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Multimorbidity in adult patients diagnosed with atopic dermatitis

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Informed consent: informed consent was obtained from all subjects involved in the study.

Availability of data and materials: the data presented in this study are not publicly available due to ethical restrictions but are available from the corresponding author upon request.

Abstract

Atopic dermatitis (AD) may be associated with other diseases, which could impact the patient's overall health. The aim of this study was to assess the comorbidities observed in patients diagnosed with AD and psoriasis compared to healthy patients.

Patients over 18 years old were recruited using the medical databases of dermatology clinics. Initially, 378 patients were selected via an analysis of the ICD-10 codes. Ultimately, 231 patients with atopic dermatitis were included in the study group based on their fulfillment of the Hanifin and Rajka criteria. They included 104 women and 127 men with an age range of 18-62.

In patients with AD, selected lifestyle diseases such as obesity and atherosclerosis occurred significantly less frequently than in patients without AD, including those with other dermatoses. In addition, allergic asthma and type 2 diabetes occurred significantly more often in AD patients than in those without AD ($p<0.05$).

In some AD patients, comorbidities are more prevalent, and these are often associated with allergic asthma and type 2 diabetes.

Introduction

Atopic dermatitis (AD) is a chronic, complex, inflammatory skin disease that occurs most frequently in children but also affects adults.[1] AD has been consistently associated with other atopic and allergic conditions, often via a progression known as the atopic march.[2]

One of the key problems of modern medicine is the coexistence of many diseases, and searching for mutual relationships between them is crucial to the administration of comprehensive patient treatment. This also applies to adult patients diagnosed with AD and other comorbidities.

For example, AD and psoriasis are known to co-occur with cardiovascular disease (CVD), metabolic syndrome, and autoimmune diseases, resulting in an “inflammatory skin march.” Patients with AD are likely at a significantly higher risk of obesity and metabolic disorders, which increase the risk of cardiovascular disease.[3] Some studies have shown an association between an increased body mass index (BMI) and AD in children and adults, but this requires further research. An increase in the severity of AD has been associated with an elevated risk of CVD.[4-7]

Moderate-to-severe AD has been found to coexist with an increased prevalence of hypertension compared to healthy controls. Hypertension, particularly systemic cyclosporine A, has also frequently been reported as an adverse event secondary to AD treatment.[8,9]

The same also applies to the coexistence of atopic dermatitis and bronchial asthma, whose main cause is immune imbalance.[10] Researchers have indicated that the risk of asthma is higher if AD is diagnosed earlier or if its clinical course is severe.[11,12]

In the case of diabetes, such relationships may be different. The incidence of AD has been reported to be lower among patients with diabetes mellitus (DM) compared to their counterparts without DM.[13] In one study, the risk of T2D in the AD group was significantly higher than that in the control group.[14] Eczema in adults is a predictor of cardiovascular risk,[15] and genetically predicted AD is a risk factor for both type 1 and type 2 DM.[15]

The aim of this study was to assess the co-occurrence of lifestyle diseases, including cancer, in adult patients diagnosed with AD and compare their incidence with patients with or without other dermatoses.

Materials and Methods

Study design

This research involved a retrospective observational study conducted at a single center. The study carried out a comparative analysis of the multi-morbidity profiles of patients with AD in relation to patients with other dermatoses and a control group to assess the possible distinctiveness of this group. To achieve this, medical databases containing detailed histories of the disease, with test results and treatment documentation, were used.

Study groups, control group

Patients over 18 years of age were recruited using the medical databases of dermatology clinics and the hospital's dermatology ward. Initially, 378 patients were selected via an analysis of the ICD-10 codes L-20, L-20.8, and L-20.9. Ultimately, 231 patients with atopic dermatitis were included in the study group based on their fulfillment of the Hanifin and Rajka criteria. Additionally, patients were only included if a documented dermatological examination had been conducted to confirm the diagnosis of AD; this included the attainment of at least 7 points (at least moderate form of the disease) on the EASI scale (Eczema Area and Severity Index), an increased total IgE concentration in blood serum and at least one positive allergen-specific IgE for an inhalant or food allergen in blood serum, and at least 12 months of documented treatment. Finally, 104 women and 127 men with an age range of 18-62 were included (Table 1).

