	5	6	5	3.5	0.386
9	IPPD	4	4.8	5	3.5	0.639
10	Formaldehyde	4	4.8	2	1.4	0.506
11	Rosin	3	3.6	8	5.6	0.491
12	Fragrance mix I	3	3.6	6	4.2	0.814
13	NO	3	3.6	3	2.1	0.506
14	Methylisothiazolinone	3	3.6	6	4.2	0.814
15	Caine mix	3	3.6	0	0	0.023
16	Sesquiterpene lactone mix	2	2.4	4	2.8	0.848
17	Quaternium-15	2	2.4	4	2.8	0.848
18	Fragrance mix II	2	2.4	4	2.8	0.848
18	Thiuram mix	2	2.4	2	1.4	0.589
20	Lyril	2	2.4	4	2.8	0.848

Conclusions from the analysis of contact allergy in 455 epicutaneously tested individuals in Pleven and Ruse regions for the period 2009-2022:

- ✚ The frequency of CA in the general population tested epicutaneously is 49% - 224 individuals with an average age of 39.27 ± 14.68 years. 445 positive reactions were reported, which represents 1.9 positive test reactions per person.
- ✚ The distribution of positive patients by gender and age, that men are 21.9% at an average age of 41.10 ± 16.82 years, and women are 78.1% at an average age of 38.76 ± 14.04 years.
- ✚ The χ^2 -test shows that a significant difference in the distribution between men and women under and over 40 years of age is found in the atopic subpopulation ($p < 0.05$)
- ✚ The frequency of CA is highest in the general professional group (30.3%), followed by the group of office workers (25%), non-workers (22.8%), estheticians (11.2%) and doctors (10.7 %).
- ✚ In positive patients, the most common localization of the rash was the palms (55.3%), the face (34.4%), the upper limbs (33.9%), torso (28.1%), lower limbs (26.3%)

- ✚ Hand eczema was most common (38.4% of 224 positive individuals), followed by atopic dermatitis (20.5%), facial dermatitis (14.7%) and lower extremity dermatitis (9.8%)
- ✚ In the two subpopulations, there is a statistically significant difference in the distribution for Textile dye mix - 23% in atopics versus 7% in persons without atopy ($p < 0.001$) and MDBGN - 10% in atopics versus 2% in those without atopy ($p < 0.012$).

IV.2. Results of the contact hypersensitivity study in 189 individuals with evidence of atopy

The aim of this cross-sectional clinico-epidemiological analysis was to determine the frequency of contact allergy diagnosed by epicutaneous tests with the European standard series S -1000 in 189 individuals with clinical and anamnestic data of atopic diseases.

The tasks to achieve the goal are:

- Individuals should be stratified by sex, age, professional status, and diagnosis upon inclusion in the study.
- Based on the affected parts of the body and the clinical-morphological characteristics of the exanthema, determine the type of dermatitis.
- After analysis of the clinical and anamnestic data to investigate the atopic march in the study participants.
- With the allergological method to investigate the prevalence of contact allergy, determining the most common allergens and existing cross-reactivity.
- To look for statistical regularities between the various indicators

Atopics were 189 cases (41.7% of 455 patients) on average age 37.71 ± 16.55 years, men were 46 (24.4%) and women were 143 (75.6%), in a ratio of 1:3. Data from the anamnesis showed that 61 (32.2%) of the examined have personal and family data on atopic conditions, 97 (51.3%) have only personal data and 31 (16.5%) have only family burden. There are 83 (43.9%) with positive patch-tests with a total of 180 positive reactions. The results of epicutaneous testing with S-1000 objectified positive 83 patients (44% of all 189) – 20 men (24% of 83) and 63 (76% of 83) women. **(fig. 7)**

In order to track the ratio of positive individuals in relation to gender and age in both age groups (below 40 years and over 40 years), the result of the χ^2 -test showed that in positive individuals a significant difference was found in the ratio between men and women under and over 40 years of age – 7.2% for men and 45.8% for women under the age of 40 and 16.9% for men and 30.1% for women over 40 ($\chi^2=5.602$, $df=1$, $p=0.018$).

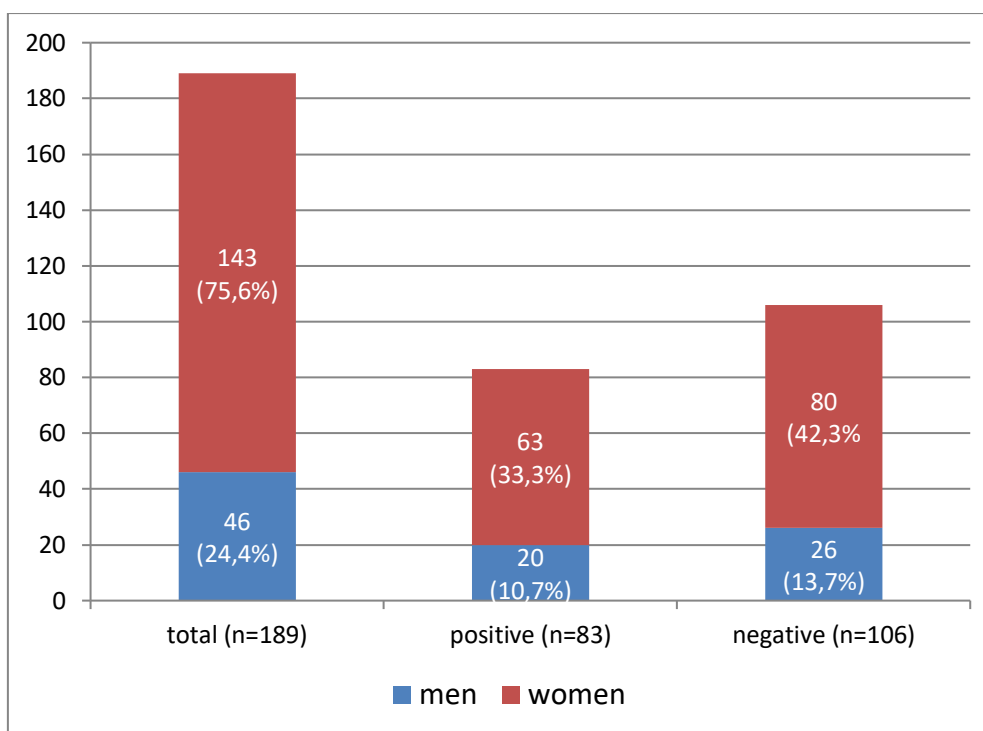


Figure 7: Gender distribution of 189 individuals with data on atopy

The distribution by professions shows the highest share of the group with diverse professions and education – 77 persons (40.7%), 32 of whom have a contact allergy, followed by the unemployed - 60 (31.7%), 25 of whom have a positive patch test. It should be borne in mind that the "Others" group unites persons with different qualifications, with the majority being representatives of material production who are in daily contact with various professional allergens. In the "Non-working" group are women on maternity leave, housewives and domestic helpers, students, who are often exposed to the action of aggressive detergents and detergents, as well as mobile devices. **(Table 7)**

Table 7: Crosstabulation of the distribution of atopics according to occupational status and the presence of contact allergy

Atopic subpopulation	n=189	unemployed	office	medicine	aesthetics	others	total
Negative faces	number	35	7	16	3	45	106
	% within profession	58.30%	33.30%	66.70%	42.90%	58.40%	56.10%
	% of Total	18.50%	3.70%	8.50%	1.60%	23.80%	56.10%
Positive faces	number	25	14	8	4	32	83
	% within profession	41.70%	66.70%	33.30%	57.10%	41.60%	43.90%
	% of Total	13.20%	7.40%	4.20%	2.10%	16.90%	43.90%
Total	number	60	21	24	7	77	189
	% within profession	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%
	% of Total	31.70%	11.10%	12.70%	3.70%	40.70%	100.00%

The description of the atopic march in the subpopulation of 189 atopics presents: AD only (61 patients, 32%), AR only (37 patients, 20%), BA only (8 patients, 4%), AD and AR (31 patients, 16%), AD and BA (11 patients, 6%), AD and AR and BA (5 patients, 3%), AR and BA (11 patients, 6%), only with anamnesis and with other diagnoses (25 individuals, 13%).

Most often, pathological changes affect the palms (42.8%), upper limbs (29.6%), face (26.9%), trunk (22.2%) and lower limbs (16.4%). In total, folds were affected 42 times (22.22%), mucous membranes 18 times (9.5%). In most patients, more than one part of the body is affected, so the sum of the topographical changes is more than 189. **(Fig.8)**

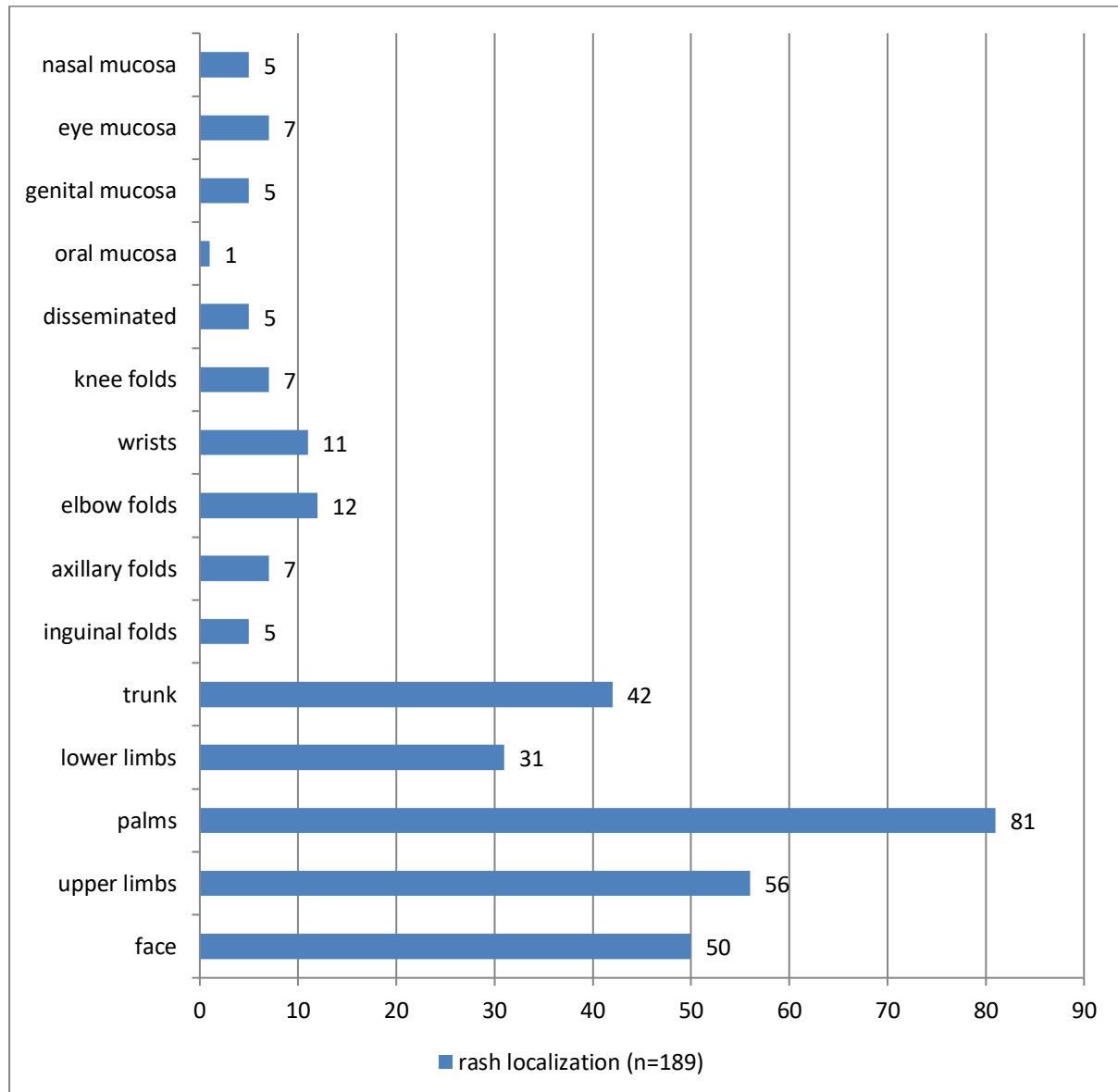


Figure 8: Frequency of involvement of observed anatomical body areas in 189 subjects

