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Clinical correlates of lifetime and current comorbidity patterns in autoimmune and inflammatory diseases

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ABSTRACT

Background: Autoimmune and inflammatory diseases (AIDs) are a heterogeneous group of disorders with diverse etiopathogenic mechanisms. This study explores the potential utility of family history, together with present and past comorbidities, in identifying distinct etiopathogenic subgroups. This approach may facilitate more accurate diagnosis, prognosis and personalized therapy.

Methods: We performed a multiple correspondence analysis on patients' comorbidities, followed by hierarchical principal component clustering of clinical data from 48 healthy volunteers and 327 patients with at least one of 19 selected AIDs included in the TRANSIMMUNOM cross-sectional study.

Results: We identified three distinct clusters characterized by: 1) the absence of comorbidities, 2) polyautoimmunity, and 3) polyinflammation. These clusters were further distinguished by specific comorbidities and biological parameters. Autoantibodies, allergies, and viral infections characterized the polyautoimmunity cluster, while older age, BMI, depression, cancer, hypertension, periodontal disease, and dyslipidemia characterized the polyinflammation cluster. Rheumatoid arthritis patients were distributed across all three clusters. They had higher DAS28 and prevalence of extra-articular manifestations when belonging to the polyinflammation and polyautoimmunity clusters, and also lower ACPA and RF seropositivity and higher pain scores within the polyinflammation cluster. We developed a model allowing to classify AID patients into comorbidity clusters.

Conclusions: In this study, we have uncovered three distinct comorbidity profiles among AID patients. These profiles suggest the presence of distinct etiopathogenic mechanisms underlying these subgroups. Validation, longitudinal stability assessment, and exploration of their impact on therapy efficacy are needed for a comprehensive understanding of their potential role in personalized medicine.

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1. Introduction

Autoimmune and inflammatory diseases (AIDs) affect 10 % of the population in Western civilization countries [1] and constitute a high socio-economic burden as a cause of disability in young persons. The cause of these diseases is incompletely understood and a complex interaction of genetic and environmental factors is thought to play a role [2]. Different autoimmune diseases may occur in members of a nuclear family [3–6], and often more than one autoimmune disease coexist in the same patient [1,6–8] confirming a role for both genes and environmental factors and suggesting etiopathogenic mechanisms common to a subset of these diseases. Although studies have suggested an impact of polyautoimmunity on disease burden [9–11], familial aggregation and disease co-occurrence have not been taken into account in the investigation of inflammatory diseases as thoroughly as they have been in autoimmune diseases.

In rare monogenic AIDs, either cells of the innate or adaptive immune system are disturbed leading to a clear-cut distinction between autoinflammation and autoimmunity, but this distinction is not always apparent for the majority of AIDs with a complex polygenic origin. To take into account the variable contribution of both autoimmune and autoinflammatory mechanisms to a variety of AIDs in 2006 an immunological disease continuum model was proposed [12], but the use of biomarkers to aid in the classification of the patients' diseases within this continuum is only at its infancy [13]. The large heterogeneity in symptoms, as well as in severity and response to therapy observed in diseases such as rheumatoid arthritis (RA) suggests that patients with the same disease might be classified differently within this continuum, and a classification tool would improve the precision of their diagnosis, prognosis and allow personalized medicine. For this purpose, the “Translational phenomics in immunopathology and inflammation: from cross phenotyping to biotherapy” clinical protocol (TRANSIMMUNOM, NCT02466217) was designed to re-examine the nosology of a selection of AIDs using a multiparametric systems immunology experimental design [14]. Until present attempts to stratify autoimmune disease patients into subgroups through unsupervised clustering strategies have mostly concentrated on one single autoimmune disease and used either symptoms [15], autoantibodies [16], clinical data [17] or multiple omic datasets [18].

In addition, non-immunological comorbidities such as cardiovascular disease are known to be associated with autoimmune diseases [19] and to affect their morbidity and mortality. Comorbidities may be associated to AID because of a shared aetiology, as a consequence of long-standing inflammation or they may develop secondary to a treatment adverse effect, and together with medical history they might give hints on AID etiopathogenesis. Up to date comorbidity and multimorbidity studies on AIDs have focused on the impact of multimorbidity on global health, quality of life [20–22] and therapy efficacy [23,24], but these studies have overlooked the possibility that these outcomes might reflect patient subgroups with distinct etiopathogeneses. In the present study, we applied an unsupervised analysis to the TRANSIMMUNOM study to explore the stratification of AIDs in disease subgroups using their comorbidities, medical history and familial history of disease, which for ease of description from now on we will commonly refer to as comorbidities.

2. Patients and methods

2.1. Study population

Here we analyze data from patients included in a multicentre observational study (TRANSIMMUNOM, NCT02466217) in which diseases were chosen to represent the AID continuum [12]. Selected diseases were: Familial Mediterranean Fever (FMF), ulcerative colitis (UC), Crohn's disease (CD), knee osteoarthritis (OA), type 2 diabetes (T2D), axial spondyloarthritis (SpA), myositis (in particular, polymyositis,

dermatomyositis, inclusion-body myositis, necrotising and antisynthetase-related myositis), ANCA-related vasculitis (Churg–Strauss disease and granulomatosis with polyangiitis (GPA)), non-ANCA-related vasculitis (Behçet's disease, giant cell arteritis (GCA) and Takayasu's disease), Rheumatoid arthritis (RA), type 1 diabetes (T1D), latent autoimmune diabetes of the adult (LADA), Anti-phospholipid Syndrome (APLS), Systemic Lupus Erythematosus (SLE), Mixed Connective Tissue Disease (MCTD) and unclassified AIDs. The patients recruited in this study are affected by at least one of the selected diseases. If a patient had multiple diseases in the study, the main diagnosis was not necessarily the index disease (the first AID in order of appearance), but the disease with the largest clinical component in terms of severity and morbidity. Inclusion criteria and classification in cohorts are detailed in the supplementary methods.

In this analysis we described the first 328 patients and 48 healthy volunteers recruited in several departments of the Pitié-Salpêtrière Hospital, the Saint-Antoine Hospital and the Tenon Hospital in Paris, France, between July 29, 2015 and March 01, 2019. In a 1-day visit, we collected all samples and all clinical and biological data (hematology, coagulation, biochemistry and urine analysis). A great effort was made by all the clinicians involved in the study to code the clinical data in a harmonious manner [25].

The TRANSIMMUNOM study was done in accordance with the Declaration of Helsinki and good clinical practice and approved by the ethics committee (CPP-IdFVI approval number 48-15). Written informed consent was obtained from all participants before enrolment in the study.

2.2. Study variables

The global workflow of variable curation, selection and analysis for the TRANSIMMUNOM study is depicted in [Supplementary Fig. 1](#).

Clinical data of the TRANSIMMUNOM study comprising demographics, personal and family medical and surgical history, concomitant medications, ECG and vital signs, Quality of Life (QoL) questionnaires, concomitant treatments, routine biology and disease-specific assessments were collected into an electronic Case Report Form (eCRF) [25]. Presence of comorbidities was assessed through clinical interview of the patient and through a detailed review of the patient's medical charts by a physician. If a comorbidity was not recorded it was considered absent. Familial history of autoimmunity or inflammatory disease was defined as having a first degree relative with any autoimmune or inflammatory disease, including the main diagnosis of the patient. A large set of medical history and treatment variables had been pre-defined [25] but additional items were collected as free text and were subsequently standardized using the SNOMED CT international terminology [26] for the medical terms including diseases, procedures, symptoms and findings ([Supplementary Tables 1 and 2](#)) and the MeSH Supplementary Chemical Records for the drugs ([Supplementary Table 3](#)). New customized disease or treatment group variables were created from standardized free text terms ([Supplementary Tables 1 and 3](#)). All the free text terms corresponding to AIDs, including mixed pattern diseases, were classified as predominantly autoimmune or inflammatory ([Supplementary Table 2](#)) according to the AID continuum [12] or according to the literature if the disease had not been included in the AID continuum. The number of autoimmune or of inflammatory diseases (classified according to [Supplementary Table 2](#)) co-occurring in a patient were counted including the main diagnosis for which the patient was recruited in the study.

Autoantibody serology and calculations to derive the Rheumatic Disease Comorbidity Index (RDCI), the Framingham cardiovascular disease risk score, QoL and AID continuum score are described in supplementary methods.

2.3. Clustering

The data analysis strategy for the TRANSIMMUNOM study, including unsupervised analyses, was previously described [14]. All the statistical analyses were performed using R version 4.2.1 and additional R packages (FactoMineR 2.6, factoextra 1.0.7, ca 0.71.1, nnet 7.3–17, FSA 0.9.4, FDRestimation 1.0.1, polycor 0.8–1, correlation 0.8.3, glmnet 4.1–7, cvms 1.5.0).

In order to search for clusters of patients with similar comorbidity patterns we performed a multiple correspondence analysis (MCA) as a multivariate dimension reduction on the comorbidities followed by a hierarchical clustering on the first 12 dimensions to regroup the patients into clusters, comprising 71.5 % of the variance (Supplementary Fig. 1). Greenacre adjustment was performed on the percentage of variance explained and the number of dimensions to be used for the hierarchical clustering was selected for having Greenacre adjusted eigenvalues higher than zero [27]. Euclidean distance and Ward agglomerative method were used for the clustering. Personal and family medical history variables were selected to be used for the MCA if their prevalence in the study was higher than 5 % (Supplementary Fig. 1, Supplementary Tables 4 and 5). In addition to the most prevalent comorbidities, the number of autoimmune and of inflammatory comorbidities were included in the MCA as qualitative variables after regrouping the categories with the lowest number of subjects to obtain at least 10 patients in each category (number of autoimmune diseases: 0, 1, 2, 3–6; number of inflammatory diseases: 0, 1, 2–5). Finally, 30 variables with 63 different categories were included in the analysis. The comorbidity variables excluded from the analysis are listed in Supplementary Table 6. The number of clusters was selected through the elbow method on inertia gain.

2.4. Association testing

Patient characteristics were described by frequencies, mean and standard deviation. The number of autoimmune and inflammatory diseases and the number of autoantibodies were described by median and interquartile range (IQR). Variables with more than 5 % missing data were excluded from analyses (Supplementary Fig. 1, Supplementary Table 7), else analyses were performed on complete cases. Association tests with main diagnoses were only performed on 8 pathologies with at least 10 subjects included. The association between the number of autoantibodies and number of AIDs (the latter as qualitative variables) was tested through a Kruskal-Wallis test. Similarly, the association between the mean AID rank score or the number of autoimmune or inflammatory diseases or of autoantibodies (as quantitative variables) and the main diagnosis was tested through a Kruskal-Wallis test. P-values for pairwise comparisons (Dunn test) were corrected through the Benjamini-Hochberg method. The association between the number of autoimmune and of inflammatory diseases, both considered as quantitative variables, was tested through Spearman correlation. Enrichment of main diagnoses in the clusters was tested through a chi-square test comparing to a homogeneous distribution of 1/3 per cluster; only main pathologies with at least 15 subjects were tested. All the comparisons of qualitative variables between the comorbidity clusters were done through Fisher's exact tests and comparisons of quantitative variables through Kruskal-Wallis tests (Supplementary Fig. 1). A correction for multiple tests was done through the Benjamini-Hochberg method and tests were considered significant if they had a False Discovery Rate (FDR) lower than 5 %.