Due to the hypothesis that the co-morbidity profile of patients with AD may differ from patients with other non-allergic dermatoses, the multimorbidity observed in the group of patients with AD was compared with the group of patients without an AD diagnosis (without

an ICD L-20, L-20.8, and L-20.9; without clinical features of the disease; without dedicated treatment for AD; and medical documentation excluding AD). This control group included patients with non-allergic skin diseases (eczema and allergic urticaria were excluded), with a low total IgE value and negative allergen-specific and post-acute IgE values. This group included 351 patients with an age range of 18-72 years. The control group obtained from the family doctor's clinic consisted of patients without skin diseases (n=291).

A group of patients diagnosed with AD and a group of patients with other dermatoses were compared with patients without skin disease with regard to comorbidities; the patients in this group were randomly selected from the database of family doctors from the same area and with the same gender and age restrictions. In this group, dermatological diagnoses were excluded based on the ICD-10 code, possible treatment documents, and an analysis of their medical documentation.

In the assessment of comorbidities, the possible occurrence of only chronic, well-documented diseases was evaluated: cardiovascular diseases, asthma, diabetes, COPD, osteoporosis, cancer, hyperlipidemia, hyperuricemia and other diseases. For the final analysis, these diseases were only diagnosed if they were present in at least 5% of the respondents.

In particular, all past cardiological medical interventions were analyzed based on the database of the National Health Fund, verified with regard to the correct diagnosis, and categorized, as shown in Table 2.

A cluster analysis was performed to identify the different clusters (models) of AD, either associated (ADM) or not associated (ADNM) with atopic dermatitis. The k-means method was used. In the cluster analysis, the following parameters were taken into consideration: sex, BMI, smoking, documented diagnosis of ischemic heart disease, arterial hypertension, diabetes mellitus type 2, COPD, asthma, cancers, atherosclerosis, and osteoporosis. The analysis also used documentation from hospital outpatient clinics and family doctors, in addition to ICD-10 codes, to determine the remaining diseases from the presented list using the database of the National Health Fund.

All patients gave informed consent to participate in the study and consented to sharing all data. Consent was obtained from the Bioethics Committee at the Medical University of Silesia in Katowice (KNW/0022KB1/139/09).

Results

The occurrence of lifestyle diseases

In patients with AD, selected chronic diseases such as obesity and atherosclerosis occurred significantly less frequently than in patients without AD, including those with other dermatoses. Allergic asthma and type 2 diabetes, as well as the use of oral glucocorticosteroid therapy, were more common in AD patients than in others. Detailed data are presented in Table 2.

Other chronic diseases

No significant differences were observed between groups regarding the remaining chronic diseases to be analyzed (Figure 1). In all analyzed groups, the most common disease was hyperlipidemia, followed by depression.

Profiles of cancer incidence

There were no significant statistical differences in the distribution or incidence of the most common cancers in the individual study groups. All groups were dominated by lung, colon, prostate, and breast cancer (Figure 2).

The cluster analysis of the studied groups

Five cluster models were created (Table 3). Patients with atopic dermatitis were highly concentrated in clusters 1 and 5 (Figure 3). In these two clusters, a generally lower incidence of other diseases was observed; in particular, a lower incidence of cancer and type 2 diabetes was noted. However, asthma and depression were more common in these two clusters.

The characteristics of individual clusters were as follows:

- Cluster 1: frequent occurrence: atopic dermatitis, asthma, Hashimoto, depression, diabetes type 2; rare occurrence: atherosclerosis.
- Cluster 2: frequent occurrence: cancers, hyperlipidemia; rare occurrence: dermatoses.
- Cluster 3: frequent occurrence: cancers, osteoporosis, rheumatoid diseases, dermatoses.
- Cluster 4: frequent occurrence: comorbidities, cancers, obesity, hyperlipidemia; rare occurrence: celiac diseases.
- Cluster 5: frequent occurrence: atopic dermatitis, asthma, diabetes type 2.

Discussion

The assessment of comorbidities in relation to AD is a complex process, and the presented observations must be related to the specificity of the Polish population under study. This is due to the fact that lifestyle, eating habits, environmental factors, and medical care have