As a form of skin inflammation and regardless of the pathophysiological mechanism of the dermatitis (IgE-mediated or T-cell reaction of the delayed type) from a clinical point of view, it is mild to moderately pronounced, with signs of chronification also present. Eczema presents with:

- erythematous papules, plaques and scales on the face, limbs and trunk, incl. nettles;

- lichenification, erythema, papules and excoriations in body folds;
- miliary papules and nummular plaques, vesicles, bullae, crusts and scales on the palms and fingers;
- erythema, desquamation and excoriations on the scalp, eyelids and retroauricular.

At the time of examination, the following diagnoses were made, reflected in **table 8**:

Diagnosis	Frequency	Percentage
No complaints	16	8.5
Atopic dermatitis	64	33.9
Allergic contact dermatitis/eczema	77	40.7
Other allergic dermatoses (urticaria, etc.)	14	7.4
Dyshidrotic eczema	7	3.7
Another dermatosis	11	5.8
Total	189	100.0

Out of all 189 cases of atopy, 108 (57%) suffered from AD with varying duration of complaints, 64 (59%) of them had manifestations of mild to moderately pronounced dermatitis during the examination, and 44 (41%) were without complaints. The ANOVA analysis showed that there is a statistically significant difference in the mean age of patients with AD (35.25 ± 16.43 years) compared to that of individuals without AD (40.99 ± 16.25 years) – $F=5.698$, $p=0.018$. (**Table9**)

ANOVA Table

		Sum of Squares	df	Mean Square	F	Sig.
age * AD	Between Groups (Combined)	1523.757	1	1523.757	5.698	.018
	Within Groups	50005.238	187	267.408		
	Total	51528.995	188			

According to the frequency of the affected anatomical areas and the localization of the exanthema, the type of dermatitis is also determined (**table 10**)

Table 10: Type of dermatitis in the atopic subpopulation (n=189)

Dermatitis	Frequency	Percentage
No dermatitis	16	8.5
Facial dermatitis	24	12.7
Dermatitis of the hands	65	34.4
Dermatitis of hands and face	27	14.3
Dyshidrotic eczema	7	3.7
Dermatitis of the lower extremities	30	15.9
Dermatitis of the torso	15	7.9
Disseminated dermatitis	5	2.6
Total	189	100.0

The results of epicutaneous testing with S-1000 objectified 83 positive patients (44% of all 189) – 20 men (24%) and 63 (76%) women in a ratio of 1:3. They reported 180 positive reactions to various contact allergens. The results of the allergological examination show that 34 tested (41% of 83) had one positive reaction, 27 (32.5%) had two positive tests, 5 (6.2%) had 3 reactions, 13 (15.6%) with 4 reactions, one (1.2%) with 5 reactions, two (2.4%) with 6 reactions and one (1.2%) with 8 positive reactions.

In 189 studied individuals, the highest frequency of positive patch tests was for Nickel (48 times, 25.4% of atopics), followed by positives for Cobalt (27 times, 14.2%), Textile dye mix (19 times, 10.1%), Potassium dichromate (11 times, 5.8%), PPD (9 reactions, 4.8%), Methylidibromoglutaronitrile (8 reactions, 3.7%), MI/MCI and Balsam Peru (5 reactions each, 2.6%), all widespread in household and professional environment. **(fig.9)**

With data on cross-reactivity Nickel*Cobalt there are 16 persons (19.3%), for Nickel*Potassium dichromate there are 8 (9.6%), Nickel*Cobalt*Potassium dichromate there are 6 (7.2%), for MCI/ MI*MI – four (4.8%), PPD*IPPD 2nd respectively (2.4%), for Fragrance Mix I*Fragrance mix II – two (2.4%).

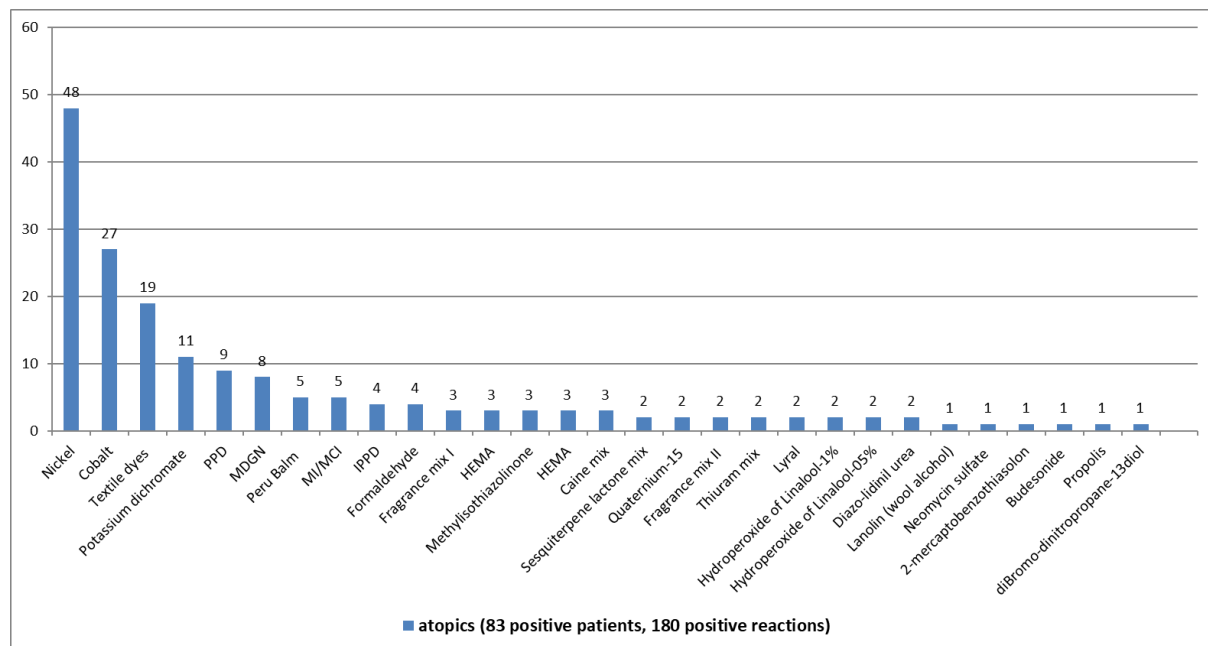


Figure 9: Frequency of allergens as a cause of CA in the studied 189 subjects with atopy

The statistical analysis performed using the Pearson correlation coefficient shows that there is, albeit a weak, statistically significant linear relationship between palm involvement and Textile dye mix ($r=0.256$, $p<0.05$, $N=189$)

In nickel-positive individuals, a difference in the percentage distribution of cases with palm involvement was found between different occupations, with 81% of non-workers and 67% of healthcare workers having hand eczema ($\chi=9.852$, $df=4$, $p=0.043$). **(fig. 10)**

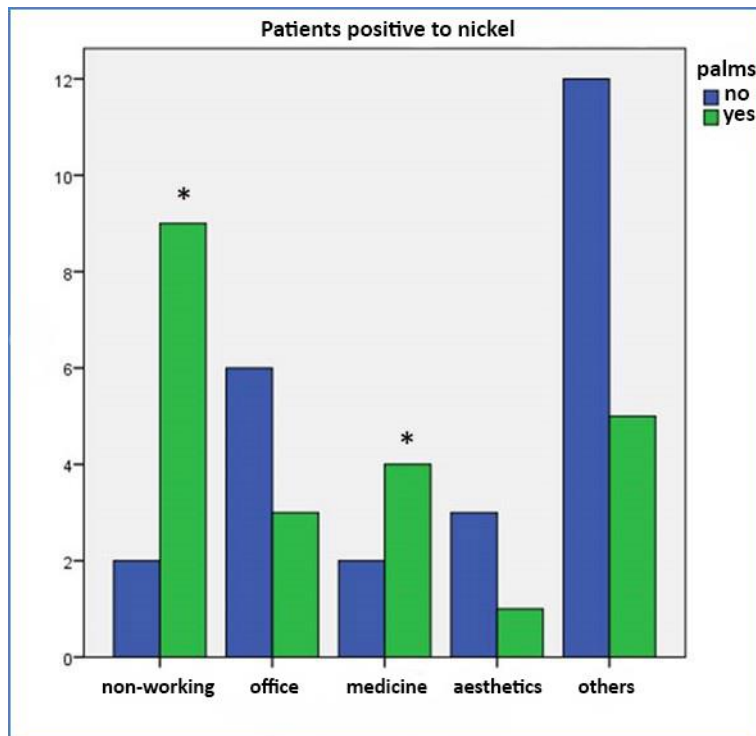


Figure 10: Distribution of nickel-positive patients with palm involvement in the different occupational groups

Findings from the study:

- ✚ Of 189 individuals with data on atopy at an average age of 37.71 ± 16.55 years, men were 24% (average age 38.15 ± 19.27) and women 76% (average age 37.57 ± 15.66), people with diverse professions prevailed (41%) and unemployed (31%), with the highest frequency being the diagnosis of ACD (in 41%) and AD (in 34%). 56% of the study participants are under 40 years of age.
- ✚ Most often, the pathological changes affect the palms (43%), the upper limbs (30%) and the face (27%). Hand eczema was most common (34%), followed by lower limb dermatitis (16%) and hand and face dermatitis (14%).
- ✚ In the "atopic" subpopulation, out of 189 examined, 44% had positive tests and a total of 180 positive reactions - 25% to nickel, 14% to cobalt, 10% to textile dyes. The most common cross-reactivity was found for metals - nickel*cobalt (19%), as well as for preservatives - MCI/MI*MI (5%)
- ✚ A statistically significant difference was found in the ratio between men and women under and over 40 years of age ($p < 0.05$), and in nickel-positive individuals a significant difference was found in the percentage distribution of cases with involvement of the palms between the different professions ($p < 0.05$). There is a statistically significant difference in the average age for patients with AD (35.25 ± 16.43 years), compared to that of persons without AD (40.99 ± 16.25 years) - $p < 0.05$.
- ✚ The presence of AD in the atopic subpopulation is not a risk factor for higher contact sensitivity in atopics compared to controls ($p > 0.05$)

IV.3. Results of the contact hypersensitivity study in patients with and without atopic dermatitis

The aim of this cross-sectional clinico-epidemiological analysis was to determine the frequency of contact allergy diagnosed by epicutaneous tests with the European standard series S -1000 in 83 individuals with or without clinical and anamnestic evidence of atopic dermatitis.