Pairwise comparisons between clusters were done only for variables passing the 5 % FDR at the global comparison among all the clusters through Benjamini-Hochberg-corrected Dunn's test (quantitative variables) or univariate logistic regression models (qualitative variables). Polychoric correlation was performed between all the comorbidities significantly associated to the clusters and a 5 % FDR was applied. Association of the clusters with age and number of autoimmune and of inflammatory diseases (the two latter considered as qualitative

variables) or with age and a comorbidity variable was assessed through multivariate polytomous logistic regression models. For AIDs present in the 3 clusters with at least 10 subjects per cluster we considered all the patients presenting the disease as main or secondary diagnosis (Supplementary Table 8) and we tested the association of the clinical characteristics, RDCI and autoantibodies with the clusters for each of the diseases responding to the criteria (RA, OA, T2D and SpA). Association of cardiovascular disease with clusters adjusted on Framingham score was tested through a multivariate logistic regression model. Comorbidity cluster classification model construction is described in supplementary methods.

3. Results

3.1. Number of immunological diseases and autoantibodies in TRANSIMMUNOM patients

The initial study population comprised 376 subjects. One patient initially enrolled in the T1D cohort was kept in the analysis but reclassified as LADA, while another T1D patient suffered from a particular genetic form of diabetes and was excluded from the analysis. The eligible population thus comprised 375 subjects, including 48 healthy volunteers, with a mean age of 44.7 years; 59.2 % of them were female and 69.9 % were born in France (Table 1). The mean disease duration for the patients was 5.10 years and their mean age at diagnosis was 40.5 years (Table 1). The most frequent treatments were conventional synthetic DMARDs (csDMARDs) for RA, SLE and IBD, oral glucocorticoids for vasculitis, NSAIDs for SpA, paracetamol for OA, insulin for T1D and oral antidiabetics for T2D (Supplementary Table 9). The number of autoimmune diseases per patient ranged between 0 and 6 with a median of 1, whereas for inflammatory diseases the range was 0–5 with a median of 1 (Supplementary Figs. 4A and B). 13.5 % of the patients had more than one autoimmune disease and 15.3 % more than one inflammatory disease.

Both patients and healthy volunteers had autoantibodies (Supplementary Fig. 4C). There was a positive association between the number of autoantibodies and the number of autoimmune diagnoses ($p < 10^{-15}$, Fig. 1A) and a negative association between the number of autoantibodies and the number of inflammatory diagnoses ($p < 10^{-15}$, Fig. 1A). Of note, 31.2 % of healthy controls displayed at least one autoantibody compared to 53.8%–98.4 % of patients (Supplementary Fig. 4D) and the Odds Ratio of autoantibody positivity compared to healthy was significantly higher than 1 for all the autoimmune main diagnoses, which was expected since some autoantibodies have a diagnostic value, but surprisingly this was the case also for most inflammatory main diagnoses except for T2D (Supplementary Fig. 4E).

The number of autoimmune diseases was inversely correlated to the number of inflammatory diseases (Spearman rho [95 % CI], -0.65 [$-0.71, -0.58$], $p < 10^{-15}$). Patients with an inflammatory main diagnosis had a median of 0 associated autoimmune diseases (Fig. 1B and Supplementary Table 10), while those with an autoimmune main diagnosis had a median of 0 associated inflammatory diseases (Fig. 1B). To evaluate the main type of immunological dysfunctions carried by patients, we calculated a mean AID rank score using the rank order of the diseases on the autoimmune to autoinflammatory continuum described by McGonagle and McDermott [12]. The score was the mean of scores for each of the primary and secondary AID diagnoses of a given patient. While this would not change the classification of patients with one single diagnosis, it might help to improve the classification of patients with multiple diagnoses. For RA, which has been considered an autoimmune disease in the AID continuum, 6.4 % of patients had a mixed phenotype, while 12.8 % were dominantly inflammatory and 80.8 % dominantly autoimmune (Fig. 1C and Supplementary Table 11). Two other interesting cases were the mixed diseases SpA and Behçet: although the majority had a mixed phenotype according to the mean AID rank score, 5 % were classified as autoimmune and more than 20 %

Table 1
Demographic characteristics of the TRANSIMMUNOM study.

	Healthy volunteer (N = 48)	Rheumatoid arthritis (N = 78)	Diabetes mellitus type 1 (N = 61)	Ankylosing spondylitis (N = 37)	Vasculitis (N = 33)	Osteo-arthritits (N = 32)	Diabetes mellitus type 2 (N = 26)	Other AID (N = 18)	Systemic lupus erythematosus (N = 17)	IBD (N = 15)	Unclassified AID (N = 10)	Overall (N = 375)
Age (years)												
Mean (SD)	38.9 (12.8)	49.6 (13.8)	34.6 (11.3)	39.8 (12.5)	44.6 (13.9)	67.0 (8.53)	51.3 (13.1)	46.1 (13.5)	42.8 (9.04)	30.5 (12.9)	47.4 (17.2)	44.7 (15.4)
Median [Min, Max]	37.5 [19.0, 68.0]	51.0 [20.0, 76.0]	32.0 [19.0, 73.0]	40.0 [20.0, 67.0]	43.0 [18.0, 81.0]	69.0 [40.0, 83.0]	50.0 [28.0, 74.0]	46.5 [23.0, 67.0]	42.0 [28.0, 56.0]	26.0 [19.0, 71.0]	52.0 [22.0, 72.0]	44.0 [18.0, 83.0]
Sex												
Female	25 (52.1 %)	62 (79.5 %)	26 (42.6 %)	19 (51.4 %)	16 (48.5 %)	20 (62.5 %)	11 (42.3 %)	12 (66.7 %)	16 (94.1 %)	6 (40.0 %)	9 (90.0 %)	222 (59.2 %)
Male	23 (47.9 %)	16 (20.5 %)	35 (57.4 %)	18 (48.6 %)	17 (51.5 %)	12 (37.5 %)	15 (57.7 %)	6 (33.3 %)	1 (5.9 %)	9 (60.0 %)	1 (10.0 %)	153 (40.8 %)
Region of birth												
France	45 (93.8 %)	57 (73.1 %)	45 (73.8 %)	25 (67.6 %)	18 (54.5 %)	20 (62.5 %)	14 (53.8 %)	12 (66.7 %)	10 (58.8 %)	12 (80.0 %)	4 (40.0 %)	262 (69.9 %)
North Africa	1 (2.1 %)	10 (12.8 %)	8 (13.1 %)	6 (16.2 %)	9 (27.3 %)	3 (9.4 %)	4 (15.4 %)	2 (11.1 %)	1 (5.9 %)	0 (0 %)	3 (30.0 %)	47 (12.5 %)
Other European country	0 (0 %)	2 (2.6 %)	1 (1.6 %)	1 (2.7 %)	4 (12.1 %)	2 (6.3 %)	1 (3.8 %)	0 (0 %)	3 (17.6 %)	3 (20.0 %)	0 (0 %)	17 (4.5 %)
Africa	0 (0 %)	2 (2.6 %)	1 (1.6 %)	1 (2.7 %)	2 (6.1 %)	2 (6.3 %)	4 (15.4 %)	1 (5.6 %)	1 (5.9 %)	0 (0 %)	0 (0 %)	14 (3.7 %)
Other region	2 (4.2 %)	6 (7.7 %)	6 (9.8 %)	3 (8.1 %)	0 (0 %)	4 (12.5 %)	3 (11.5 %)	3 (16.7 %)	2 (11.8 %)	0 (0 %)	2 (20.0 %)	31 (8.3 %)
Missing	0 (0 %)	1 (1.3 %)	0 (0 %)	1 (2.7 %)	0 (0 %)	1 (3.1 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	1 (10.0 %)	4 (1.1 %)
Disease duration (years)												
Mean (SD)	NA (NA)	5.50 (7.93)	3.10 (2.20)	5.24 (7.51)	2.53 (2.36)	8.09 (8.52)	2.54 (2.97)	12.3 (17.2)	7.06 (7.06)	3.67 (2.32)	4.80 (6.78)	5.10 (7.47)
Median [Min, Max]	NA [NA, NA]	3.50 [0, 48.0]	3.00 [0, 9.00]	3.00 [0, 38.0]	1.50 [0, 9.00]	5.00 [0, 33.0]	1.00 [0, 9.00]	2.50 [0, 63.0]	4.00 [0, 24.0]	3.00 [0, 8.00]	1.50 [0, 21.0]	3.00 [0, 63.0]
Missing	48 (100 %)	0 (0 %)	0 (0 %)	0 (0 %)	1 (3.0 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	49 (13.1 %)
Age at diagnosis (years)												
Mean (SD)	NA (NA)	44.1 (14.7)	31.5 (11.1)	34.5 (13.1)	42.5 (13.7)	58.9 (14.0)	48.9 (14.3)	33.7 (21.5)	35.6 (12.8)	26.7 (12.4)	42.7 (15.5)	40.5 (16.3)
Median [Min, Max]	NA [NA, NA]	45.5 [4.00, 72.0]	30.0 [17.0, 70.0]	30.0 [18.0, 64.0]	40.5 [18.0, 75.0]	62.0 [20.0, 77.0]	48.5 [23.0, 74.0]	40.5 [3.00, 61.0]	37.0 [16.0, 53.0]	23.0 [11.0, 65.0]	50.5 [17.0, 62.0]	39.0 [3.00, 77.0]
Missing	48 (100 %)	0 (0 %)	0 (0 %)	0 (0 %)	1 (3.0 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	49 (13.1 %)

AID- Autoimmune and Inflammatory Disease. IBD- Inflammatory Bowel Disease (Crohn's and ulcerative colitis). Vasculitis regroups Behçet's disease, Takayasu's disease, Granulomatosis with polyangiitis, giant cell arteritis, Churg-Strauss disease. Other AID regroups Antiphospholipid syndrome, Familial Mediterranean Fever, Latent Autoimmune Diabetes of the Adult, Mixed Connective Tissue Disease and Myositis.