a significant impact on the results, which should be treated individually. A good example is the assessment of the prevalence of diabetes in a given population and its relationship with other diseases. The obtained results indicate that type 2 diabetes occurs slightly more often in patients with AD than in other subjects. This may be explained by the fact that oral steroids are used more frequently in these patients. However, the opinions of authors with regard to this subject diverge significantly and depend largely on the type of population studied. Andresen *et al.*[16] found a higher prevalence of type 2 diabetes in patients with AD than in the general population in the US. A possible explanation for this putative relationship is the shared genetic risk loci between AD and type 2 diabetes, which results in the diabetogenic effects of chronic systemic low-grade inflammation in moderate-to-severe AD.[16] However, the small representative group used in the current study does not allow us to assess any possible correlation between the occurrence of type 2 diabetes and the severity of AD. A contrary opinion is presented by Gonzalez-Uribe *et al.*,[17] who concluded that the risk of diabetes is linked primarily to obesity and tobacco use and did not consider AD to represent an independent risk factor. In their meta-analysis, Thyssen *et al.*[18] also confirmed that there is no association between AD and unspecified but suspected type 2 diabetes. The same authors also pointed out that AD, in some populations, is associated with an increased prevalence of cardiovascular risk factors, such as obesity and smoking. However, it is unlikely that AD represents an independent and clinically relevant risk factor for cardiometabolic disease.[18,19,20] The incidence of obesity varies depending on the population studied, *e.g.*, European *vs.* American, which makes it exceedingly difficult to unify such relationships.[18] The most interesting finding of our study may be the lower prevalence of obesity and the lower risk of developing atherosclerosis observed in patients with AD. However, when comparing these data with the observations of other authors, it seems that obesity, atherosclerosis, and risk of cardiovascular disease may be independent of the occurrence of AD; in the case of our patients, this observation does not constitute evidence of the protective effect of AD but is rather a feature of this specific population.[18,19] It is also worth noting that despite the smaller group of patients with AD and cardiovascular disease included in this study, a large group of patients had the features of hyperlipidemia in the analyzed additional tests, as shown in Figure 1. This apparent discrepancy only proves the risk of cardiovascular and other diseases for all examined patients. However, some authors have confirmed that there is a higher incidence of obesity in patients with severe AD, which may result from the use of glucocorticosteroids or comorbidities in general.[17,21,22] Analyzing this finding in detail would require international prospective comparative studies.

A more expected result is the higher prevalence of asthma observed in the AD group. This is evidence of the presence of atopic comorbidities, which have been described and confirmed in many studies. Asthma was confirmed in 22% of adult patients with AD. This prevalence is comparable to that observed in the Ravenborg study, which confirmed the presence of asthma in 25.7% of AD patients, with the risk of this disease possessing an odds ratio of 3.3.[12] Epidemiological studies of adults in the Polish population (ECAP) have confirmed a similar relationship.[23] These studies have examined various atopic comorbid disease trajectories and found that it is probable that several pathways and mechanisms are at play. Some of these may be shared across all atopic/T helper (TH) 2-dominant diseases, while others could be specific to diseases.[24] Some authors have suggested that early childhood AD fosters the emergence of food allergies and respiratory allergies. This is believed to be a result of systemic sensitization, which is a consequence of compromised skin barrier function. This hypothesis, which attributes the primary cause of atopic diseases to a deficiency in epithelial barrier integrity, has been endorsed by several studies.[25,26]

The results of this study indicate that, in general, the frequency profile of many non-atopic diseases does not differ significantly among different patients. However, the data in the literature regarding this topic are ambiguous.[3,4,26] This may once again prove that AD or other dermatoses do not constitute a separate risk factor for these diseases. For example, some authors have emphasized that the incidence of cardiovascular diseases is higher in patients with dermatoses than in the general population. However, this applies to all vascular diseases, including peripheral circulation disorders and strokes.[27-29]

Some authors have observed an increase in the presence of osteoporosis in patients with atopic dermatitis, but the present study did not confirm this.[27,28] Such authors have attempted to explain this finding by referring to the lower quantity of systemic steroids used in treatment. In addition, unlike those cited, the predominant inclusion of men in this type of study may result in a lower incidence of osteoporosis (a minor component of menopausal osteoporosis).[27,28]

The occurrence of cancer also requires discussion. A similar profile of occurrence was recorded for all groups, regardless of the statistical method used, including cluster analysis. This may be in opposition to previous hypotheses suggesting that atopy protects, to some extent, against cancer.[29] On the other hand, when considering the remaining groups, it also appears that the presence of other dermatoses is not an independent factor that affects the induction of cancer. However, this conjecture must be met with caution, as individual types of dermatoses other than AD have not been analyzed separately. In this study, the prevalence of

cancer did not differ significantly from that observed by other authors.[30] On the other hand, the cluster analysis showed that models 1 and 5, comprising predominantly AD patients, had a lower incidence of comorbidities, especially cancers. It is worth emphasizing that some studies have confirmed that skin keratinocyte cancer occurs more frequently in patients with AD, but this was not confirmed in the present study.[31]