The tasks to achieve the goal are:

- Individuals in the two subgroups should be divided by sex, age, professional status and diagnosis.
- Based on the affected parts of the body and the clinical-morphological characteristics of the exanthema, determine the type of dermatitis.
- After analysis of the clinical and anamnestic data, to study the atopic march in the subjects.
- With epicutaneous tests to investigate the prevalence of contact allergy in the two subgroups, determining the most common allergens and the existing cross-reactivity.
- To look for statistical regularities between the various indicators

Atopics are 189 cases, with positive patch-tests being 83 (43.9%) with a total of 173 positive reactions - 20 men (24% of 83) and 63 (76% of 83) women. The average age of the persons is 39.78 ± 16.18 years, 43 are under 40 years of age and 40 are over 40 years of age. In both subgroups, the mean age of 46 patients with AD was 38.13 ± 15.51 years, and in 37 individuals without AD is 41.84 ± 16.98 years (**fig. 11**)

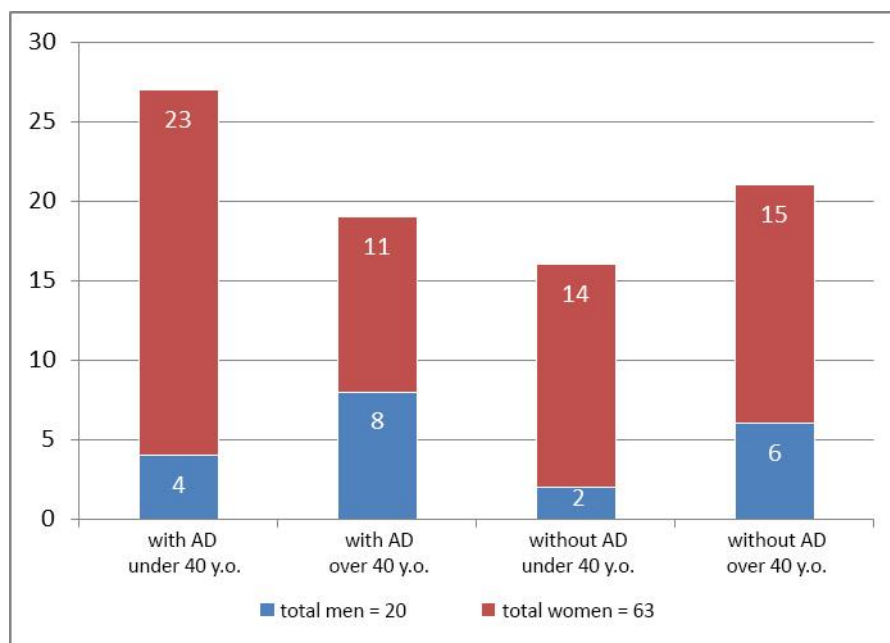


Figure 11: Distribution of patients with and without atopic dermatitis by gender and age

In order to track the proportion of patients with and without AD in relation to gender and age, descriptive statistics were performed. We found a statistical difference in the distribution of men and women by age groups in **all** positive patients – 30% for men and 58.7% for women under 40 years and 70% for men and 41.3% for women over 40 years ($\chi^2=5.019$, $df =1$, $p=0.025$). In **positive persons with AD**, a significant difference in the distribution between the sexes under and over 40 years of age is found - 33.3% for men and 67.6% for women under the age of 40 and 66.7% for men and 32.4% for women over 40. ($\chi^2=4.308$, $df=1$, $p=0.038$). The distribution by professions again shows the highest share of the group with diverse professions and education - 32 persons (38.6%), followed by the unemployed - 25 (30.1%), office workers - 14 (16.9%), doctors - 8 (9.6%) and those engaged in aesthetic procedures are 4 (4.8%). Only among women with AD are the unemployed more than the persons in the "Other" group (24%:22%). No significant difference was found in the distribution of positive persons by gender and profession ($p=0.104$) (**fig. 12**)

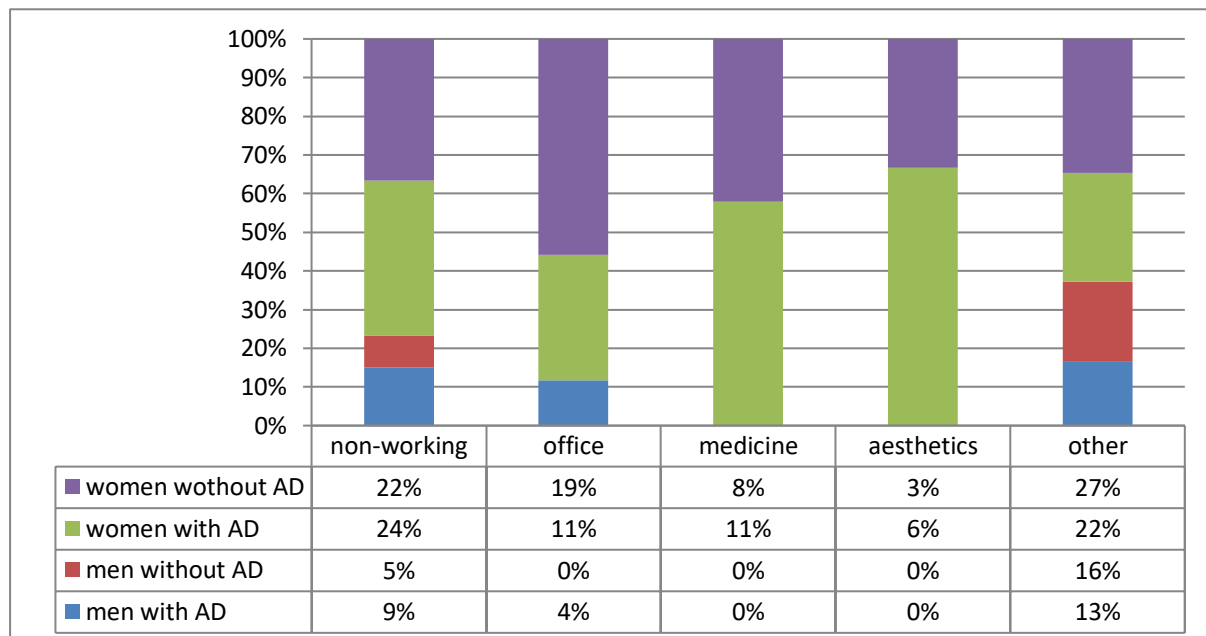


Figure 12: Percentage distribution of positive atopics by gender and profession

In the diversity of the pathological spectrum of the atopic march in all 83 individuals with positive epicutaneous tests, the number of patients without a clinic of atopic disease, but with a history of such, is striking - 23 (27.7%), of which 3 are without complaints, against the 25th in the total subpopulation of 189 people, which represents 13.2% of them. The description of the atopic march in positive atopics presents: AD only (26 patients, 31%), AR only (8 patients, 10%), BA only (0 patients, 0%), AD and AR (14 patients, 17%), AD and BA (4 patients, 5%), AD and AR and BA (2 patients, 3%), AR and BA (6 patients, 7%), only with anamnesis and with other diagnoses (23 persons, 27%).

Most often, pathological changes affect the palms (40, 48.2%), upper limbs (22, 26.5%), trunk (19.22%), lower limbs (17, 20.5%) and face (14, 16.9%). In total, folds of the body were affected a total of 10 times (12%), various mucous membranes 9 times (10.8%). In multiple

patients, more than one body part is affected, therefore the sum of the topographical changes is greater than 83. (**Fig. 13**)

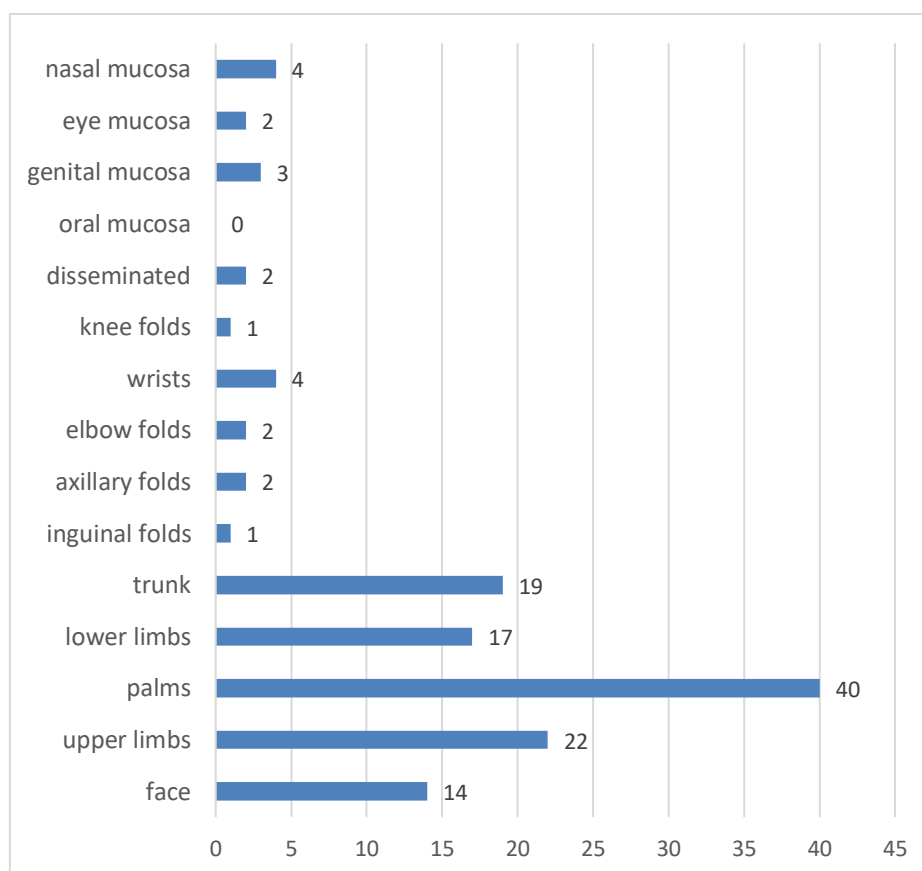


Figure 13: Frequency of involvement of the observed anatomical areas of the body in 83 positive individuals

In patients, more than one body part was affected, so the sum of the topographic changes was greater than 46 for individuals with AD and greater than 37 for those without AD. Descriptive statistics did not reveal a statistically significant distribution of positive individuals with and without AD by body area. (**Table 11**)

Table 11: Description of the frequency of the affected anatomical areas in the two subgroups - with and without AD

affected areas	People with AD (n =46)		Patients without AD (n =37)		X ² (p)	T-test (p)
	number	percent	number	percent		
Face	11	24%	3	8.1%	0.056	0.051
Palms	21	45.6%	19	51.3%	0.6	0.4
Upper limbs	15	32.6%	7	18.9%	0.16	0.12
Lower limbs	5	10.9%	12	32.4%	0.16	0.13
Truncus	14	30.4%	5	13.5%	0.07	0.06

The results of the allergological examination showed 173 positive reactions. Patients with AD tested positive for 99 of them (57.2%), and persons without AD 74 (42.8%). In the subgroup of patients with AD, the tests for nickel were most often positive - 29 times or 29.2% of the

99 reactions, for cobalt - 15 times (15.2%), potassium dichromate - 10 times (10.1%), the mix of textile dyes and preservatives (MI+MCI/MI) 7 times (7% each). There is cross-reactivity with metals - Nickel*Cobalt - 6 times, Nickel*Cobalt*Potassium dichromate - 4 times, Nickel*Potassium dichromate - 2 times. (fig. 14, table 12).