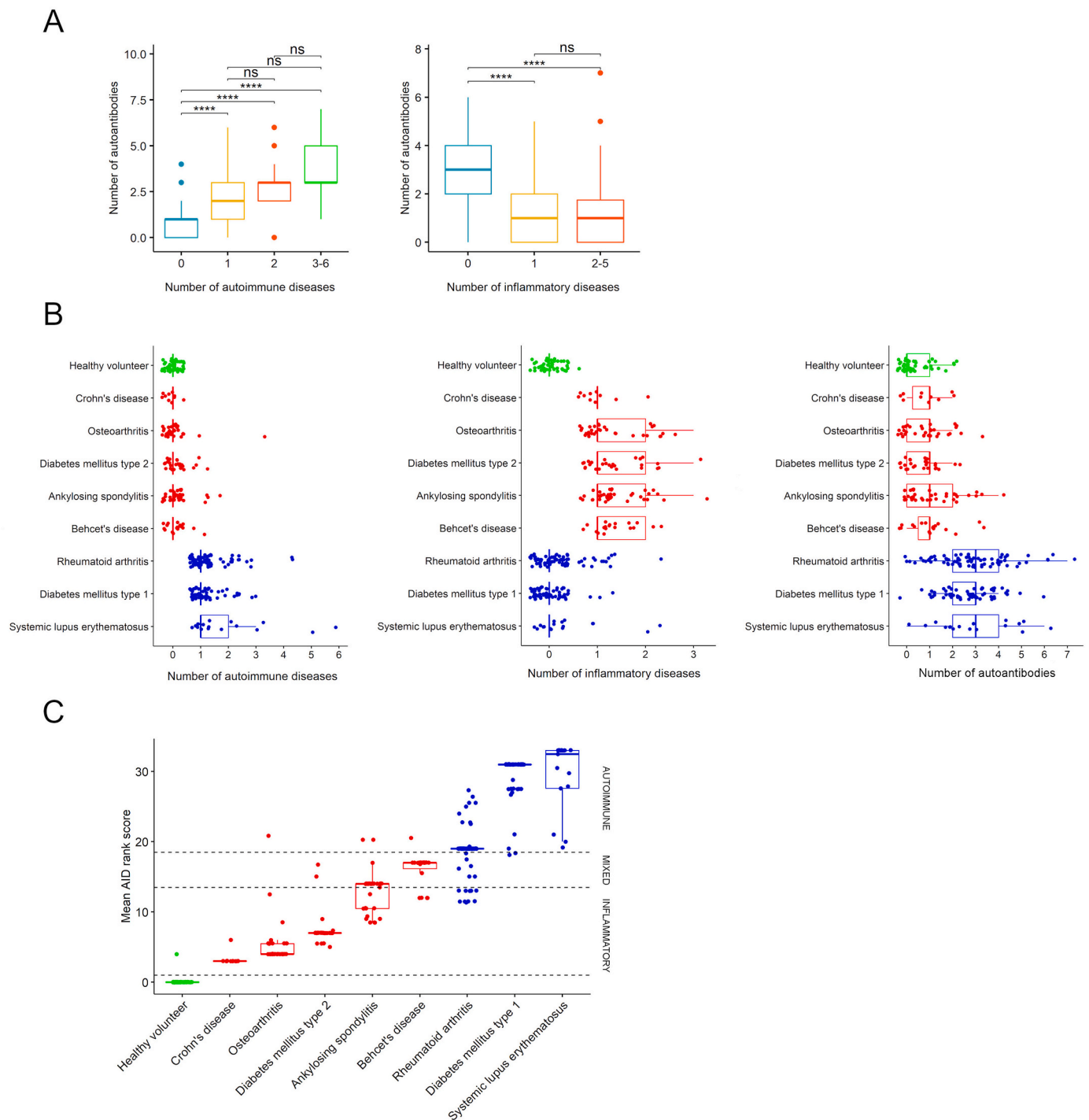


Fig. 1. Number of immunological diseases and autoantibodies in the TRANSIMMUNOM study. (A) Median and IQR of number of autoantibodies (quantitative) by (left) number of autoimmune diseases (qualitative in 4 categories) or (right) number of inflammatory diseases (qualitative in 3 categories). Healthy volunteers were excluded from these analyses. The asterisks indicate the level of significance (**** Benjamini-Hochberg –adjusted Wilcoxon, $P_{adj} < 10^{-6}$; NS, not significant). (B) Median and IQR values of the number of (left) autoimmune diseases, (center) inflammatory diseases and (right) autoantibodies by main diagnosis. Each point represents a patient and for visualization purposes the jitter function has been applied. Colors represent disease type (green: healthy volunteers; red: inflammatory diseases; blue: autoimmune diseases). Detailed p-values of all the pairwise comparisons are described in [Supplementary Table 10](#). (C) Median and IQR of the mean AID rank score by main diagnosis calculated on all the coexisting immunological diseases in each patient. Horizontal dashed lines indicate the thresholds for being classified by the AID rank score as inflammatory, mixed or autoimmune respectively. AID- Autoimmune and Inflammatory Disease.

as inflammatory (Fig. 1C and [Supplementary Table 11](#)).

3.2. Clustering reveals different comorbidity patterns in dominantly autoimmune and dominantly inflammatory diseases

The mean AID rank score is biased by the AID continuum rank as a priori. To strive for an improved classification of immunological disease

patient subgroups, an unsupervised analysis was performed using the most frequent family history of disease and non-immunological comorbidities, in addition to the number of autoimmune and inflammatory diagnoses for each patient. Three clusters were identified (Fig. 2A and B). Cluster 1 (n = 223) comprised both healthy volunteers and patients with autoimmune or inflammatory main diagnoses; cluster 2 (n = 73) and cluster 3 (n = 79) contained predominantly patients with autoimmune main diagnoses or inflammatory main diagnoses, respectively (Fig. 2C).

Of note, except for OA and T2D which were significantly enriched in cluster 3 (p = 0.002 and p = 0.003 respectively, Fig. 2D), all the main disease diagnoses were spread within the three clusters. Subjects in cluster 3 were older (p < 0.001) and had a higher BMI reaching overweight (p < 0.001) compared to cluster 1 and 2 (Supplementary Table 12), while both cluster 2 and 3 had a higher prevalence of women compared to cluster 1 (p = 0.057, Supplementary Table 12). There were no significant differences in disease duration between the clusters (p = 0.26, Supplementary Table 12). A projection of the number of autoimmune and inflammatory diseases on the first two axes of the MCA revealed that the number of inflammatory diseases increased along the first dimension while the number of autoimmune diseases increased along the second one (Supplementary Fig. 5A). A projection of the variables contributing most to the first two axes showed that cluster 1 was characterized by an absence of comorbidities, cluster 2 by atopy, virus infections and a high number of autoimmune diseases, and cluster 3 by hypertension, dyslipidaemia, familial history of inflammatory

disease and a high number of inflammatory diseases (Fig. 3A).

Polychoric correlation confirmed that the comorbidities characterising the clusters were significantly correlated with each other (Fig. 3B). A closer look at comorbidities associated with the clusters further revealed an increased prevalence of allergy and fractures in cluster 2 compared to cluster 1 and 3 (Fig. 3C and Supplementary Table 13); an increased prevalence of menopause, depression, periodontal disease, gastrointestinal disease, cancer, joint disease, vision disorders and appendectomy in cluster 3 compared to cluster 1 and 2 (Fig. 3C and Supplementary Table 13); an increased prevalence of atopy, anxiety, cardiovascular disease, benign neoplasm, surgical conditions, endocrine disorders, hepatobiliary disorders, respiratory tract disorders and familial history of cardiovascular disease in both cluster 2 and 3 compared to cluster 1 (Fig. 3C and Supplementary Table 13). To verify whether the higher number of inflammatory diseases and other comorbidities in cluster 3 could be completely explained by a confusion bias due to the older age a multivariate polytomous logistic regression of clusters explained by age and number of autoimmune and inflammatory diseases was performed. Both age and number of inflammatory diseases were independently associated with cluster 3 compared to 1 (OR [95 % CI], Age: 1.10 [1.07–1.13]; inflammatory disease nr 1: 19.44 [6.6–57.3]; inflammatory disease nr 2–5: 200.9 [47.7–845.6], Supplementary Table 14), while only the number of autoimmune diseases and not the age was associated with cluster 2 compared to 1 (OR [95 % CI], Age: 1.01 [0.99–1.03]; autoimmune disease nr 1: 2.34 [1.00–5.51]; autoimmune disease nr 2, 41.4 [12.7–135.2]; autoimmune disease nr

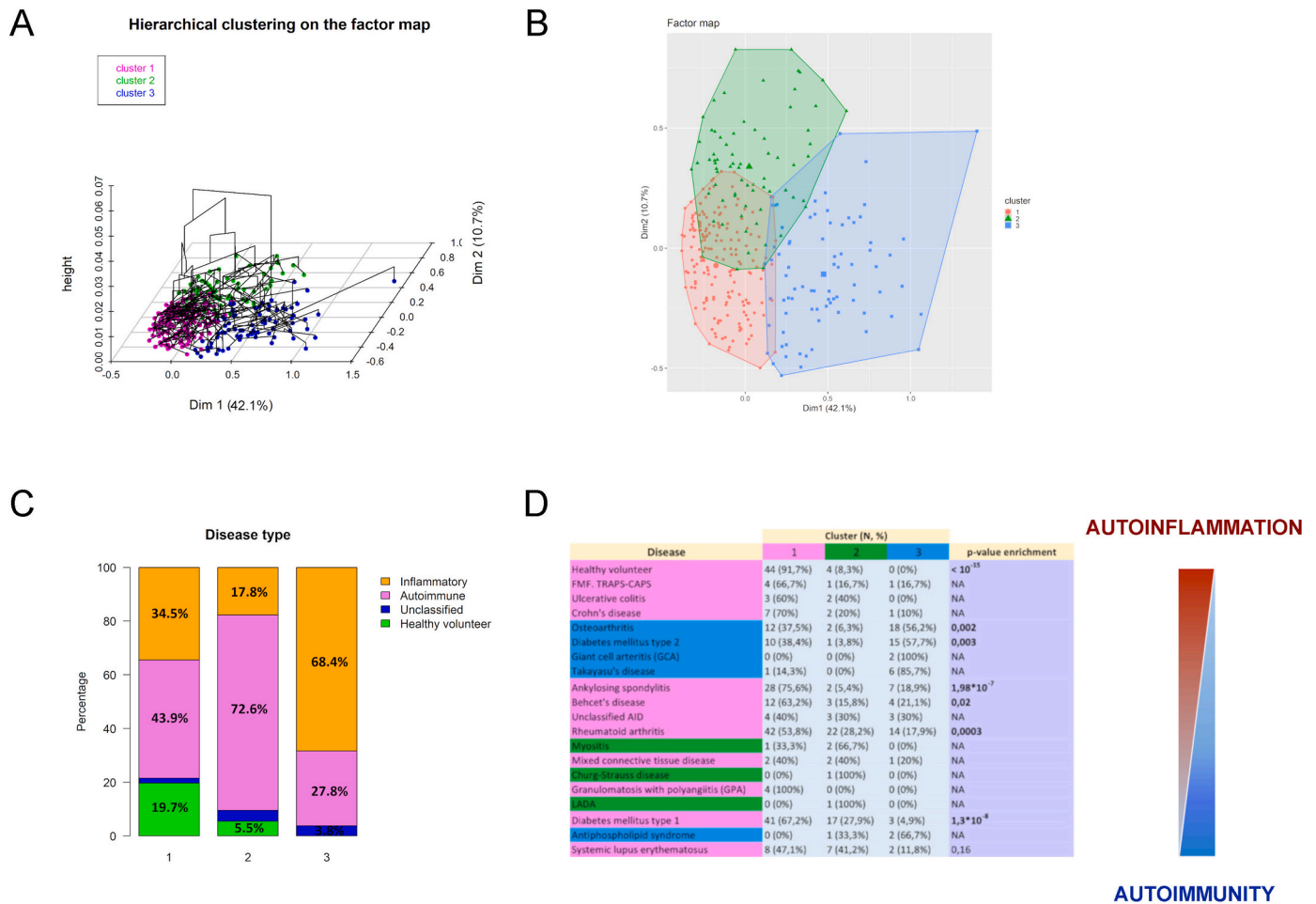
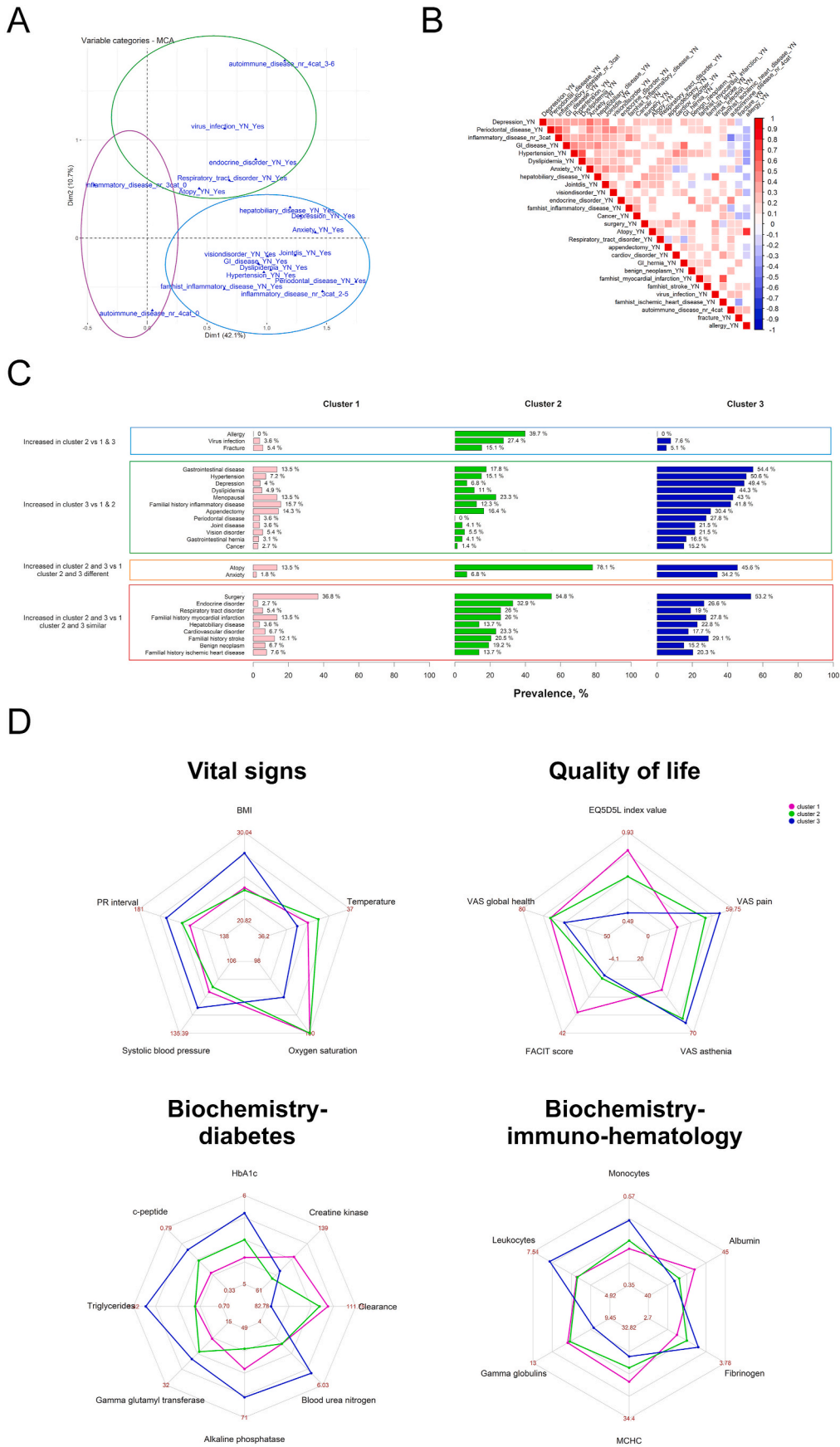