The data obtained regarding the confirmation of depression in patients with AD seem to be lacking, which may be due to a lack of prospective assessments. A higher risk of depression was only visible in the cluster analysis (cluster 1). Most authors have indicated that this group is most likely to be diagnosed with depression but emphasize that it is often underdiagnosed.[32,33]

The limitations of this study include the relatively small study groups used, its retrospective nature, and the limited number of assessed disease entities, which was caused by the focus on the ICD-10 code. On the other hand, such a restriction made the obtained data seem reliable.

Analyzing age subgroups may have enhanced the reliability of these data, but the inadequate representation of the oldest group of patients did not make this possible.

Conclusions

In some AD patients, comorbidities associated with allergic asthma and type 2 diabetes are more prevalent. However, the prevalence of other chronic diseases, such as osteoporosis, hyperlipidemia, and allergic rhinitis, has also been noted. For this reason, patients with AD particularly require comprehensive medical care.

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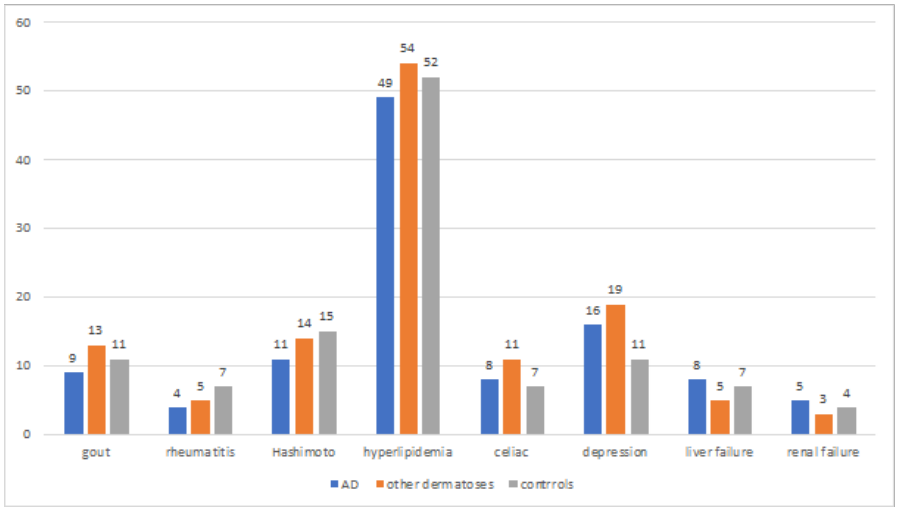
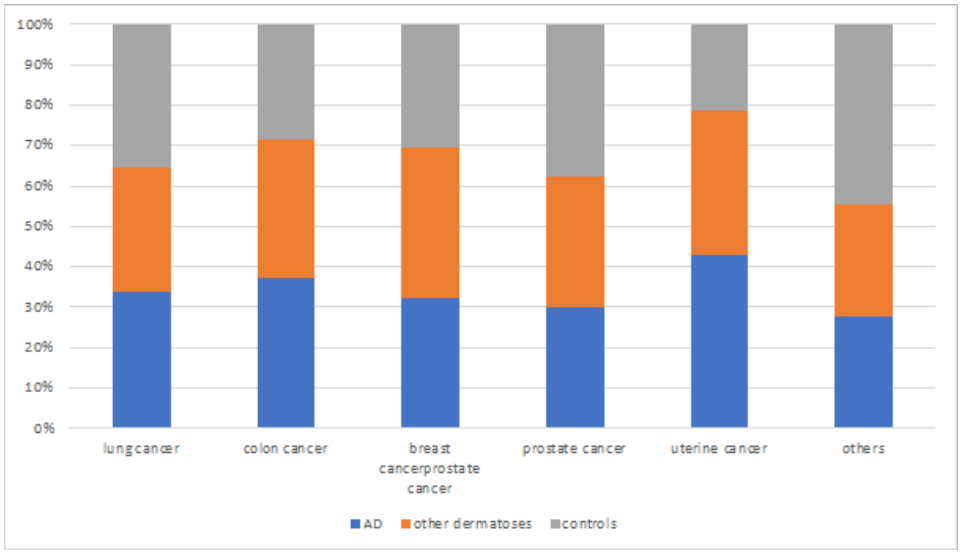
Figure 1. Percentage of selected chronic diseases in the study groups.