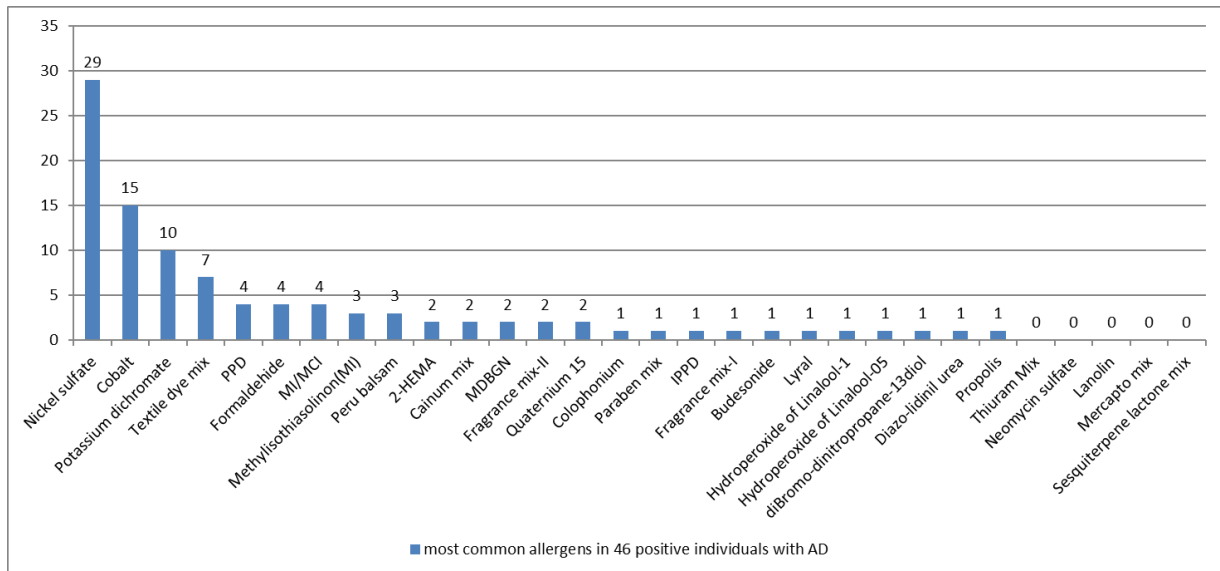


Figure 14: Frequency of positive allergens in atopic patients with AD (n=46)

In patients without AD, the most common positive allergens were nickel sulfate 18 positive tests (24.3% of a total of 74 reactions), 11 reactions to the mixture of textile dyes (14.9%), 8 to cobalt chloride (10.8%), 5 times to para-phenylenediamine and methyldibromoglutaronitrile (6.75% each). (fig. 15, table 12).

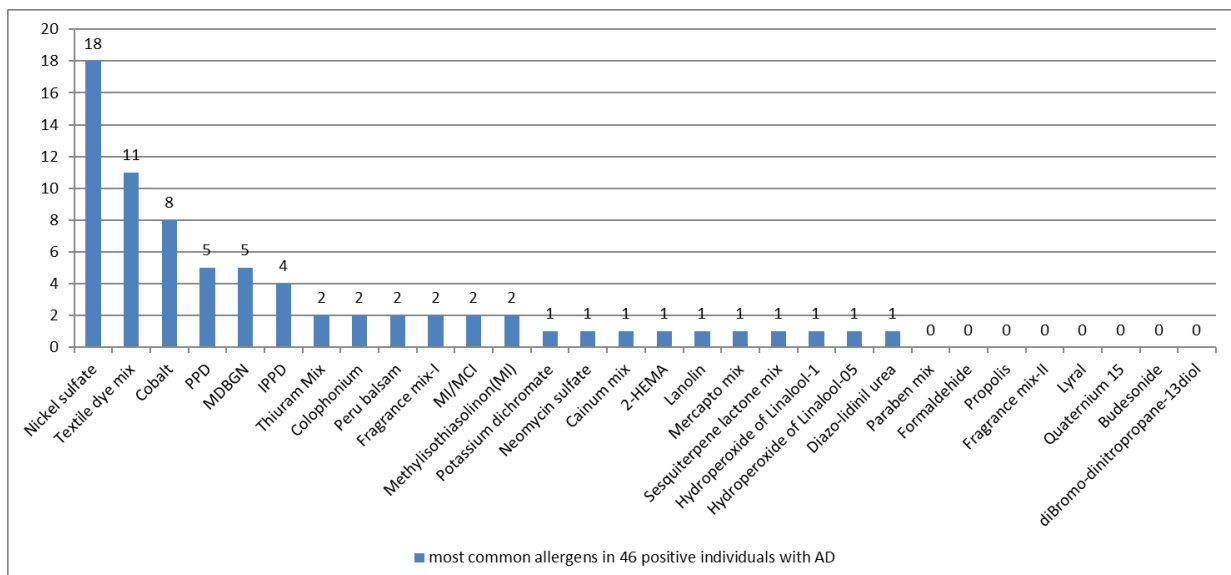


Figure 15: Frequency of positive allergens in atopics without AD (n=37)

Table 12: Positive results of epicutaneous tests in patients with atopic dermatitis and patients without atopic dermatitis

allergens	Patients with AD (n =46)		Patients without AD (n =37)		X ²	T-test
	number	percent	number	percent	R	R
Potassium dichromate	10	21.7	1	2.7	0.01	0.01
PPD	4	8.7	5	13.5	0.38	0.36
Cobalt chloride	15	32.6	8	21.6	0.26	0.19
Nickel sulfate	29	63.0	18	48.6	0.18	0.13
IPPD	1	2.2	4	10.8	0.10	0.12
Peru balsam	2	4.3	3	8.1	0.47	0.39
MDBGN	2	4.3	5	13.5	0.13	0.13
Textile dye mix	7	15.2	11	29.7	0.11	0.09
Methylisothiazolinone	3	6.5	2	5.4	0.83	0.60
MCI/MI	4	8.4	2	5.4	0.56	0.44

Findings from the study:

- ✚ Of 83 individuals with contact allergy, 46 (55.4%) were diagnosed with AD at a mean age of 38.13 ± 15.51 years, and 37 (44.6%) were persons without AD, but with clinical and/or anamnestic evidence of atopy and a mean age of 41.84 ± 16.98 years. People with diverse professions (38.6%) and unemployed (30.1%) prevail. 55.4% of the study participants are under 40 years of age.
- ✚ Most often, the pathological changes affect the palms (48.5%), the upper limbs (26.5%) and the torso (19.2%). Among patients with AD, the most common are eczema of the hands (37%), dermatitis of the face (13%) and dermatitis of the hands and face (11%).
- ✚ The pathological spectrum of the atopic march is shown, both for the diseases with atopic genesis and with rich comorbidity.
- ✚ Out of 83 people examined with 173 positive reactions, those with AD tested positive in 57.2% of the applied tests. The most common is allergy to nickel (29%), cobalt (18%) and potassium dichromate (10%). The most common cross-reactivity was found to metals – nickel*cobalt (6%), nickel*cobalt*potassium dichromate (4%), as well as MI+MCI/MI also 4%.
- ✚ In the positive patients, a significant difference was found in the gender distribution by age group ($p < 0.05$). In individuals with AD, a statistically significant difference in the distribution between the sexes under and over 40 years of age was also found ($p < 0.05$). There is no significant difference in the distribution of positive persons with and without AD on the affected areas of the body, as well as in the frequency of allergens, the cause of CA.

IV.4. Description of clinical cases

IV.4.1. A case of facial ACD from cosmetics

It's the patient 69-year-old woman, pensioner. She worked in a petrochemical plant. He reports allergic diseases with a 20-year history, mainly on the hands and face. He attributes his complaints to prolonged professional contact with various chemical substances, oils, petroleum, gasoline, metals.

At the time of examination, the pathological skin changes involve the face and neck, presenting with moderately expressed erythema, miliary and lenticular papules on the forehead, retroauricular and submandibular - a picture of subacute facial dermatitis. Skin appendages are not affected.

He reported no family history of allergic and atopic diseases.

It has been tested with 30 allergens from S -1000. The results were recorded at 48 and 72 hours and are presented in Table 12 and Figure 16.

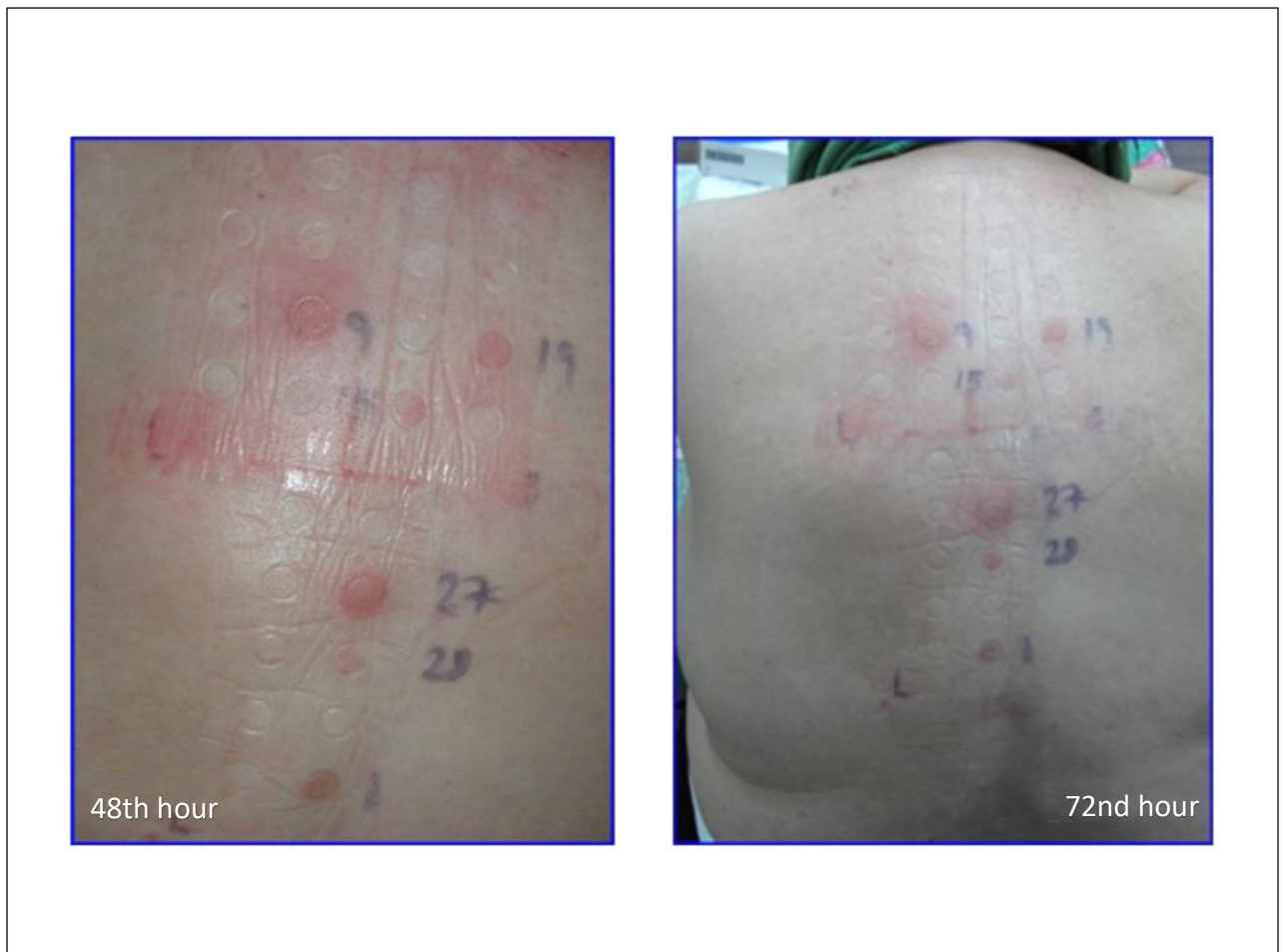


Figure 16: Contact sensitization to allergens used in cosmetics and make-up in the patient