Fig. 2. Hierarchical clustering of factors of a multiple correspondence analysis (MCA) on the 30 most prevalent comorbidities. (A) 3D dendrogram on the first two dimensions of the MCA. (B) Factor map on the first two dimensions of the MCA. (C) Composition of clusters in percentage of main diagnosis AID classes. (D) Prevalence of main diagnoses in the three comorbidity clusters and p-value of enrichment. Each diagnosis is labeled with the color of the cluster in which it is most prevalent. AID- Autoimmune and Inflammatory Disease.



(caption on next page)

Fig. 3. Qualitative and quantitative clinical variables associated to the comorbidity clusters. (A) Projection of the first 18 variable categories contributing most to the first two dimensions of the MCA. Ovals visualize the superposition of the clusters (magenta: cluster 1; green: cluster 2; blue: cluster 3). (B) Correlogram of the polychoric correlation between the 27 cluster-associated comorbidity variables. Significant correlations with $FDR < 5\%$ are shown in red for positive rho, blue for negative rho according to the color scale on the right side. White squares represent non-significant correlations. (C) Prevalence in the clusters of cluster-associated comorbidities. (D) Radar plots of the quantitative variables significantly associated to the clusters. 25th and 75th percentiles of each variable are shown. Detailed p-values and pairwise comparisons may be found in [Supplementary Table 13](#). MCA- Multiple Correspondence Analysis. FDR- False Discovery Rate.

3–6: 77.7 [8.78–687.3], [Supplementary Table 14](#)). Similarly, 4 other comorbidities (cancer, joint disorders, vision disorders and menopause) known to be associated with aging were used as covariates in polytomous regression models. Age was always positively associated with cluster 3 vs 1 in these models, while only cancer (OR [95 % CI], 3.85 [1.15–12.92]) and joint disorders (8.45 [3.1–23.05]) were still associated with cluster 3 vs 1 after adjustment on age ([Table S15](#)).

To further characterize the comorbidity clusters, quantitative parameters collected during the study were analysed. No cluster had median values out of the biological norms except for BMI, which was increased above norm in cluster 3 (median [IQR]: 28.3 kg/m² [7.78]) and renal clearance, which was decreased below norm in cluster 3 (median [IQR]: 84.19 mL/min/1.73 m² [25.63]). Concerning vital signs and ECG, systolic blood pressure and PR interval were significantly increased, and oxygen saturation was decreased in cluster 3 compared to cluster 1 and 2, while body temperature was increased in cluster 2 compared to cluster 1 and 3 ([Fig. 3D](#) and [Supplementary Table 13](#)). Cluster 2 and even more cluster 3 displayed a worse Quality of life as witnessed by a significantly decreasing EQ-5D-5L index value and increasing Visual Analogic Scale (VAS) pain going from cluster 1 to cluster 3, a lower FACIT score and higher VAS asthenia in cluster 2 and 3 compared to cluster 1 and a lower VAS global health in cluster 3 compared to 1 ([Fig. 3D](#) and [Supplementary Table 13](#)). Biochemical parameters related to diabetes and metabolic disease were consistent with the enrichment of T2D in cluster 3, which displayed higher HbA1c, c-peptide, triglycerides, gamma glutamyl transferase, alkaline phosphatase and blood urea nitrogen and lower renal clearance compared to cluster 1 and 2, while despite enrichment of T1D in cluster 1 none of these parameters was significantly different in cluster 1 compared to 2 ([Fig. 3D](#) and [Supplementary Table 13](#)). Immuno-hematology parameters were also consistent with a highly inflammatory phenotype in cluster 3, with higher numbers of monocytes and leukocytes and lower gamma globulins compared to cluster 1 and 2; higher fibrinogen levels, lower MCHC and albumin compared to cluster 1 ([Fig. 3D](#) and [Supplementary Table 13](#)).

AIDs are often treated with glucocorticoids, csDMARDs, biological DMARDs or NSAIDs, which are known to induce some comorbidities as secondary effect [28,29]. For instance, long-term use of glucocorticoids may induce infections, hypertension, insulin resistance and osteoporosis while NSAIDs may induce gastrointestinal ulcers [30,31]. Analyses of drug usage did not find any significant difference among the clusters ([Supplementary Table 16](#)).

Prevalence of cardiovascular disease was increased in both cluster 2 and 3 compared to 1. In order to verify whether other factors associated to cardiovascular disease such as age, hypertension, cholesterol, smoking and diabetes were associated to the clusters, the Framingham cardiovascular risk score which incorporates all these factors was compared and found to be significantly increased in cluster 3 compared to cluster 1 and 2 ([Supplementary Fig. 5B](#), cluster 3 vs 1, $p = 3.6 \times 10^{-13}$; cluster 3 vs 2, $p = 1.8 \times 10^{-6}$; cluster 1 vs 2, $p = 0.18$), suggesting that increased cardiovascular risk in cluster 3, but not in cluster 2, might be explained by an increased prevalence of known risk factors such as T2D and hypertension. A multivariate logistic regression model of cardiovascular disease confirmed an increased cardiovascular disease risk in cluster 2 compared to 1 ([Supplementary Table 17](#), OR [95 % CI], 3.98 [1.8–8.89]) independently of the Framingham score, which was itself associated with an additional increased risk ([Supplementary Table 16](#), OR [95 % CI], 1.14 [1.08–1.21]), while cluster 3 was no longer associated after

adjustment on the Framingham score ([Supplementary Table 17](#), $p = 0.97$).

3.3. Clusters suggest immunological disease subtypes with distinct clinical characteristics

Most diseases were spread across the three clusters. To investigate whether patients with the same diagnosis but in different clusters had different clinical characteristics, we analysed patients with the same diagnoses, whether main or secondary ([Supplementary Table 8](#)), for which there were at least 10 subjects in at least two clusters. RA patients were similar for diagnosis age and disease duration across the clusters, but they displayed an increasing DAS28 going from cluster 1 to cluster 3 ([Table 2](#), $p = 0.00018$), a higher frequency of extra-articular manifestations in cluster 2 and 3 compared to cluster 1 (OR [95 % CI], cluster 2 vs 1, 4.18 [1.04–18.51]; cluster 3 vs 1, 6.82 [1.73–30.74]; [Table 2](#)), higher VAS pain in cluster 3 compared to 1 ([Table 2](#), $p = 0.056$). T1D patients were not different in age diagnosis, disease duration nor in QoL scores but they displayed a higher IDAA1c score in cluster 1 compared to cluster 2 ([Supplementary Table 18](#), $p = 0.0089$). OA patients were similar in age at diagnosis, disease duration and KOOS and WOMAC pain scores but they had borderline significantly higher metabolic score and lower EQ-5D-5L index in cluster 3 compared to 1 ([Supplementary Table 18](#), $p = 0.053$ and $p = 0.061$ respectively). T2D patients had a higher age at diagnosis and higher VAS asthenia with lower EQ-5D-5L index in cluster 3 compared to 1 ([Supplementary Table 18](#), $p = 0.0003$, $p = 0.045$ and $p = 0.0052$ respectively), but no difference in metabolic score, HOMA-IR nor HOMA-beta ([Supplementary Table 18](#), $p = 0.84$, $p = 0.78$ and $p = 0.80$ respectively). SpA patients did not display any difference in BASDAI, BASFI nor QoL scores between the clusters but had a higher diagnosis age in cluster 3 compared to 1 ([Supplementary Table 18](#), $p = 0.04$).

Comorbidity and multimorbidity in RA have previously been associated with hospitalization, disability and healthcare utilization and a RDCI predicting these outcomes has been developed [20,32]. RDCI was significantly increased in cluster 2 and 3 compared to 1, but also in cluster 3 compared to 2 when all the AID patients were compared ([Figs. 4A and 1](#) vs 2 $p = 5 \times 10^{-6}$; 1 vs 3 $p = 2.2 \times 10^{-17}$; 2 vs 3 $p = 0.0022$), while in RA patients RDCI was increased only in cluster 2 and 3 compared to 1 with no difference between cluster 2 and 3 ([Figs. 4A and 1](#) vs 2 $p = 0.0036$; 1 vs 3 $p = 0.0003$; 2 vs 3 $p = 0.23$).

Autoantibodies are considered a hallmark of autoimmunity and they are included in the diagnostic criteria of some diseases such as T1D. When we compared the seroprevalence of autoantibodies in all AID patients (defined as presence of at least one autoantibody out of the 27 evaluated) a higher seroprevalence was observed in cluster 2, but not in cluster 3, compared to cluster 1 ([Fig. 4B](#), OR [95%CI], 2 vs 1: 3.11 [1.27–9.39]; 3 vs 1: $p = 0.092$). In RA patients no significant difference between the clusters was observed ([Figs. 4B and 2](#) vs 1 $p = 0.99$; 3 vs 1 $p = 0.25$). In all AID patients the number of autoantibodies was significantly increased in cluster 2 compared to cluster 1 and 3 and significantly decreased in cluster 3 compared to 1 ([Figs. 4C and 1](#) vs 2 $p = 0.0020$; 1 vs 3 $p = 0.003$; 2 vs 3 $p = 7.2 \times 10^{-7}$). In RA patients there was no significant difference in the number of autoantibodies between the clusters ([Fig. 4C](#), global Kruskal Wallis test, $p = 0.26$), while there was a significantly lower seroprevalence of the RA-specific autoantibodies RF and ACPA in cluster 3 but not in cluster 2 compared to 1 ([Fig. 4D](#), OR [95%CI], RF: 3 vs 1, 0.22 [0.05–0.79]; 2 vs 1 $p = 0.67$; ACPA: 3 vs 1,

Table 2
Clinical characteristics of RA subgroups in comorbidity clusters.