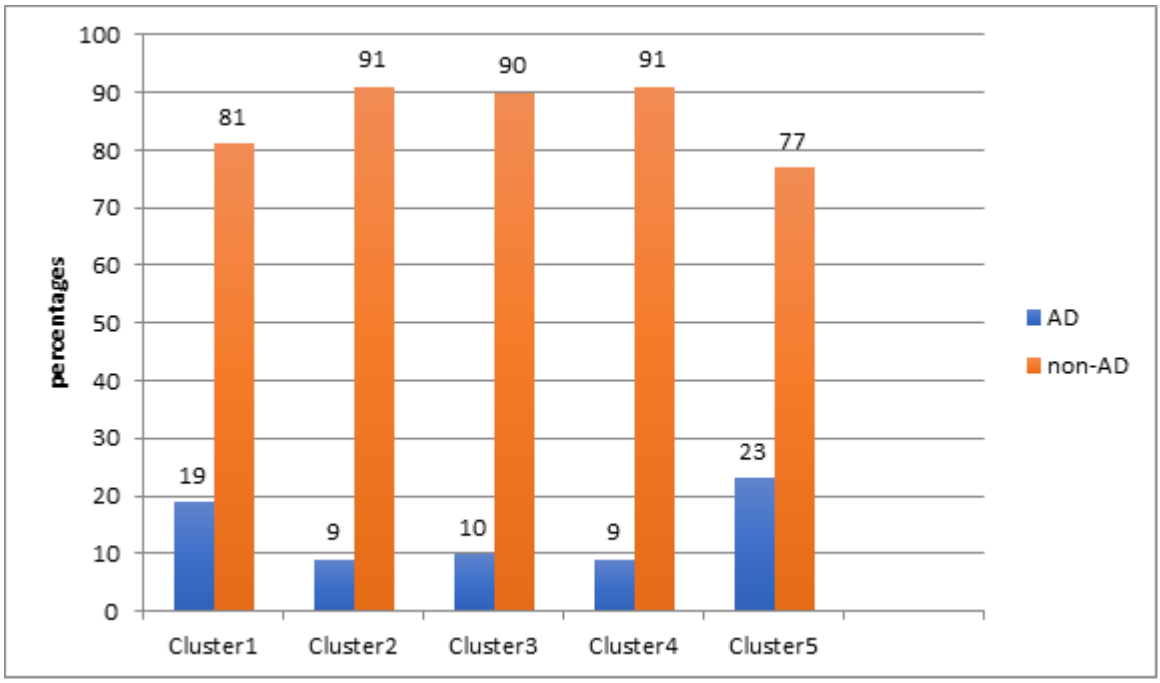
AD, atopic dermatitis; other dermatoses: chronic urticaria, psoriasis, cutaneous vasculitis, lupus, scleroderma. There were no significant differences between the study groups for each disease analyzed using the Kruskal–Willis ANOVA test ($p>0.05$).

Figure 2. Percentage distribution of types of cancer in the studied groups.



100% is the sum of all diagnosed cancers in the study group; AD, atopic dermatitis; other dermatoses: chronic urticaria, psoriasis, cutaneous vasculitis, lupus, scleroderma. There were no significant differences between the cancer profiles of the groups (Kruskal–Willis ANOVA test $p>0.05$).

Figure 3. Proportion of patients with AD (atopic dermatitis) or without (non-AD) for each cluster (1-5).



Percentage dominance of AD patients in clusters 1 and 5 ($p < 0.05$) compared to the others.

Table 1. Characteristics of the study groups.

variable	AD n=231	Other dermatoses* n=351	Controls n=291
Mean age (range) in years	38.4 (18-62)	41.2 (18-71)	35.1 (18-66)
Women %	45.2% (104)**	67% (235)	65.2% (190)
BMI (± SD)	26.5 ±2.6	24.7±3.6	25.9±2.1
Smokers %	19.9% (46)	20.1% (70.6)	22.6% (66)
Urban area %	78.6% (181)^	52.1% (182)	54.3% (158)
The mean duration of the dermatoses in years	24.1[#]	7.1	-
Any hospitalizations per year	0.45	0.55	0.47
Higher education %	34.1% (79)[##]	20.1% (71)	22.9% (66)
The same dermatosis in the family	16.2% (37)	13.9% (49)	-
Any immunosuppressive therapy	33.1% (76)	29.8% (105)	-
Any biological therapy	9.2% (21)	15.7% 55)[$]	-