Table 13: Epicutaneous test results reported at 48 and 72 hours.

allergen	48th hour	72nd hour
Colophonium	+++	++
Myroxylon pereirae (Balsam of Peru)	++	+
Fragrance mix I	+++	+++
Fragrance mix II	+++	++
Hydroxyisohexyl-3-cyclohexene (Lyrall)	++	++

Colophonium in cosmetics is included in mascara, rouge and lipstick, it helps to fix the make-up. Toiletries such as dental floss, sunscreen, and depilatories also often contain colophonium. (Karlberg, Albadr, and Nilsson 2021)

Peru balsam (Myroxylon pereirae, Balsam of Peru) and Fragrance mixtures are used in the perfumery industry. The addition of hydroxyisohexyl-3-cyclohexene carboxaldehyde, limonene hydroperoxides, and linalool hydroperoxides to screening series may further aid in the diagnosis of fragrance allergy. Since Myroxylon pereirae is hardly used alone nowadays, it is assumed that Fragrance mix I is more sensitive in detecting fragrance allergy. (Reeder 2020) (Guarneri et al. 2021)

Lyrall (Hydroxyisohexyl-3-cyclohexene carboxaldehyde) is a synthetic fragrance known by the trade names Kovanol, Mugonal, Landolal. It is found in soaps, toilet waters, aftershaves and deodorants. (Uter et al. 2013)

The described case report presents a case of facial ACD caused by cosmetics and demonstrates fragrance cross-reactivity.

2. Case of a patient with atopic dermatitis and contact polyallergy

We present a 70-year-old male patient. with AD since childhood and with a history of a 15-year-old itchy rash disseminated on the face, torso and limbs. The disease was initially provoked by the consumption of strawberries. Over the years, it has a chronic-relapsing course, worsening mainly after eating certain foods (eggs and nuts) and from contact with fabric softeners, industrial and industrial paints. The patient is an architect by profession and is often exposed to the influence of various chemicals. One of the worst relapses was provoked after contact with paint, during the renovation of his home. He has been suffering from hypertensive disease for 30 years, for which he takes Valsartan/Hydrochlorthiazide 160/25 tablets. x 1 tablet/day. Family history for atopic dermatitis.

Repeatedly treated with local and systemic corticosteroids, antihistamines with a temporary effect. For 6 months, he has been on systemic therapy with Methotrexate 15 mg/week, Desloratidine 5 mg/day and emollients.

At the time of examination, pathological changes involved the skin of the face and the extensor surfaces of the upper and lower extremities. They are represented by symmetrically located, erythematous plaques with insignificant infiltrate, with single excoriations. Subjectively-moderately expressed itching. Visible mucous membranes and skin appendages - no pathological changes.

Cardiovascular and respiratory systems – no pathological findings, limbs - no swelling, peripheral lymph nodes - not enlarged. Biochemical indicators and blood count values are within reference limits.

The patient underwent epicutaneous allergy testing with the standard European S-1000 series, and two weeks before, the patient's systemic medications were stopped.

At the 48-hour follow-up, the patient reported severe, excruciating itching in the region of the tested area. A positive allergic reaction to 8 of the 30 applied allergens was found. (**fig. 17 and table 14**)

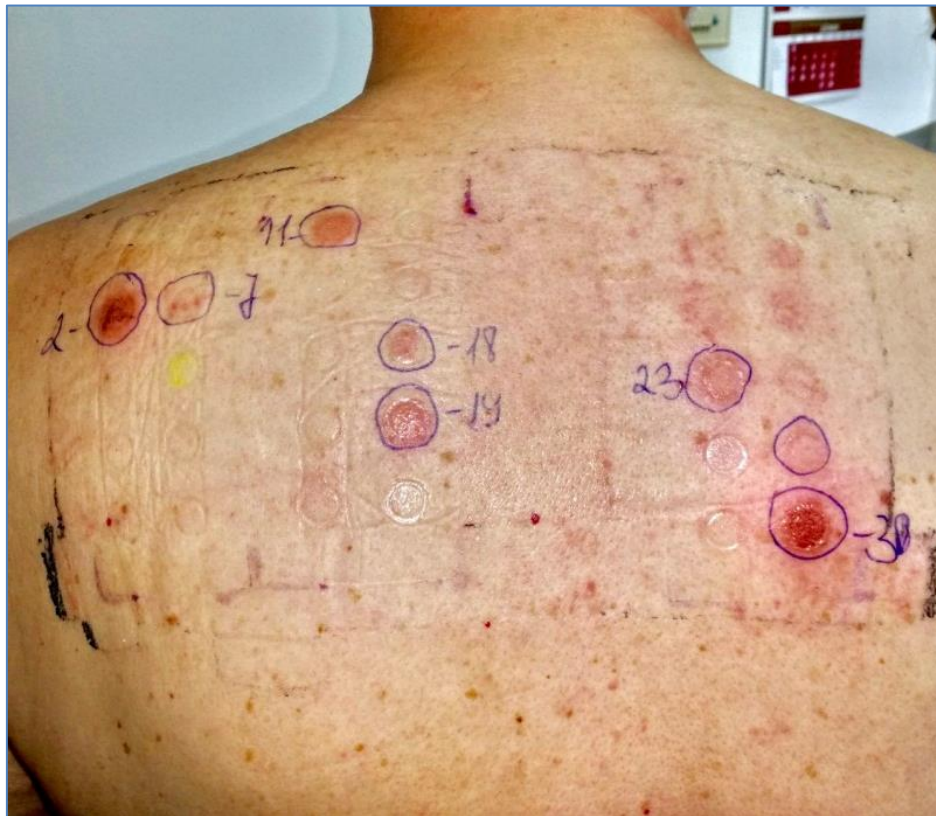


Figure 17: Contact sensitization to dyes, preservatives and fragrances in the patient

Table 14: Epicutaneous test results reported at 48 and 72 hours.

allergen	48th hour	72nd hour
2 2-PPD	+++	++
7 Nickel	+	+
11 IPPD	++	+
18 Formaldehyde	++	++
19 Fragrance mix I	++	+
23 Methylisothiazolinone	++	++
27 Fragrance mix II	++	+
28 Hydrohyisohehexyl 3-cyclohexene	I R	–
30 Textile dye mix	+++	+++

An extremely positive reaction (+++) to PPD and Textile dye mix was reported at the 48th hour, with the presence of erythema, edema and vesicles.

Allergens to which the patient showed a positive reaction (contained in cleaning and laundry preparations, softeners, rubber, rubber stabilizers, cosmetics, perfumes, textile dyes) are those that correspond to the anamnestic data of intolerance.

In atopic dermatitis, there is a violation of the skin barrier, which in itself is a predisposing factor for the occurrence of ACD. Also, the inflammatory changes present in AD lead to an increased risk of sensitization, even to allergens with a lower allergic potential. (Aquino and Fonacier 2014) (Rundle et al. 2017)

The described case presents a case of polyallergy with disseminated exanthema on the face, torso and limbs, caused by hypersensitivity to allergens from the groups of dyes, preservatives and fragrances, incl. with the appearance of cross-reactivity.

3. Allergic contact dermatitis to hand sanitizers used for prevention of COVID-19 in an atopic patient

The patient is a 31-year-old woman with chronic hand eczema for about 10 years. Diagnosed with atopic dermatitis since childhood. Over the years, in periods of exacerbation, she has been intermittently treated with systemic H1-blockers, local corticosteroids and emollients, with a temporary effect. In connection with the epidemiological situation in the country and the recommendations for prevention of COVID infection, in March 2020 she has started an intensive daily and repeated use of hand sanitizers, which led to exacerbation of eczema.

She is a lawyer by profession, works with a computer daily (5 hours a day). Family burden - father with food allergy and 1-year-old son with severe atopic dermatitis.

The somatic status is without pathological deviations.

Dermatological status: phototype III; the pathological skin changes involve the palms and fingers of both hands and are represented by irregularly shaped, ill-defined, erythematous-infiltrated papules and plaques with scant whitish desquamation and solitary rhagades.

Visible mucous membranes are intact. Hair - no features. Nails - onychodystrophy of the nail plate of the ring finger of the right hand. **(fig. 18)**



Figure 18: The described dermatological changes in the patient

The routine paraclinical tests performed were within reference limits. Epicutaneous testing (S-1000 with 40 allergens) found positive reactions to Nickel (II)sulfate, 2-Bromo-2-Nitropropane-1,3-diol and Diazolidinyl urea, which are preservatives and antibacterial ingredients in leave-on hand sanitizer gels. **(table 15) (fig. 19)**

Table 15: Result of epicutaneous testing in the patient

no	Positive allergens	48th hour	72nd hour
07	Nickel (II) sulfate	+++	++
32	2-Bromo-2-Nitropropane -1,3 -diol (Bronopol)	++	+
33	Diazolidinyl urea (Garmaben)	++	++



Figure 19: The positive allergens in the patch tests

After a ten-day treatment with Methylprednisolone aceponate cream and an emollient with a good effect, the patient replaced the use of disinfectants with SYNDET type washing products.

The presented patient has evidence of atopy and contact allergy of the hands, which developed as a consequence of intensive use of hand disinfectant gels. The results of epicutaneous testing showed positive samples for nickel (the world's #1 allergen) and formaldehyde (via cross-reactivity to the sensitizers diazolidinyl urea and 2-bromo-2-nitropropane-1,3-diol, which proves the relationship between positive reactions to FA-releasing preservatives and contact allergy to FA).

V. DISCUSSION OF THE RESULTS

V.1. Discussion of the results of a retrospective clinico-epidemiological analysis to determine the incidence of contact hypersensitivity in the general population.