	Cluster			p-value	p-value pairwise comparisons		
	1 (n = 42)	2 (n = 23)	3 (n = 14)		1 vs 2	1 vs 3	2 vs 3
Age diagnosis (years)							
Median (IQR)	42 (21)	46.5 (22)	49 (18.25)	0.71	NA	NA	NA
Missing	0	1	0				
Disease duration (years)							
Median (IQR)	3 (4)	2.5 (5)	5 (3.5)	0.11	NA	NA	NA
Missing	0	1	0				
DAS28-CRP							
Median (IQR)	2.78 (1.65)	3.94 (1.67)	4.72 (2.13)	0.00018	<i>0.056</i>	0.0002	<i>0.057</i>
Missing	0	2	0				
Erosive RA							
N (%)	21 (51 %)	11 (50 %)	7 (53.8 %)	1	NA	NA	NA
Missing	1	1	1				
Extrarticular manifestations							
N (%)	3 (7.5 %)	6 (30 %)	7 (50 %)	0.0014	0.046	0.0076	ND
Missing	2	3	0				
EQ5D5L index value							
Median (IQR)	0.51 (0.40)	0.45 (0.39)	0.39 (0.47)	0.26	NA	NA	NA
Missing	1	1	0				
VAS pain							
Median (IQR)	45 (30)	60 (25)	70 (11)	0.035	0.14	<i>0.056</i>	0.38
Missing	0	0	0				
FACIT score							
Median (IQR)	14.5 (42.82)	2.56 (33.7)	-7 (37.32)	0.17	NA	NA	NA
Missing	4	3	1				
VAS asthenia							
Median (IQR)	50 (50)	70 (35)	75 (10)	<i>0.084</i>	NA	NA	NA
Missing	0	0	1				

IQR- InterQuartile Range; RA- Rheumatoid arthritis; CRP- C-Reactive Protein; VAS- Visual Analogic Scale.

0.18 [0.04–0.73]; 2 vs 1 $p = 0.99$) with 100 % ACPA seropositivity in cluster 2 (Fig. 4D).

To classify AID patients into comorbidity clusters, we trained an elastic net-penalized multinomial regression model on the TRANSIMMUNOM dataset using the 30 comorbidities that defined the clusters in the unsupervised analysis. Model performance was assessed on TRANSIMMUNOM test data (Supplementary Figs. 3 and 6A) and yielded 93.6 % accuracy (95 % CI: 86.6, 97.6). All the comorbidities were selected by the model, with highest regression coefficients for allergy, which was positively associated with cluster 2, anxiety, positively associated with cluster 3, and endocrine disorder, negatively associated with cluster 1 (Supplementary Fig. 6B and Supplementary Table 19).

4. Discussion

Familial aggregation of AID, AID co-occurrence and clinical heterogeneity all point to the existence of multiple distinct etiopathogenic mechanisms of AIDs. We took advantage of the broad spectrum of AIDs recruited and the vast amount of high quality clinical data collected in the TRANSIMMUNOM cross-sectional study to stratify AID patients into etiopathogenic subgroups. We identified three comorbidity clusters of AID patients. Their hallmarks were the absence of comorbidity (cluster 1), the presence of polyautoimmunity (cluster 2) or of polyinflammation (cluster 3), respectively. The clusters were distinguished by different non-immunological comorbidities, by different vital signs, biochemistry, serology and quality of life parameters. Noteworthy, we ruled out that the clustering could be driven by AID-specific therapies. Most AIDs had patients classified in all the clusters, suggesting different disease endotypes. The majority of healthy controls were found in the low comorbidity cluster and a minority in the polyautoimmunity cluster, which was due to the presence of non-AID comorbidities such as allergy or history of viral infection.

Despite the high quality of the comorbidity data, medical events such as infections may have been missed or underreported as they rely on patient's self-reporting. Also, no verification could be made for the reporting of familial history of disease, and it is known that patients

often misclassify autoimmune diagnoses, for example T2D instead of T1D and OA instead of RA [33]. Actually, we found familial history of inflammatory disease associated to the cluster characterized by polyinflammation, but no association of familial history of autoimmune disease with the polyautoimmunity cluster. This is consistent with a previous report [11], but should be interpreted with caution.

As all our patients had adult-onset AIDs, with the exception of FMF, the comorbidity profiles that we describe cannot be inferred for pediatric-onset AIDs, which will warrant a dedicated study.

Several observations related to the clusters' definition are intriguing and deserve further exploration.

It is interesting to observe a more prevalent history of viral infections in the polyautoimmunity cluster. The study was conducted before the COVID19 pandemic period and only highly symptomatic viral infections such as viral hepatitis, dengue, labial or genital herpes, Human Papilloma Virus-induced warts or shingles were reported. An association between viruses and autoimmunity has been known for a long time [34], but up to date causality has only been proven for EBV in Multiple Sclerosis [35]. Molecular mimicry of an autoantigen by a viral antigen has been described as one mechanism behind the association of viruses with autoimmunity, e.g. anti-C1q autoantibodies in SLE cross-react with the EBNA1 protein from EBV and the similarity between influenza nucleoprotein A and human hypocretin receptor 2 underlies the pandemic flu vaccine-induced narcolepsia [36,37]. However, we describe for the first time that some symptomatic viral infections are associated with the development of multiple rather than single autoimmune diseases. The different autoimmune diseases developed by the same patient are involving different autoantigens, which does not fit well with a classical molecular mimicry involving sequence or structure similarity between a viral and a self-antigen epitope [37]. We recently described a population of polyspecific CD8⁺ T cells which are enriched during thymic selection and which preferentially recognize viral antigens from multiple viruses [38]. It would be interesting to investigate whether these polyspecific T cells are also able to recognize multiple autoantigens, which would give a reasonable explanation for the development of polyautoimmunity upon viral trigger.

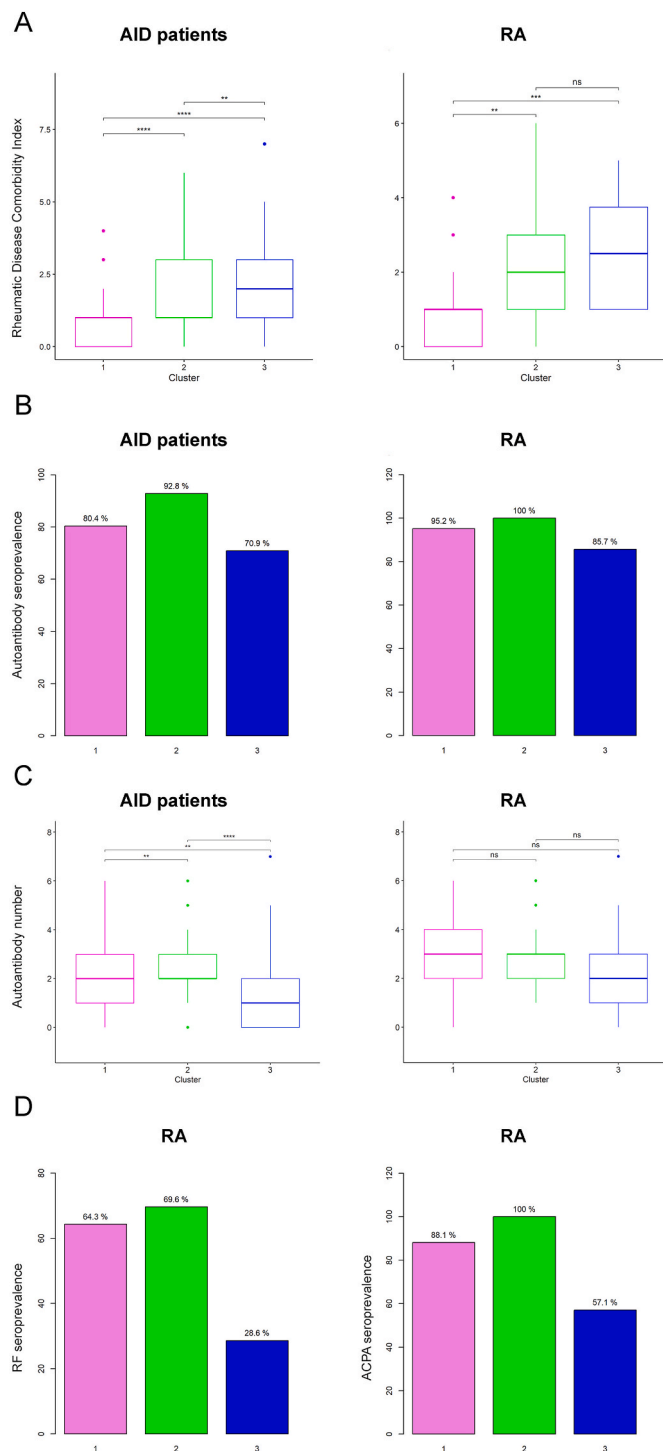


Fig. 4. Association of the Rheumatic Disease Comorbidity Index and autoantibodies with comorbidity clusters. (A) Median and IQR of RDCI by cluster in all AID patients (left panel) and RA only (right panel). The asterisks indicate the level of significance (Benjamini-Hochberg –adjusted Wilcoxon; **, $P_{adj} < 0.01$; ***, $P_{adj} < 0.001$; ****, $< 10^{-5}$; NS, not significant). (B) Autoantibody seroprevalence by cluster in all AID patients (left panel) and RA only (right panel). (C) Number of autoantibodies by cluster in all AID patients (left panel) and RA only (right panel). The asterisks indicate the level of significance (Benjamini-Hochberg –adjusted Wilcoxon; **, $P_{adj} < 0.01$; ****, $P_{adj} < 10^{-6}$; NS, not significant). (D) RF (left panel) and ACPA (right panel) seropositivity in RA patients by comorbidity cluster. IQR- InterQuartile Range. RDCI- Rheumatic Disease Comorbidity Index. RA- Rheumatoid arthritis. ACPA- Anti-Citrullinated Peptide Antibodies. RF- Rheumatoid Factor.

In contrast, we observed a more prevalent history of appendectomy in the polyinflammation cluster. The association of appendectomy with AID has previously been described, sometimes with conflicting results [39–44]. In IBD appendectomy is usually associated with a decreased incidence of UC and an increased incidence of Crohn’s disease, but the latter might be due to diagnostic errors in the recognition of the first symptoms of the disease as the risk decreases to background level 5 years after the appendectomy [41]. Other AIDs for which an increased incidence has been reported after appendectomy are T2D, primary sclerosing cholangitis and multiple sclerosis [42–44]. An increased risk of developing a strong inflammation in the appendix, rather than the consequent removal of the appendix might be the actual factor behind this association, which might in part explain some of the contradictory results reported to date. Thus, the association would not be causal, but rather be a surrogate of an inflammatory phenotype carried by the patients, and therefore a marker of a common etiopathogenesis. The appendix has been associated with increased longevity in mammals [45] and its role as a “safe house” for beneficial gut bacteria has recently emerged [46]. Another possible explanation is therefore that the removal of the appendix predisposes to gut dysbiosis, which causes inflammation.

Atopic dermatitis was highly prevalent in the polyautoimmunity (78 %) and polyinflammation (46 %) clusters. This chronic inflammatory disease of the skin comprises an IgE-mediated and a non-IgE-mediated endotype [47], the latter being less frequent. IgE-mediated or extrinsic atopic dermatitis has previously been associated to different AIDs [48] and particularly to multiple AID syndromes [49] as well as to the presence of IgE autoantibodies to skin antigens [50]. Interestingly we find allergy exclusively associated to the polyautoimmunity cluster and absent from the other clusters, suggesting that atopy might be IgE-mediated in the polyautoimmunity cluster and non-IgE-mediated in the polyinflammation cluster. A measurement of total serum IgE in the clusters is needed to confirm this hypothesis as the clinical phenotype of the two endotypes is undistinguishable.