AD, atopic dermatitis; *chronic urticaria, psoriasis, cutaneous vasculitis, lupus, and scleroderma; parametric variables were compared using the ANOVA test, and non-parametric variables were compared using the Kruskal–Wallis ANOVA test (significance at $p<0.05$); **male dominance in the AD group compared to the other groups ($p<0.05$); ^AD patients more often live in urban areas compared to the other groups ($p<0.05$); [#]the duration of AD is significantly longer than that of other analyzed dermatoses ($p<0.05$); [##]AD patients have a higher education level than those in the other groups ($p<0.05$); [$]patients with other dermatoses are more often treated with biological therapy (especially those with diagnosed psoriasis, $p<0.05$).

Table 2. The occurrence of the most common chronic diseases in the studied groups.

Diseases	AD n=231	Other dermatoses* n=351	Controls n=291
Ischemic heart disease	8 (3.5%)	15 (4.3%)	11 (3.8%)
Arterial hypertension	76 (32.9%)	127 (36.2%)	102 (35.1%)
Type 2 diabetes	11 (4.8%)**	8 (2.3%)	10 (3.4%)
COPD	29 (12.5%)	48 (13.6%)	39 (13.4%)
Asthma	51 (22%)***	24 (6.8%)	19 (6.5%)
Cancers	38 (16.5%)	61 (17.3%)	82 (28.2%)
Atherosclerosis	8 (3.5%)^	27 (7.8%)	21 (7.2%)
Osteoporosis	12 (5.2%)	31 (8.8%)^^	19 (6.5%)
Obesity (BMI³30)	31 (13.4%)$	68 (19.3%)$	69 (23.7%)$
Oral GCS	113 (48.9)#	101 (28.8)#	32 (10.9)#

AD, atopic dermatitis; oral GCS, oral glucocorticosteroid therapy (minimum 5-day treatment course) ; *chronic urticaria, psoriasis, cutaneous vasculitis, lupus, scleroderma; all non-parametric variables were compared using the Kruskal–Wallis ANOVA test (significance at $p<0.05$); **type 2 diabetes moderately predominates in the AD group compared to the other groups ($p<0.05$); ***AD patients more often have asthma compared to the other groups ($p<0.05$); ^AD patients are less likely to be diagnosed with atherosclerosis than those in the other groups ($p<0.05$); ^^osteoporosis occurs more often in patients with other dermatoses ($p<0.05$); $all studied groups differed significantly in the prevalence of obesity: lowest prevalence in the AD group, highest prevalence in the control group ($p<0.05$); #all studied groups differed significantly in the prevalence of using oral glucocorticosteroids: highest prevalence in AD group, lowest prevalence in control group ($p<0.05$).

Table 3. Cluster analysis of the entire study population (n=813).

N=813	**Cluster 1 N=178**	**Cluster 2 N=243**	**Cluster 3 N=115**	**Cluster 4 N=159**	**Cluster 5 N=118**
Comorbidities	13.8	18.9	31.2	49.4	8.9
Ischemic heart disease	11.2	10.2	13.8	7.8	4.3
Arterial hypertension	18.5	16.3	11.3	17.4	10.9
Type 2 diabetes	10.8	3.5	2.1	5.5	11.8
COPD	3.8	11.2	2.8	2.2	4.5
Asthma	11.4	3.2	1.9	1.2	16.5
Cancers	7.8	13.8	15.9	11.2	5.3
Atherosclerosis	3.2	8.11	9.3	5.1	4.9
Osteoporosis	5.5	4.7	9.9	5.7	5.2
Obesity (BMI³30)	9.1	10.9	10.1	19.3	12.8
Gout	8.1	7.4	5.9	10.2	11.2
Rheumatoid	5.8	1.9	11.5	4.3	7.3
Hashimoto	14.5	9.8	11.2	10.4	10.3
Hyperlipidemia	25.9	28.1	22.7	28.2	19.1
Celiac	1.8	2.4	3.1	0.9	4.5
Depression	12.3	7.8	4.1	6.5	7.4
Liver failure	2.1	1.8	5.3	4.9	6.1
Renal failure	0.9	1.1	3.2	0.5	0.9
No dermatoses	12.7	30.1	9.5	24.6	23.1

^the proportion of variables in each cluster is shown as a percentage.