Contact sensitization is the main pathophysiological mechanism for the development of allergic contact dermatitis. ACD is a widespread allergodermatosis and affects up to 20% of the population in European countries. At present, little is still known about the individual factors that may influence the clinical response to contact sensitizers. The total number of sensitized individuals in the population depends mainly on the duration and extent of skin exposure, and it is an indisputable fact that some individuals are more easily sensitized to common haptens than others, and this is probably due to their genetic background.

The fact that exposure patterns change over time due to continuous changes in ecology and environmental factors, technological developments, fashion trends, regional and career characteristics, cultural traditions should also be taken into account. This is also the reason for the significant variability of data related to sensitization to individual allergens in different research centers in a national and international aspect.

Our results reflect contact allergy among 455 dermatological patients selected for the period 2009-2022 and allergologically tested with the standard European S-1000 series. 224 (49.23%) of them had a total of 445 positive epicutaneous samples to 36 contact allergens. Among the 224 positive persons, 22% are men and 78% are women, with 46% being over 40 years of age. These demographics are close to those published in 2014 by Narsimha Rao Netha that women are more likely to suffer from ACD due to the use of cosmetics rich in fragrances and preservatives, as well as the use of metal-rich jewellery. At the same time, contact eczema is more often observed in older individuals as a result of duration of allergen exposure, changes in epidermal barrier function and changes in immune reactivity.

Of our positive patients, 20.5% had atopic dermatitis, 37% had eczema on the hands, 9.8% on the lower extremities, and 14.7% on the face. Our data approximate those published in the literature for the highest incidence of hand eczema, the incidence of contact allergy in atopics, and the percent variability in clinically unmanifest sensitization among apparently healthy individuals.

Based on the demographic and clinical characteristics of the patients of the observed spectrum and frequency of contact allergy, the German Information Network of Departments

of Dermatology (IVDK) introduces the classification of dermatitis as atopic, ACD of the hands, lower limbs and face, as well as the MOAHLFA index as instrument for tracking trends in the distribution of allergic pathology.

To assess the MOAHLFA index, a comparison was made with those published by Anna Tagka et al. in 2018, data from an epidemiological study of contact allergy in Greece for the period 2014-2018 (**table 16**)

Table 16: Comparison of index data in the two studies

	Our study (n=224)	Tagka et al. (n=667)
parameter	%	%
Men	22%	31%
Occupational dermatitis	10%	31%
Atopic dermatitis	21%	35%
Dermatitis of the hands	37%	50%
Dermatitis of the feet	10%	24%
Facial dermatitis	15%	32%
Age over 40 years	46%	59%

Differences in the data are common given the fact that the two neighboring countries have their own specific dynamics of changes in all spheres of life - ecology, economy, industrialization, health and professional profile, culture. However, in both studies there were fewer men than women, the incidence of hand eczema was highest, followed by atopic dermatitis and facial dermatitis, and was lowest in patients with lower extremity involvement. At the same time, in the Greek study, the top allergens were Nickel (24% positive reactions), Cobalt (9%), Peru balsam (8%) and PPD (6%) - results very close to ours.

In the present study, contact hypersensitivity to Nickel accounted for 35% of the positive 445 reactions, 18% for Cobalt, 6% each for PPD and Potassium dichromate, 5% each for Peru balsam and Textile dye. These data also characterize the trends in the manifestation of contact hypersensitivity among the Bulgarian population, with the frequency of allergy to nickel and cobalt remaining high over the years. Results partially overlap with those of Stranski and Krasteva's study in the period 1975-1987 in 1237 patients with contact sensitization tested with a standard epicutaneous series. The increasing importance of the most common allergens in industrialized countries is indicated - nickel sulfate, potassium dichromate, p-phenylenediamine, isopropyl-aminodiphenylamine and formalin.

Our results also converge with those published by V. Mahler and H. Dickel in 2019, who analyzed contact hypersensitivity in 56 170 patch-tested patients from 2014 to 2018. They reported the highest incidence of dermatitis on the hands and that on the face. 30% of these patients suffer from hand eczema, of which 46% have occupational ACD. The most common are positive reactions to Nickel, Cobalt, MCI/MI, Fragrance mix I, Thiuram mix, Balsam Peru, Chromium and Fragrance mix II.

In the general population, it is striking that there were 57 positive reactions to various preservatives (25.4% of all positive tests). In 2013, E. Chow et al. publish their results from the

first follow-up of preservative allergy pooling data from 4 Australian centers. 6845 individuals were selected for the period 1993-2006 and the frequency of CA to allergens from the group of preservatives was determined. Comparing the Australian results with our results, quite close data are found as evidence of the widespread distribution of preservatives in all spheres of life and the serious allergic potential of these chemical substances. **(Table 17)**

Table 17: Comparison of data on contact allergy to preservatives in the two studies

Allergens	Chow et al. (2013)	Our Study (2022)
methyldibromoglutaronitrile	3.3%	5%
methylchloroisothiazolinone/methylisothiazolinone	2.3%	4.5%
methylisothiazolinone	1.5%	4%
methylchloroisothiazolinone	—	2.7%
formaldehyde	4.6%	2.7%
quaternium-15	2.9%	2.7%
parabens	1.1%	2.7%
diazolidinyl urea	2.4%	0.9%
2-bromo-2-nitropropane-1, 3-diol	0.9%	0.45%

According to the authors, the tracking of preservative allergies is a dynamic process, with prevalence rates generally reflecting trends in preservative use in modern times. Ongoing studies of the level of local prevalence of allergies are important, as this provides essential information that, based on patch test data, would allow regulatory authorities to control the production and distribution of allergens.

Methyldibromoglutaronitrile is a commonly used preservative in cosmetics and personal care products. The most common sources are cosmetic products and toiletries (creams, balms, lotions for babies, hands, face and body, sunscreens, shower gels, shampoos and massage oils), scented wipes and napkins, lubricating oils, a component of various detergents (washing powders, household detergents, etc.) and various adhesives and glues (formaldehyde, formaldehyde resins).

V.2. Discussion of the results of the contact hypersensitivity study in 189 individuals with evidence of atopy

The total population includes 455 individuals, 224 of which have one or more positive reactions to the allergens of the standard European series, i.e. the frequency of CA was 49.2%. Two subpopulations were considered, with two subgroups in one:

- 266 patients (58.5% of 455) without data for atopic pathology, of which 141 are positive - the frequency of CA is 52.65% with 1.35 reactions/person
- 189 patients with atopic diathesis (41.5% of 455), of which 83 were positive - the incidence of CA was 43.9% with 2.08 reactions/person
 - ✓ 46 positive atopics (54%) with AD with 2.15 positive reactions/person

- ✓ 37 positive atopics (46%) without AD, CA with a frequency of 2 reactions/person

We found more positive responses to patch testing in patients in the general population (53%) compared to patients with AD (48%). The results of our study are consistent with previous findings that there is no significant difference in the prevalence of CA between the atopic and non-atopic population.

In a meta-analysis by Hamann et al. (2017) reported on 5 studies with a total population of 6161 patients, the mean incidence of CA in patients with AD was 29.6%, while in those without AD it was 22.5%. All 5 studies reported a higher incidence of contact sensitization in individuals with AD than without AD, finding that AD was a risk factor for developing contact sensitization (OR 1.54, 95% CI 1.23-1.93).

In the same meta-analysis, thirty-one studies with a pooled total population of 50,544 patients reported a mean prevalence of contact sensitization in individuals with AD of 49.9%, compared with 54.9% in individuals without AD, finding that that when calculating the odds there is even an inverse correlation and $OR < 1$. These data are close to what we obtained - 52.65% frequency of CA in the general population and 42.6% frequency of CA in those with AD. (OR=1.1180, 95%CI 0.6810-1.8354, $p=0.61$). When calculating the odds in our study, an inverse correlation was found when calculating the risk of CA in individuals with atopic diathesis, compared to people in the general group, without atopy (OR=0.7042, 95%CI 0.4838-1.0249, $p=0.06$). The risk of developing CA in positive patients with AD and those without AD was also calculated, which showed that the presence of AD is not a risk factor for developing CA (OR=1.3215, 95%CI 0.8101 to 2.1557, $p=0.26$). The results of our study are consistent with the results published in previous studies, namely that there is no significant difference in the prevalence of contact sensitization between individuals with atopic diathesis and the non-atopic population.

It should be noted that the patients in our analysis were referred by a colleague or self-solicited a dermatologist examination with or without specific complaints during the annual BDS allergy testing campaigns. The data for the atopic subpopulation were selected on the basis of clinical and anamnestic data for atopic diseases that become part of the general population. This may explain the higher proportion of positive epicutaneous reactions in patients without atopy and AD.

In 2011, Landeck et al. investigated patterns of contact sensitization in individuals with evidence of atopy compared with nonatopic subjects. For a period of 17 years, they have been subjected to epicutaneous testing 1247 patients, of which 172 with data on atopic pathology and 1075 were classified as non-atopic individuals. The rate of sensitization was 65.0% in the atopic group and 1.5 mean number of positive responses and 57.4% CA frequency and mean number of positive responses 1.2 in the non-atopic group. The most common diagnosis is ACD of the hands. The observed leading allergens were similar for both groups – nickel (16.9% vs. 14.2%), fragrance mix (14.5% vs. 15.8%), Peruvian balsam (11.0% vs. 11.6%), cobalt (8.7% vs. 7.3%), potassium dichromate, suggesting common sources of sensitization. There were no statistical differences between groups for any of the positive allergens.

We compared the above data with our results in which after analysis we found no significant differences between the two subpopulations both in the parameters of the MOAHLFA-index and for each positive allergen. **(table 18)**

Table 18: Comparison of the overall epidemiological data for the studied atopic and non-atopic patients in both studies (*atopic dermatitis is not included in the table*)

studies	Our Study (2022)				χ^2	Landeck et al. 2011				χ^2
Groups of patients	With atopy n=83		No atopy n=141		R	With atopy n=172		No atopy n=1075		R
parameter	number	%	number	%		number	%	number	%	
Men	20	24.1	29	20.6	0.537	51	29.7	322	30	0.963
Occupational dermatitis	9	10.8	13	9.21	0.601	5	3	109	10	0.020
Dermatitis of the hands	32	40.5	50	35.4	0.458	42	24.4	371	34.5	0.009
Dermatitis of the feet	9	10.8	13	9.21	0.383	21	12.2	168	5,6	0.246
Facial dermatitis	9	10.8	24	17.0	0.467	48	27.9	261	24.3	0.306
Age	39.78 ± 16.18		36.98 ± 13.26		0.540	46.7 ± 15.21		46.2 ± 15.19		0.702

In 2018, after feedback and analysis in the ESCD working group, an update of the European standard series was approved - due to infrequent reporting of positive results and lack of relevance to remove primin 0.01% pet. and clioquinol 5% pet., being replaced by propolis 10% pet. and 2-hydroxyethyl methacrylate (2-HEMA) 2%pet. The latest addition to the standard European S-1000 series is the Textile dye mix allergen, but a large number of positive reactions were reported in a short time, placing it among the most common allergens, which we also observed in our epicutaneous test results. Textile dyes have proven essential in allergic skin pathology. The blue pigment used to color denim has been proven to be the most allergenic. To achieve a blue color, a large amount of cobalt is used, which is why often patients with a positive reaction to Textile dye mix also give one to the allergen cobalt. Our results show that simultaneous positive reactions to cobalt and mixed textile dyes in the general population is 2.25% and in the atopic subpopulation is 3.6%.