The polyautoimmunity and polyinflammation clusters are associated with an increased risk of cardiovascular disease and of familial history of ischemic heart disease and myocardial infarction compared to the low comorbidity cluster. A large recent population-based study clearly established the association of cardiovascular disease with 19 different AIDs independently of known cardiovascular risk factors, with a further risk increase in patients with multiple AIDs [19], but they did not distinguish autoimmune from inflammatory diagnoses. Yet in the same study the main diagnoses with the highest hazard ratio of cardiovascular disease were autoimmune diseases (systemic sclerosis, Addison’s disease, SLE and T1D). When we considered risk factors of cardiovascular disease through the Framingham score, only the polyautoimmunity cluster was still associated to an increased risk of cardiovascular disease, suggesting that the increased risk of the polyinflammation cluster was mainly due to other risk factors such as T2D, hyperlipidaemia and hypertension, which were more prevalent in this cluster.

Periodontitis is a chronic inflammatory disease known to be associated with some AIDs including IBD, RA and T2D [51]. This association might not only be explained by common risk factors, but also by an increased risk to develop an AID as a consequence of the low-grade inflammation and microbiome dysbiosis induced by periodontal disease [51]. Some oral bacterial species associated with periodontitis express citrullinating enzymes and have been implicated in the induction of ACPA in RA [52]. In this study, we find an increased risk of periodontitis in the polyinflammation cluster compared to the other clusters, and this was also the case when comparing the prevalence of periodontitis in ACPA seropositive RA patients which was 36 % in the polyinflammation cluster, 5 % in the low comorbidity cluster and 0 % in the polyautoimmunity cluster. This suggests that the citrullinating mechanisms responsible for ACPA production could have different triggers: periodontitis in the polyinflammation cluster and other sources in the polyautoimmunity and low comorbidity clusters.

An association of both cancer and mood disorders with chronic low-grade inflammation is well recognized [53,54] and perhaps it is not surprising that these comorbidities were more prevalent in the polyinflammation cluster. Noteworthy, while cancer prevalence was only increased in the polyinflammation cluster, benign neoplasm was increased to similar levels both in the polyinflammation and the polyautoimmunity cluster compared to the low comorbidity cluster. Altogether, this supports that an inflammatory environment promotes cancer, while benign neoplasm have other unknown triggers [53].

The association of endocrine disorder with AID is widely established in the autoimmune polyendocrine syndromes, which constitute a heterogeneous group of disorders characterized by loss of immune tolerance to self-antigens. In the polyendocrine syndrome, secondary endocrine disorders most frequently associated with autoimmune diseases are thyroid anomalies, T1D, pernicious anaemia, vitiligo, premature ovarian failure and autoimmune thrombocytopaenia [55]. Endocrine disorders were highly prevalent in the polyautoimmunity cluster, as expected, but also in the polyinflammation cluster.

The number of autoantibodies correlated positively with the number of autoimmune diseases as previously reported [11], and negatively with the number of inflammatory diseases. Nevertheless, the autoantibody seroprevalence was increased in inflammatory diseases compared to healthy controls (53–73 % vs 31 %), suggesting that inflammation may favour secondary autoimmune responses. Apart from the T1D-, RA- and SLE-specific autoantibodies, the other specificities were only present in a small number of patients, and we were not able to perform an association analysis of each autoantibody with the clusters. However, in RA patients, we clearly saw a lower RF- and ACPA-seropositivity in the polyinflammation cluster than in the polyautoimmunity and low comorbidity clusters. Furthermore, RA patients in the polyinflammation cluster also displayed a higher DAS28, VAS pain and number of extra-articular manifestations, corroborating the hypothesis that RA patients belonging to the different clusters represent distinct disease endotypes.

Because of the cross-sectional design of the TRANSIMMUNOM study, stability in time of cluster assignment could not be addressed and warrants further investigation. However, numerous omic datasets were collected during the TRANSIMMUNOM study [14], which will allow a molecular characterization of the comorbidity clusters. This should provide further insights into the underlying etiopathogenic mechanisms and will allow a finer classification of patients in the low comorbidity cluster. It would be particularly interesting to analyze the results of the microbiota studies performed on these patients, notably for gut microbiota metabolic pathways. Nevertheless, waiting for such refinements, comorbidities that are easily collected even in primary care could be useful for a first patient stratification. For this purpose, we have developed a classification model that will allow researchers and clinicians to investigate comorbidity clusters in their studies.

One crucial question raised by this study is whether the disease endotypes defined by the comorbidity profiles are associated with a different therapy efficacy and could be used for personalized medicine. Previous studies on this subject have focused mainly on RA and on either some specific comorbidities or on comorbidity indexes not taking into account different comorbidity profiles, yielding contradictory results [20,21,56]. It will therefore be a high priority to evaluate the theranostic value of the comorbidity clusters, which could be first analysed using appropriate medico-administrative databases.

5. Conclusion

Through an unsupervised analysis of comorbidities in a broad spectrum of autoimmune and inflammatory diseases covering the immunological continuum we have defined three main profiles characterized by low comorbidity, polyautoimmunity and polyinflammation. These comorbidity profiles may be used for patient stratification in primary care, but an external validation and evaluation of their theranostic value is

warranted to fully establish their impact on medical care.

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Data sharing statement

Data will be shared upon reasonable request to the corresponding author.

CRediT authorship contribution statement

Signe Hässler: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Formal analysis, Data curation, Conceptualization. **Roberta Lorenzon:** Writing – review & editing, Writing – original draft, Visualization, Investigation, Data curation, Conceptualization. **Marie Binvignat:** Writing – review & editing, Data curation. **Claire Ribet:** Writing – review & editing, Data curation. **Alexandra Roux:** Writing – review & editing, Investigation. **Catherine Johant:** Writing – review & editing, Investigation. **Chloé Amouyal:** Writing – review & editing, Conceptualization. **Serge Amselem:** Writing – review & editing, Conceptualization. **Francis Berenbaum:** Writing – review & editing, Conceptualization. **Olivier Benveniste:** Writing – review & editing, Conceptualization. **Patrice Cacoub:** Writing – review & editing, Conceptualization. **Gilles Grateau:** Writing – review & editing, Conceptualization. **Agnès Hartemann:** Writing – review & editing, Conceptualization. **David Saadoun:** Writing – review & editing, Conceptualization. **Joe-Elie Salem:** Writing – review & editing, Conceptualization. **Jérémie Sellam:** Writing – review & editing, Conceptualization. **Philippe Seksik:** Writing – review & editing, Conceptualization. **Eric Vicaut:** Writing – review & editing, Conceptualization. **Encarnita Mariotti-Ferrandiz:** Writing – review & editing, Conceptualization. **Michelle Rosenzweig:** Writing – review & editing, Investigation, Conceptualization. **David Klatzmann:** Writing – review & editing, Writing – original draft, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

JS declares honoraria from Roche, Chugai, Pfizer, BMS, MSD, AbbVie, Sandoz, Hospira, Janssen, Novartis, Fresenius Kabi, Sanofi Genzyme, Galapagos. PC declares consultancies, honoraria, advisory board, and speakers' fees from Alnylam, Innotech, Servier and Vifor. PS declares financial support for scientific works from Biocodex, MSD, Takeda, Janssen, and Sandoz, and consultant fees from Abbvie, Merck, MSD, Gilead, Pfizer, Sandoz, Janssen, and Fresenius Kabi. EV declares consulting fees from Abbott, Coloplast and Boston Scientific.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jaut.2024.103318>.