V.3. Discussion of the results of the study of contact hypersensitivity in atopics with and without evidence of atopic dermatitis.

We tested 189 individuals with clinical and anamnestic data for atopy on average age 37.71 ± 16.55 years, men are 46 (24.4%) and women are 143 (75.6%), in a ratio of 1:3. 83 of them have at least one positive reaction after epicutaneous testing with the European standard series S -1000 – 20 men and 63 women.

There are 46 patients with AD (12 men and 36 women) on average age 38.13 ± 15.51 years with a total of 99 positive tests. In the subgroup, the tests for nickel are most often positive - 63% of the individuals and 29% of the 99 positive reactions, for cobalt chloride - 33% of the tested and 15% of the reactions, for potassium dichromate - 22% of the people and 10% from the tests, to the mix of textile dyes - 15% of the individuals with AD and 7% of the positive tests.

Patients without AD are 37 (8 men and 29 women) on average. age 41.84 ± 16.98 years in which 74 hypersensitivity reactions were reported. In people without AD, the most common positive allergens are nickel sulfate - 48% of people in the subgroup and 24% of a total of 74 reactions, to the mixture of textile dyes - 30% of people and 15% of reactions, to cobalt chloride - 22% of persons and 11% of the reactions, to para-phenylenediamine and methylidibromo-glutaronitrile - 14% of those without AD and 7% of 74 positive reactions.

Contact sensitization to nickel sulfate, cobalt chloride, potassium dichromate and methylisothiazolinone is more common in patients with AD, while CA to Textile dye mix, PPD, MDBGN and IPPD is of higher frequency in those without AD. No statistically significant difference was found in the percentage distribution of allergens in the two subgroups.

Debate about the relationship continues in the literature between AD and ACD. Several studies reported a reduced incidence of CA, others found a positive association, while some found that atopy and contact dermatitis were independent of each other.

As early as 1987, Huber et al. investigated the risk of delayed-type hypersensitivity in 65 patients with AD and a non-AD control group (n = 78), matched for age and occupational status. After epicutaneous testing, they found no significant difference in the occurrence of contact sensitivity, but patients with AD showed a significantly higher frequency of reactions to nickel - 28% of atopics versus 6% of controls ($p < 0.01$), especially in women – women with AD 29% versus 9% of control women ($p < 0.05$). The authors suggest that nickel sensitivity may be considered as an additional secondary atopic criterion.

Due to the presumed impact of the proportion of patients with AD on the general pattern of contact sensitization in the population, based on the results of epicutaneous patch tests, applied at the beginning MOHL - index is extended to the index MOAHLFA, as "A" initially includes rhinitis, asthma and/or AD. The abbreviation " MOAHLFA " gives CA data for M = male, O = occupational dermatitis, A = atopic dermatitis, H = hand dermatitis, L = leg dermatitis, F = facial dermatitis, A = age > 40 years, as the first "A" represents positive individuals with AD regardless of mucosal symptoms.

We compared our parameters from the MOAHLFA-index with the results of the studies of Heine et al. of 2006 and Slodownik et al. from 2022 The established differences in the data in the 3 centers are explainable, due to the characteristics common to each geographical region and the household-professional and socio-economic status of the different countries. (**table 19**)

Table 19: Comparison of MOAHLFA-index data in the three studies

MOAHLFA- index	Our research		Slodownik et al. (2022)		Heine et al. (2006)	
	Number (n=83)	%	Number (n=301)	%	Number (n =9020)	%
Men	20	24.1	124	41.3		34.7
Occupational dermatitis	13	15.7	51	16.9		21.6
Atopic dermatitis	46	55.4	60	19.9		—
Dermatitis of the hands	32	40.5	69	22.9		38.4
Dermatitis of the feet	9	10.9	29	9.6		2.6
Facial dermatitis	9	10.9	52	17.2		20.1
Age over 40 years	40	48.2	119	40		—

Considering that the index determines the trends in contact sensitization of a given population over the years, the variations in sex, age and clinical characteristics of the contact allergy is logically explainable. However, in all three studies men were less than women, the frequency of eczema on the hands was the highest, it was the lowest in patients with involvement of the lower extremities, the most common allergen was nickel. At the same time, in the Israeli study, cobalt (6.4 %), potassium dichromate (4.3%), PPD, formaldehyde are also among the top-allergens and MCI/MI (4 % each) – results very close to ours.

Results from various studies evaluating the association of ACD in patients with AD have led to the identification of common allergens, including nickel, cobalt, potassium dichromate, chromium, lanolin, neomycin, formaldehyde, sesquiterpene lactone, a mixture of composite plants, and aroma markers (e.g. Fragrance mix I, Fragrance mix II, Myroxylon pereirae and hydroxyisohexyl-3-cyclohexene carboxaldehyde).

It has been proven that metals (nickel, chromium, cobalt) are the most common allergens leading to ACD in patients with atopy. Worldwide, nickel is the most common contact allergen, which is consistent with our study data. The high number of affected patients is due to it, as nickel is released in large quantities from the surfaces of mobile devices (phones, tablets and laptops) as well as from piercings. It is this group of patients that most often complains of eczema on the hands, a fact that we also proved using χ^2 -statistics.

It is a well-known fact that the long-term use of local medications containing drugs and steroids, emollients and preservatives can increase the risk of contact hypersensitivity, due to impaired barrier function, increased transepidermal water loss and dryness of the skin, which is a prerequisite for increased antigens penetration.

Cleaning agents also expose the skin to irritants that, after repeated use, can potentially damage it. Soaps and detergents are also known to further contribute to the pathophysiological imbalance of the already damaged skin barrier by exacerbating AD.

When reporting the results of epicutaneous testing, it is necessary to take into account cross-reactivity, a phenomenon in which a patient with a positive reaction to one allergen may also show a positive result to another chemically similar allergen. Cross-reactivity can occur due to molecular mimicry of allergens with similar MCH-II class epitopes. It also occurs when the

sensitizer acts as a prohapten for a second allergen or when the substances have a common metabolite, such as formaldehyde in one of the clinical case studies we present.

Németh et al. (2022) published their results in 5790 adult patients who were epicutaneously tested with S-1000 between 2007–2021. Of 639 AD patients, 10.6% had CA to preservatives – 83.8% to methylisothiazolinone (MI), 36.8% to Kathon CG® (MSI), 16.2% to methyldibromoglutaronitrile, 11.8% to paraben, 7.4% to formaldehyde, 4.4% to para-tert-butylphenol-formaldehyde resin and 1.5% to Quaternium-15. The most common accompanying combination is MCI+MI. Most patients (32.4%) belong to the age group 21-30 years, and the skin symptoms mostly affect the limbs and face.

Our results in some directions come close to those quoted above – the patients are mostly female under the age of 40 and have ACD of the limbs and face. CA is in 4% to MCI/MI and to formaldehyde, 3% to methylisothiazolinone (MI), 2% to methyldibromoglutaronitrile, 1% to paraben and to Quaternium-15. The most common concomitant cross-reaction is MI+MCI/MI (4 times). Despite the differences in the results, the fact that preservatives (especially MI and MCI/MI) are important contact allergens in persons with AD is important for Bulgarian patients, and this fact should be taken into account when prescribing local therapy and preventing exacerbations of dermatitis.

It is a fact that topical preservatives are a growing source of ACD. They prevent the growth of bacteria, molds, yeasts and algae in many products, including cosmetics in body skin care, scalp and hair care, and in hand sanitizers. There are two main groups of preservatives: formaldehyde-based (FA) preservatives and non-formaldehyde preservatives. The relationship between the first group and contact allergy to FA is indisputable. Associated formaldehyde-releasing preservatives are quaternium-15, diazolidinyl urea, imidazolidinyl urea, DMDM hydantoin and 2-bromo-2-nitropropane-1,3-diol, and to the second and fifth allergen patch tests in the patient we described were positive. All release agents can, under appropriate conditions of concentration and product composition, release > 0.02% (200 mg/l) FA, which may lead to ACD. Whether this is the case in a particular product, however, cannot be determined from the ingredient label.

Shaughnessy et al. (2014) found a significantly higher incidence of contact-allergic reactions to formaldehyde-releasing substances in women with AD compared to non-atopic individuals (in our study, 2.2% of 272 tested individuals without atopy, compared with 2.1% of 189 people in the atopic subpopulation and 4% frequency of FA positives out of a total of 99 positive tests in AD patients). At the same time, it should be taken into account that in atopics with asthma and contact allergy to FA, auto- or "airborn" transfer of the allergen with the development of asthmatic attacks is possible. Considering the period of description of this case (during the COVID-19 pandemic, 2020), we consider this fact to be particularly important and relevant in the setting of viral pandemics causing acute respiratory syndrome.

Limitations in scientific development

- ✓ The study included individuals who actively sought help from a dermatologist, who did not always provide information about current or past illness.

- ✓ It is not clear whether AD was correctly diagnosed by prick tests and/or according to the diagnostic criteria of JM. Hanifin and G. Rajka.
- ✓ At the same time, patients with and without AD differ significantly in age.
- ✓ The study was conducted on a selected population, so the data cannot be generalized to the general population in the country.
- ✓ Furthermore, we were not able to fully control the application of epicutaneous tests in a wider range of patients.

VI. CONCLUSION

The present paper examines the clinical-epidemiological and allergological spectrum of ACD in patients with clinical and/or anamnestic data of atopy in Pleven and Ruse regions. Targeted research on contact allergy in this group of individuals is the first one performed in the country. The applied epidemiological, clinical and statistical methods make it possible to define some key points that we consider important enough both for the general population and for dermatologists who are the first to encounter the clinical manifestation of CA in patients with atopic dermatitis:

- ✚ ACD is the most common allergodermatosis, it affects up to 25% of the world's population, and the clinical picture of ACD and AD is similar.
- ✚ The localization and clinical picture of ACD in AD is subacute and chronic dermatitis, and the palms and fingers, upper limbs and face are most often affected.
- ✚ The association of ACD with AD continues to be the subject of many studies, with conflicting results. According to our studies, no higher frequency of CA was detected in patients with AD compared to individuals without atopy, a fact reported by a number of researchers in scientific periodicals.
- ✚ Nickel allergy is the most common cause of CA both for the Bulgarian population and for patients with AD, and our data correspond to those published in the scientific literature.
- ✚ In general, CA in atopics is characterized not only by increased hypersensitivity to metals, but also to preservatives, dyes, fragrances, disinfectants. It is also important to consider cross-reactivity, the most common of which are nickel*cobalt and MI/MCI*MI.
- ✚ Dermatologists' behavior is recommended to be consistent with the National Consensus on the Diagnosis and Treatment of Contact Dermatitis (2011) and National consensus on atopic dermatitis (2012) with its supplement (2016) of the BDS.

Based on the review of the scientific literature in the country, this is the first study on the frequency of contact allergy among persons with data on atopy in Bulgaria, which is why we accept our results as reliable.