References

- [1] N. Conrad, S. Misra, J.Y. Verbakel, G. Verbeke, G. Molenberghs, P.N. Taylor, J. Mason, N. Sattar, J.J.V. McMurray, I.B. McInnes, K. Khunti, G. Cambridge, Incidence, prevalence, and co-occurrence of autoimmune disorders over time and by age, sex, and socioeconomic status: a population-based cohort study of 22 million individuals in the UK, *Lancet* 401 (2023) 1878–1890, [https://doi.org/10.1016/S0140-6736\(23\)00457-9](https://doi.org/10.1016/S0140-6736(23)00457-9).
- [2] S.J. Virolainen, A. VonHandorf, K.C.M.F. Viel, M.T. Weirauch, L.C. Kottyan, Gene-environment interactions and their impact on human health, *Genes Immun* 24 (2023) 1–11, <https://doi.org/10.1038/s41435-022-00192-6>.
- [3] J. Cárdenas-Roldán, A. Rojas-Villarraga, J.-M. Anaya, How do autoimmune diseases cluster in families? A systematic review and meta-analysis, *BMC Med.* 11 (2013) 73, <https://doi.org/10.1186/1741-7015-11-73>.
- [4] C.-F. Kuo, M.J. Grainge, A.M. Valdes, L.-C. See, S.-F. Luo, K.-H. Yu, W. Zhang, M. Doherty, Familial risk of sjögren's syndrome and Co-aggregation of autoimmune diseases in affected families: a nationwide population study, *Arthritis Rheumatol.* 67 (2015) 1904–1912, <https://doi.org/10.1002/art.39127>.
- [5] C.-F. Kuo, M.J. Grainge, A.M. Valdes, L.-C. See, S.-F. Luo, K.-H. Yu, W. Zhang, M. Doherty, Familial aggregation of systemic lupus erythematosus and coaggregation of autoimmune diseases in affected families, *JAMA Intern. Med.* 175 (2015) 1518–1526, <https://doi.org/10.1001/jamainternmed.2015.3528>.
- [6] E.C. Somers, S.L. Thomas, L. Smeeth, A.J. Hall, Autoimmune diseases co-occurring within individuals and within families: a systematic review, *Epidemiology* 17 (2006) 202–217, <https://doi.org/10.1097/01.ede.0000193605.93416.df>.
- [7] A. Matusiewicz, J. Stróżyńska-Byrska, M. Olesińska, Polyautoimmunity in rheumatological conditions, *Int J Rheum Dis* 22 (2019) 386–391, <https://doi.org/10.1111/1756-185X.13454>.
- [8] E.C. Somers, S.L. Thomas, L. Smeeth, A.J. Hall, Are individuals with an autoimmune disease at higher risk of a second autoimmune disorder? *Am. J. Epidemiol.* 169 (2009) 749–755, <https://doi.org/10.1093/aje/kwn408>.
- [9] S.A. Chambers, S.C. Charman, A. Rahman, D.A. Isenberg, Development of additional autoimmune diseases in a multiethnic cohort of patients with systemic lupus erythematosus with reference to damage and mortality, *Ann. Rheum. Dis.* 66 (2007) 1173–1177, <https://doi.org/10.1136/ard.2006.062984>.
- [10] J. Avouac, P. Airo, P. Dieude, P. Caramaschi, K. Tiev, E. Diot, J. Sibilia, S. Cappelli, B. Granel, A. Vacca, J. Wipff, O. Meyer, A. Kahan, M. Matucci-Cerinic, Y. Allanore, Associated autoimmune diseases in systemic sclerosis define a subset of patients with milder disease: results from 2 large cohorts of European Caucasian patients, *J. Rheumatol.* 37 (2010) 608–614, <https://doi.org/10.3899/jrheum.090815>.
- [11] M. Rojas, C. Ramírez-Santana, Y. Acosta-Ampudia, D.M. Monsalve, M. Rodríguez-Jimenez, E. Zapata, A. Naranjo-Pulido, A. Suárez-Avellaneda, L.J. Ríos-Serna, C. Prieto, W. Zambrano-Romero, M.A. Valero, Y. Rodríguez, R.D. Mantilla, C. Zhu, Q.-Z. Li, C.E. Toro-Gutiérrez, G.J. Tobón, J.-M. Anaya, New insights into the taxonomy of autoimmune diseases based on polyautoimmunity, *J. Autoimmun.* 126 (2022) 102780, <https://doi.org/10.1016/j.jaut.2021.102780>.
- [12] D. McGonagle, M.F. McDermott, A proposed classification of the immunological diseases, *PLoS Med.* 3 (2006) e297, <https://doi.org/10.1371/journal.pmed.0030297>.
- [13] N. Tchitchek, M. Binvinat, A. Roux, F. Pitoiset, J. Dubois, G. Marguerit, D. Saadoun, P. Cacoub, J. Sellam, F. Berenbaum, A. Hartemann, C. Amouyal, R. Lorenzon, E. Mariotti-Ferrandiz, M. Rosenzweig, D. Klatzmann, Deep immunophenotyping reveals that autoimmune and autoinflammatory disorders are spread along two immunological axes capturing disease inflammation levels and types, *Ann. Rheum. Dis.* (2024), <https://doi.org/10.1136/ard-2023-225179>.
- [14] R. Lorenzon, E. Mariotti-Ferrandiz, C. Aheng, C. Ribet, F. Toumi, F. Pitoiset, W. Chaara, N. Derian, C. Johanet, I. Drakos, S. Harris, S. Aselem, F. Berenbaum, O. Benveniste, B. Bodaghi, P. Cacoub, G. Grateau, C. Amouyal, A. Hartemann, D. Saadoun, J. Sellam, P. Seksik, H. Sokol, J.-E. Salem, E. Vicaut, A. Six, M. Rosenzweig, C. Bernard, D. Klatzmann, Clinical and multi-omics cross-phenotyping of patients with autoimmune and autoinflammatory diseases: the observational TRANSMUNOM protocol, *BMJ Open* 8 (2018) e021037, <https://doi.org/10.1136/bmjopen-2017-021037>.
- [15] J.R. Tarn, N. Howard-Tripp, D.W. Lendrem, X. Mariette, A. Saraux, V. Devauchelle-Pensec, R. Seror, A.J. Skelton, K. James, P. McMeekin, S. Al-Ali, K.L. Hackett, B. C. Lendrem, H. Hargreaves, J. Casement, S. Mitchell, S.J. Bowman, E. Price, C. T. Pease, P. Emery, P. Lanyon, J. Hunter, M. Gupta, M. Bombardieri, N. Sutcliffe, C. Pitzalis, J. McLaren, A. Cooper, M. Regan, I. Giles, D. Isenberg, V. Saravanan, D. Coady, B. Dasgupta, N. McHugh, S. Young-Min, R. Moots, N. Gendi, M. Akil, B. Griffiths, S.J.A. Johnsen, K.B. Norheim, R. Omdal, D. Stocken, C. Everett, C. Fernandez, J.D. Isaacs, J.-E. Gottenberg, W.-F. Ng, V. Devauchelle-Pensec, P. Dieude, J.J. Dubost, A.-L. Fauchais, V. Goeb, E. Hachulla, C. Larroche, V. Le Guern, J. Morel, A. Perdriger, X. Puéchal, S. Rist, D. Sen, J. Sibilia, O. Vittecoq, J. Benessiano, S. Tubiana, K. Inamo, S. Gaete, D. Batouche, D. Molinari, M. Randrianandrasana, I. Pane, A. Abbe, G. Baron, P. Ravaut, J.-E. Gottenberg, P. Ravaut, X. Puéchal, V. Le Guern, J. Sibilia, C. Larroche, A. Saraux, V. Devauchelle-Pensec, J. Morel, G. Hayem, P. Hatron, A. Perdriger, D. Sene, C. Zarnitsky, D. Batouche, V. Furlan, J. Benessiano, E. Perrodeau, R. Seror, X. Mariette, S. Brown, N.C. Navarro, C. Pitzalis, P. Emery, S. Pavitt, J. Gray, C. Hulme, F. Hall, R. Busch, P. Smith, L. Dawson, M. Bombardieri, W.-F. Ng, C. Pease, E. Price, N. Sutcliffe, C. Woods, S. Ruddock, C. Everett, C. Reynolds, E. Skinner, A. Poveda-Gallego, J. Rout, I. Macleod, S. Rauz, S. Bowman, W.-F. Ng, S.J. Bowman, B. Griffiths, F. Hall, E.C. Bacaba, H. Frankland, R. Moots, K. Chadravarty, S. Lamabadusuriya, M. Bombardieri, C. Pitzalis, N. Sutcliffe, C. Breston, N. Gendi, K. Culfeer, C. Riddell, J. Hamburger, A. Richards, S. Rauz, S. Brailsford, J. Dasgin, J. Logan, D. Mulherin, J. Andrews, P. Emery, A. McManus, C. Pease, D. Pickles, A. Booth, M. Regan, J.K. Kin, A. Holt, T. Dimitroulas, L. Kadiki, D. Kaur, G. Kitas, A. Khan, T. Cosier, Panthakalam, K. Mintrim, M. Lloyd, L. Moore, E. Gordon, C. Lawson, M. Gupta, J. Hunter, L. Stirtion, G. Ortiz, E. Price, S. Pelger, C. Gorman, B. Hans, G. Clunie, S. Lane, G. Rose, S. Cuckow, M. Batley, R. Einosas, S. Knight, D. Symmons, B. Jones, A. Carr, S. Edgar, F. Figueredo, H. Foggo, D. Lendrem, I. Macleod, S. Mitchell, C. Downie, J. Tarn, J. Locke, S. Al-Ali, S. Legg, K. Mirza, B. Hargreaves, L. Hetherington, A. Jones, P. Lanyon, A. Muir, P. White, S. Young-Min, S. Pugmire, S. Vadivelu, A. Cooper, M. Watkins, A. Field, S. Kaye, D. Mewar, P. Medcalf, P. Tomlinson, D. Whiteside, N. McHugh, J. Pauling, J. James, A. Dowden, M. Akil, J. McDermott, O. Godia, D. Coady, E. Kidd, L. Palmer, C. Li, S. Bartrum, D. Mead, B. Dasgupta, V. Katsande, P. Long, E. Vermaak, J. Turner, U. Chandra, K. MacKay, S. Fedele, A. Ferenkeh-Koroma, I. Giles, D. Isenberg, H. McConnell, N. Ahwren, S. Porter, P. Allcoa, J. McLaren, Symptom-based stratification of patients with primary Sjögren's syndrome: multidimensional characterisation of international observational cohorts and reanalyses of randomised clinical trials, *The Lancet Rheumatology* 1 (2019) e85–e94, [https://doi.org/10.1016/S2665-9913\(19\)30042-6](https://doi.org/10.1016/S2665-9913(19)30042-6).
- [16] Y. Pacheco, J. Barahona-Correa, D.M. Monsalve, Y. Acosta-Ampudia, M. Rojas, Y. Rodríguez, J. Saavedra, M. Rodríguez-Jiménez, R.D. Mantilla, C. Ramírez-Santana, N. Molano-González, J.-M. Anaya, Cytokine and autoantibody clusters interaction in systemic lupus erythematosus, *J. Transl. Med.* 15 (2017) 239, <https://doi.org/10.1186/s12967-017-1345-y>.
- [17] K. Mariampillai, B. Granger, D. Amelin, M. Guiguet, E. Hachulla, F. Maurier, A. Meyer, A. Tohmé, J.-L. Charuel, L. Musset, Y. Allenbach, O. Benveniste, Development of a new classification system for idiopathic inflammatory myopathies based on clinical manifestations and myositis-specific autoantibodies, *JAMA Neurol.* 75 (2018) 1528–1537, <https://doi.org/10.1001/jamaneurol.2018.2598>.
- [18] P. Soret, C. Le Dantec, E. Desvieux, N. Foulquier, B. Chassagnol, S. Hubert, C. Jamin, G. Barturen, G. Desachy, V. Devauchelle-Pensec, C. Boudjeniba, D. Corne, A. Saraux, S. Jousse-Joulin, N. Barbarroja, I. Rodríguez-Pintó, E. De Langhe, L. Beretta, C. Chizzolini, L. Kovács, T. Witte, A new molecular classification to drive precision treatment strategies in primary Sjögren's syndrome, *Nat. Commun.* 12 (2021) 3523, <https://doi.org/10.1038/s41467-021-23472-7>. PRECISEADS Clinical Consortium, PRECISEADS Flow Cytometry Consortium, E. Bettacchioli, A. Buttgerit, Z. Makowska, R. Lesche, M.O. Borghi, J. Martin, S. Courtade-Gaiani, L. Xuereb, M. Guedj, P. Moingeon, M.E. Alarcón-Riquelme, L. Laigle, J.-O. Pers.
- [19] N. Conrad, G. Verbeke, G. Molenberghs, L. Goetschalckx, T. Callender, G. Cambridge, J.C. Mason, K. Rahimi, J.J.V. McMurray, J.Y. Verbakel, Autoimmune diseases and cardiovascular risk: a population-based study on 19 autoimmune diseases and 12 cardiovascular diseases in 22 million individuals in the UK, *Lancet* 400 (2022) 733–743, [https://doi.org/10.1016/S0140-6736\(22\)01349-6](https://doi.org/10.1016/S0140-6736(22)01349-6).
- [20] F. Wolfe, K. Michaud, T. Li, R.S. Katz, Chronic conditions and health problems in rheumatic diseases: comparisons with rheumatoid arthritis, noninflammatory rheumatic disorders, systemic lupus erythematosus, and fibromyalgia, *J. Rheumatol.* 37 (2010) 305–315, <https://doi.org/10.3899/jrheum.090781>.
- [21] H. Radner, K. Yoshida, J.S. Smolen, D.H. Solomon, Multimorbidity and rheumatic conditions-enhancing the concept of comorbidity, *Nat. Rev. Rheumatol.* 10 (2014) 252–256, <https://doi.org/10.1038/nrrheum.2013.212>.
- [22] S.S. Zhao, H. Radner, S. Siebert, S.J. Duffield, D. Thong, D.M. Hughes, R.J. Moots, D.H. Solomon, N.J. Goodson, Comorbidity burden in axial spondyloarthritis: a cluster analysis, *Rheumatology* 58 (2019) 1746–1754, <https://doi.org/10.1093/rheumatology/kez119>.
- [23] H. Radner, K. Yoshida, M. Frits, C. Iannaccone, N.A. Shadick, M. Weinblatt, J. S. Smolen, D.H. Solomon, The impact of multimorbidity status on treatment response in rheumatoid arthritis patients initiating disease-modifying anti-rheumatic drugs, *Rheumatology* 54 (2015) 2076–2084, <https://doi.org/10.1093/rheumatology/kev239>.
- [24] A. Emamifar, I.M. Jensen Hansen, The influence of thyroid diseases, diabetes mellitus, primary hyperparathyroidism, vitamin B12 deficiency and other comorbid autoimmune diseases on treatment outcome in patients with rheumatoid arthritis: an exploratory cohort study, *Medicine (Baltim.)* 97 (2018) e10865, <https://doi.org/10.1097/MD.00000000000010865>.
- [25] R. Lorenzon, D. Iannis, C. Ribet, S. Harris, C. Maeva, T. Olivia, D. Eric, C. Patrice, H. Agnes, B. Bahram, S. David, B. Francis, G. Gilles, R. Pierre, B. Olivier, M. Kuberaka, S. Jeremie, S. Philippe, R. Michelle, S. Adrien, B. Claude, A. Caroline, V. Eric, K. David, M.-F. Encarnita, Clinical data specification and coding for cross-

- analyses with omics data in autoimmune disease trials, bioRxiv (2018), <https://doi.org/10.1101/360719>.
- [26] C. Gaudet-Blavignac, V. Foufi, M. Bjelogrić, C. Lovis, Use of the systematized nomenclature of medicine clinical terms (SNOMED CT) for processing free text in health care: systematic scoping review, *J. Med. Internet Res.* 23 (2021) e24594, <https://doi.org/10.2196/24594>.
- [27] M.J. Greenacre, *Correspondence Analysis in Practice*, third ed., CRC Press, Taylor & Francis Group, Boca Raton London New York, 2017 a Chapman & Hall book.
- [28] J.S. Smolen, R.B.M. Landewé, S.A. Bergstra, A. Kerschbaumer, A. Sepriano, D. Aletaha, R. Caporali, C.J. Edwards, K.L. Hyrich, J.E. Pope, S. de Souza, T. A. Stamm, T. Takeuchi, P. Verschuere, K.L. Winthrop, A. Balsa, J.M. Bathon, M. H. Buch, G.R. Burmester, F. Buttgerit, M.H. Cardiel, K. Chatzidionysiou, C. Coudaneu, M. Cutolo, A.A. den Broeder, K. El Aoufy, A. Finckh, J.E. Fonseca, J.-E. Gottenberg, E.A. Haavardsholm, A. Iagnocco, K. Lauper, Z. Li, I.B. McInnes, E. F. Mysler, P. Nash, G. Poor, G.G. Ristic, F. Rivellese, A. Rubbert-Roth, H. Schulze-Koops, N. Stoilov, A. Strangfeld, A. van der Helm-van Mil, E. van Duuren, T.P. M. Vliet Vlieland, R. Westhovens, D. van der Heijde, EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update, *Ann. Rheum. Dis.* 82 (2023) 3–18, <https://doi.org/10.1136/ard-2022-223356>.
- [29] S. Ramiro, E. Nikiphorou, A. Sepriano, A. Ortolan, C. Webers, X. Baraliakos, R.B. M. Landewé, F.E. Van den Bosch, B. Boteva, A. Bremander, P. Carron, A. Ciurea, F. A. van Gaalen, P. Géher, L. Gensler, J. Hermann, M. de Hooge, M. Husakova, U. Kiltz, C. López-Medina, P.M. Machado, H. Marzo-Ortega, A. Molto, V. Navarro-Compán, M.J. Nissen, F.M. Pimentel-Santos, D. Poddubnyy, F. Proft, M. Rudwaleit, M. Telkman, S.S. Zhao, N. Ziade, D. van der Heijde, ASAS-EULAR recommendations for the management of axial spondyloarthritis: 2022 update, *Ann. Rheum. Dis.* 82 (2023) 19–34, <https://doi.org/10.1136/ard-2022-223296>.
- [30] M. Cutolo, Y. Shoenfeld, D.P. Bogdanos, E. Gotelli, M. Salvato, L. Gunkl-Tóth, G. Nagy, To treat or not to treat rheumatoid arthritis with glucocorticoids? A reheated debate, *Autoimmun. Rev.* 23 (2024) 103437, <https://doi.org/10.1016/j.autrev.2023.103437>.
- [31] T. Wirth, P. Lafforgue, T. Pham, NSAID: current limits to prescription, *Joint Bone Spine* 91 (2024) 105685, <https://doi.org/10.1016/j.jbspin.2023.105685>.
- [32] F. Aslam, N.A. Khan, Tools for the assessment of comorbidity burden in rheumatoid arthritis, *Front. Med.* 5 (2018) 39, <https://doi.org/10.3389/fmed.2018.00039>.
- [33] J.A. O'Rourke, C. Ravichandran, Y.J. Howe, J.E. Mullett, C.J. Keary, S.B. Golas, A. R. Hureau, M. McCormick, J. Chung, N.R. Rose, C.J. McDougale, Accuracy of self-reported history of autoimmune disease: a pilot study, *PLoS One* 14 (2019) e0216526, <https://doi.org/10.1371/journal.pone.0216526>.
- [34] S. Kivity, N. Agmon-Levin, M. Blank, Y. Shoenfeld, Infections and autoimmunity—friends or foes? *Trends Immunol.* 30 (2009) 409–414, <https://doi.org/10.1016/j.it.2009.05.005>.
- [35] K. Bjornevik, M. Cortese, B.C. Healy, J. Kuhle, M.J. Mina, Y. Leng, S.J. Elledge, D. W. Niebuhr, A.I. Scher, K.L. Munger, A. Ascherio, Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis, *Science* 375 (2022) 296–301, <https://doi.org/10.1126/science.abj8222>.
- [36] K. Csorba, L.A. Schirmbeck, E. Tuncer, C. Ribi, P. Roux-Lombard, C. Chizzolini, U. Huynh-Do, D. Vanhecke, M. Trendelenburg, Anti-C1q Antibodies as occurring in systemic lupus erythematosus could be induced by an Epstein-Barr virus-derived antigenic site, *Front. Immunol.* 10 (2019) 2619, <https://doi.org/10.3389/fimmu.2019.02619>.
- [37] M. Rojas, P. Restrepo-Jiménez, D.M. Monsalve, Y. Pacheco, Y. Acosta-Ampudia, C. Ramírez-Santana, P.S.C. Leung, A.A. Ansari, M.E. Gershwin, J.-M. Anaya, Molecular mimicry and autoimmunity, *J. Autoimmun.* 95 (2018) 100–123, <https://doi.org/10.1016/j.jaut.2018.10.012>.
- [38] V. Quiniou, P. Barennes, V. Mhanna, P. Stys, H. Vantomme, Z. Zhou, F. Martina, N. Coatnoan, M. Barbie, H.-P. Pham, B. Clémenceau, H. Vie, M. Shugay, A. Six, B. Brandao, R. Mallone, E. Mariotti-Ferrandiz, D. Klatzmann, Human thymopoiesis produces polyspecific CD8+ α/β T cells responding to multiple viral antigens, *Elife* 12 (2023) e81274, <https://doi.org/10.7554/eLife.81274>.
- [39] C. Fantodji, P. Jantchou, M.-E. Parent, M.-C. Rousseau, Appendectomy and risk for inflammatory bowel disease: effect of age and time post appendectomy - a cohort study, *BMJ Open Gastroenterol* 9 (2022) e000925, <https://doi.org/10.1136/bmjgast-2022-000925>.
- [40] M. García-Argibay, A. Hiyoshi, S. Montgomery, Acute appendicitis and ulcerative colitis: a population-based sibling comparison study, *BMJ Open Gastroenterol* 9 (2022) e001041, <https://doi.org/10.1136/bmjgast-2022-001041>.
- [41] G.G. Kaplan, B.V. Pedersen, R.E. Andersson, B.E. Sands, J. Korzenik, M. Frisch, The risk of developing Crohn's disease after an appendectomy: a population-based cohort study in Sweden and Denmark, *Gut* 56 (2007) 1387–1392, <https://doi.org/10.1136/gut.2007.121467>.
- [42] Y.-M. Lee, C.-T. Kor, D. Zhou, H.-C. Lai, C.-C. Chang, W.-L. Ma, Impact of age at appendectomy on development of type 2 diabetes: a population-based cohort study, *PLoS One* 13 (2018) e0205502, <https://doi.org/10.1371/journal.pone.0205502>.
- [43] K. Wijanpreecha, P. Panjawatnan, O.Y. Mousa, W. Cheungpasitporn, S. Pungpapong, P. Ungprasert, Association between appendectomy and risk of primary sclerosing cholangitis: a systematic review and meta-analysis, *Clin Res Hepatol Gastroenterol* 42 (2018) 436–442, <https://doi.org/10.1016/j.clinre.2018.03.011>.
- [44] C. Lunny, J.A. Knopp-Sihota, S.N. Fraser, Surgery and risk for multiple sclerosis: a systematic review and meta-analysis of case-control studies, *BMC Neurol.* 13 (2013) 41, <https://doi.org/10.1186/1471-2377-13-41>.
- [45] M.K. Collard, J. Bardin, M. Laurin, E. Ogier-Denis, The cecal appendix is correlated with greater maximal longevity in mammals, *J. Anat.* 239 (2021) 1157–1169, <https://doi.org/10.1111/joa.13501>.
- [46] R. Randal Bollinger, A.S. Barbas, E.L. Bush, S.S. Lin, W. Parker, Biofilms in the large bowel suggest an apparent function of the human vermiform appendix, *J. Theor. Biol.* 249 (2007) 826–831, <https://doi.org/10.1016/j.jtbi.2007.08.032>.
- [47] T. Czarnowicki, H. He, J.G. Krueger, E. Guttman-Yassky, Atopic dermatitis endotypes and implications for targeted therapeutics, *J. Allergy Clin. Immunol.* 143 (2019) 1–11, <https://doi.org/10.1016/j.jaci.2018.10.032>.
- [48] Z.C. Chiesa Fuxench, J. Wan, S. Wang, M.N. Syed, D.B. Shin, K. Abuabara, J. M. Gelfand, Risk of inflammatory bowel disease in patients with atopic dermatitis, *JAMA Dermatol* (2023) e232875, <https://doi.org/10.1001/jamadermatol.2023.2875>.
- [49] Y.M.F. Andersen, A. Egeberg, G.H. Gislason, L. Skov, J.P. Thyssen, Autoimmune diseases in adults with atopic dermatitis, *J. Am. Acad. Dermatol.* 76 (2017) 274–280.e1, <https://doi.org/10.1016/j.jaad.2016.08.047>.
- [50] J. Holmes, L.C. Fairclough, I. Todd, Atopic dermatitis and autoimmunity: the occurrence of autoantibodies and their association with disease severity, *Arch. Dermatol. Res.* 311 (2019) 141–162, <https://doi.org/10.1007/s00403-019-01890-4>.
- [51] G. Hajishengallis, T. Chavakis, Local and systemic mechanisms linking periodontal disease and inflammatory comorbidities, *Nat. Rev. Immunol.* 21 (2021) 426–440, <https://doi.org/10.1038/s41577-020-00488-6>.
- [52] R.C. Brewer, T.V. Lanz, C.R. Hale, G.D. Sepich-Poore, C. Martino, A.D. Swafford, T. S. Carroll, S. Kongpachith, L.K. Blum, S.E. Elliott, N.E. Blachere, S. Parveen, J. Fak, V. Yao, O. Troyanskaya, M.O. Frank, M.S. Bloom, S. Jahanbani, A.M. Gomez, R. Iyer, N.S. Ramadoss, O. Sharpe, S. Chandrasekaran, L.B. Kelmenson, Q. Wang, H. Wong, H.L. Torres, M. Wiesen, D.T. Graves, K.D. Deane, V.M. Holers, R. Knight, R.B. Darnell, W.H. Robinson, D.E. Orange, Oral mucosal breaks trigger anti-citrullinated bacterial and human protein antibody responses in rheumatoid arthritis, *Sci. Transl. Med.* 15 (2023) eabq8476, <https://doi.org/10.1126/scitranslmed.abq8476>.
- [53] S.I. Grivnenikov, F.R. Greten, M. Karin, Immunity, inflammation, and cancer, *Cell* 140 (2010) 883–899, <https://doi.org/10.1016/j.cell.2010.01.025>.
- [54] K. Pape, R. Tamouza, M. Leboyer, F. Zipp, Immunoneuropsychiatry - novel perspectives on brain disorders, *Nat. Rev. Neurol.* 15 (2019) 317–328, <https://doi.org/10.1038/s41582-019-0174-4>.
- [55] E.S. Husebye, M.S. Anderson, O. Kämpe, Autoimmune polyendocrine syndromes, *N. Engl. J. Med.* 378 (2018) 1132–1141, <https://doi.org/10.1056/NEJMr1713301>.
- [56] A. Beltai, B. Combe, A. Coffy, C. Gaujoux-Viala, C. Lukas, A. Saraux, M. Dougados, J.P. Daurès, C. Hua, Impact of multimorbidity on disease modifying antirheumatic drug therapy in early rheumatoid arthritis: data from the ESPOIR cohort, *Joint Bone Spine* 89 (2022) 105326, <https://doi.org/10.1016/j.jbspin.2021.105326>.