VII. CONCLUSIONS AND CONTRIBUTIONS OF THE SCIENTIFIC WORK

VII. 1. Conclusions

1. Patch tested for the period 2009-2022 are 455 individuals, 49% of whom have CA. Males were 21.9% (mean age 41.10 ± 16.82 years) and females were 78.1% (mean age 38.76 ± 14.04 years). The frequency of CA is highest in the group of diverse professions (30.3%), followed by the group of office workers (25%). Most often, the pathological changes affect the palms (55.3%), the face (34.4%) and the upper limbs (33.9%). Hand eczema was the most common (38.4%), followed by atopic dermatitis (20.5%).
2. Of all patch tested for the period 2009-2022, 189 were the individuals with clinical and anamnestic data for atopy. Men are 24% (average age 38.15 ± 19.27) and women are 76% (average age 37.57 ± 15.66), people with diverse professions (41%) and unemployed (31%) prevail. Most often, the pathological changes affect the palms (43%), the upper limbs (30%) and the face (27%). Hand eczema was most common (34%), followed by lower limb dermatitis (16%) and hand and face dermatitis (14%).
3. CA in the total population of subjects was 49% with a total of 445 positive reactions. The top allergens are Nickel (28% of all reactions), Cobalt (18%), Textile dye mix (6.5%), PPD (6%), Potassium dichromate (5.5%) and Peruvian balsam (4%). CA in the atopic subpopulation was 44% with a total of 180 positive reactions. The top allergens are Nickel (25% of all reactions), Cobalt (14%), Textile dye mix (10%), Potassium dichromate (6%), PPD (5%) and Methylidibromoglutaronitrile (4%).
4. CA in the total population of patients studied was 49% with a total of 445 positive reactions and 1.9 reactions per person. The incidence of CA in the subpopulation without evidence of atopy was 53% with 265 positive reactions and 1.8 reactions per person. In the atopic subpopulation, CA was 44% with a total of 180 positive reactions and 2.2 reactions per person. No statistically significant difference was found when comparing the incidence of CA between the two subpopulations. ($p > 0.05$).
5. The frequency of CA in atopics with AD is 43%, and in those without AD 45%. There is no significant difference in the distribution of positive persons with and without AD by affected areas of the body, as well as in the frequency of allergens, the cause of CA. The presence of AD in the atopic subpopulation is not a risk factor for contact sensitivity ($p > 0.05$).
6. The studied positive patients with AD suffered from mild to moderately expressed ACD on the palms (48%), on the upper limbs (26.5%), on the torso (19.22%), on the lower limbs (20.5%) and on the face (16.9%). In the subpopulation of atopic individuals, the most common cross-reactivity was found to metals - nickel*cobalt (19%), as well as to preservatives - MCI/MI*MI (5%). In the AD subgroup, there is cross-reactivity with metals - Nickel*Cobalt (13%), Nickel*Cobalt*Potassium dichromate (11%), Nickel*Potassium dichromate (4.5%) and with MCI/MI*MI (6.5%).

VII. 2. Contributions

VII. 2.1. Original scientific contributions

1. For the first time in Bulgaria, the frequency of contact hypersensitivity was studied among individuals with clinical and anamnestic data for atopy in Pleven and Ruse regions.
2. For the first time in Bulgaria, an analysis of allergens, that cause of ACD in atopic patients, was performed

VII. 2.2. Scientific and theoretical contributions

1. For the first time in Bulgaria, the MOAHLFA index was applied to track the trends in the prevalence of contact allergy in individuals with atopic diathesis over the years based on gender-age characteristics and the type of ACD.
2. For the first time in Bulgaria, based on a study of contact allergy, the conclusion that AD is not a risk factor for contact hypersensitivity has been indicated.

VII.2.3. Scientific-practical and confirmatory contributions

1. Determination of upper extremity ACD as the most common form of contact dermatitis both in the general population and among atopics.
2. The described allergenic affinity of antigens from the groups of metals, preservatives and aromas both in the general population and among atopics.

LIST OF SCIENTIFIC PRODUCTION ON THE TOPIC OF THE DISSERTATION

I. Publication activity



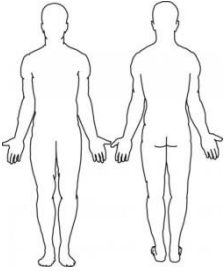
1. **Popov A**, Gospodinova K, Gincheva V, Grozeva D, Gospodinov D. Contact allergy in individuals with evidence of atopy. *Medic Plus*, 2019; 1: 68-72; ISSN 2603-5545
2. Binova M, Gincheva V, **Popov A**, Gospodinova K, Velevska Y, Yordanova I. Case of a patient with atopic dermatitis and polyallergic reaction, *GP News*, 2019; 6(229): 21 – 22. ISSN: 1311-4727 (print)
3. Grozeva D, Gospodinov D, Gincheva V, **Popov A**, Rosacea - a challenge for the dermatologist, *PRO MEDIC* 2019; 1(5): 46 – 50. ISSN: 2603-4727 (print)
4. **Popov AK**, Gincheva VH, Gospodinova KD, Gospodinov DK. Allergic contact dermatitis to disinfectants for the prevention of Covid-19 in a patient with atopy. *ermatology and venereology*, 2020, 59(4):26-29; ISSN: 0417-0792
5. **Popov AK**, Gospodinova KD, Gincheva VH, Grozeva DT, Gospodinov GK. Contact allergy in atopic patients. *Journal of Biomedical and Clinical Research*, 2023 [in press], ISSN: 1313-6917 (print) 1313-9053 (online)

II. Scientific activity

- 1. Popov A,** Haydudova H, Yordanova I, Gospodinov D. Skin sarcoidosis. Cosmetic Surgery Forum 2019, 04–07.12.2019, Nashville, Tennessee, USA. (oral presentation)
- 2. Popov A,** Gospodinova K, Gincheva V, Grozeva D, Gospodinov D. Contact allergy in persons with evidence of atopy. First summer school in dermatoallergology 2019, 12–14.07.2019, Plovdiv. (report and poster)
- 3. Popov A,** Allergic contact dermatitis of the face after the use of disinfectants during the COVID-19 pandemic. 6th Winter School of Dermatology and Venereology for Doctoral Students and Specialists, 21 – 23.01.2020, Velingrad (report)
- 4. Popov A,** Gospodinova K, Gincheva V, Yordanova I, Gospodinov D. Contact dermatitis from gel polish in a patient with atopic dermatitis. XXIX Sofia Dermatology Days "Prof. Asen Durmishev", 4-6.11.2021, Sofia (report)
- 5. Popov A.** Eczema herpeticum. EADV Course "Advanced Pediatric Dermatology". 27-28 April 2023. Budapest, Hungary

NATIONAL CAMPAIGN FOR DIAGNOSIS AND PREVENTION OF ALLERGIC SKIN DISEASES 20

Form for registering an examined patient

PASSPORT PART				
Name:		Gender: Age:		
Place of residence:				
.....				
Ethnicity: __ Bulgarian __ Turkish __ Roma __ other				
Phone: e-mail:				
CLINICAL PART				
Dermatological diagnosis:				
statute of limitations for complaints: years months				
• skin phototype (Fitzpatrick I-VI): __	rash symmetry __ YES __ NO			
• skin inflammation:	__ sharp	__ sub sharp	__ chronic	
• subjective complaints:	__ burning	__ itching	__ pain	
• rash location:	__ scalp	__ person	__ neck	
	__ lips	__ eyelids	__ truncus	
	__ palms	__ fingers	__ nails and nail shaft	
	__ palms back	__ armpits	__ forearms	
	__ ankles	__ thighs	__ lower legs	
	__ folds (<i>describe</i>)			
	__ mucous membranes (<i>describe</i>)			
			
	__ other (<i>describe</i>)			
	• Morphology of the rash	__ erythema	__ papules	__ pries
		__ vesicles	__ buli	__ pustules
	__ squams	__ crusty	__ squamo-crusty	
	__ nettles	__ EEM type	__ fissures/ragged	
	__ skin xerosis	__ others		
○ infiltrate	__ none	__ cure	__ moderate	
• Past and accompanying illnesses (<i>describe</i>)			
• Applied therapy:	__ system			
(<i>describe</i>)	__ local			
	__ physical			
• History of atopy	__ dermatitis	__ asthma	__ rhinitis/conjunctivitis	
• Family history for atopy	__ dermatitis	__ asthma	__ rhinitis/conjunctivitis	
• History of allergy	__ YES	__ NO	__ I can't answer	
○ the answer is "YES"	with patch-test	__ YES	__ NO	
	proven allergen/s			
○ allergy to	__ medicines	__ foods	__ metals __ jewellery	

- |__|cosmetics |__|plants |__| animals |__|other
- Professional history: profession work experience m/y.
 - Previous occupation (*if any*)
 - Hobbies and free time activities

ALLERGOLOGY TESTING

attached series(s) |__| **patch-test** |__| **prick-test**

Positive reactions (allergen/s)	Reporting the results			Complaints link	
	48th hour	72nd hour day	__ YES __ likely __ NO	

Relationship to work environment: |__|none |__|probable |__|certain

Additional notes:

Recommendations:

Date: |__|_|__|_| |__|_|__|_| |__|_|__|_|_|

Doctor's signature:

(.....)

APPLICATION 2

European Standard Series for Epicutaneous Testing
(cat. N: S-1000; Chemotechnique Diagnostics, Vellinge, Sweden)

no	Art.No	Name	Conc
1	P-014A	Potassium dichromate	0.5% pet
2	P-006	p-Phenylenediamine (PPD)	1.0% pet
3	Mx-01	Thiuram mix	1.0% pet
4	N-001	Neomycin sulfate	20.0% pet
5	C-017A	Cobalt(II) chloride hexahydrate	1.0% pet
6	B-004	Benzocaine	5.0% pet
7	N-002A	Nickel(II) sulfate hexahydrate	5.0% pet
8	C-015	2-Hydroxyethyl methacrylate	5.0% pet
9	C-020	Colophonium	20.0% pet
10	Mx-03C	Paraben mix	16.0% Fri
11	I-004	N-Isopropyl-N-phenyl-4-phenylenediamine (IPPD)	0.1% pet
12	W-001	Lanolin (wool alcohol)	30.0% pet
13	Mx-05A	Mercapto mix	2.0% pet
14	E-002	Epoxy resin, Bisphenol A	1.0% pet
15	B-001	Peru balsam (Myroxolon pereirar resin)	25.0% pet
16	B-024	4-tert-Butylphenolformaldehyde resin (PTBP)	1.0% pet
17	M-003A	2-Mercaptobenzothiazole (MBT)	2.0% pet
18	F-002B	Formaldehyde	2.0% aq
19	MX-07	Fragrance mix I	8.0% pet
20	MX-18	Sesquiterpene lactone mix (Lauril)	0.1% pet
21	C-007A	Quaternium-15	1.0% pet
22	M-008	2-Methoxy-6-n-pentyl-4-benzoquinone	0.01% pet
23	C-009B	Methylisothiazolinone+ M ethylchlorisothiazolinone	0.02% aq
24	B-033B	Budesonide	0.01% pet
25	T-031B	Tixocortol-21-pivalate	0.1% pet
26	D-049E	Methyldibromoglutaronitrile (MDBGN)	0.5% pet
27	MX-25	Fragrance mix II	14.0% Fri
28	L-003	Hydroxyisohexyl - 3-Cyclohexene Carboxaldehyde	5.0% pet
29	M-035B	Methylisothiazolinone	0.2% aq
30	MX-30	Textile dye mix	6.6% pet