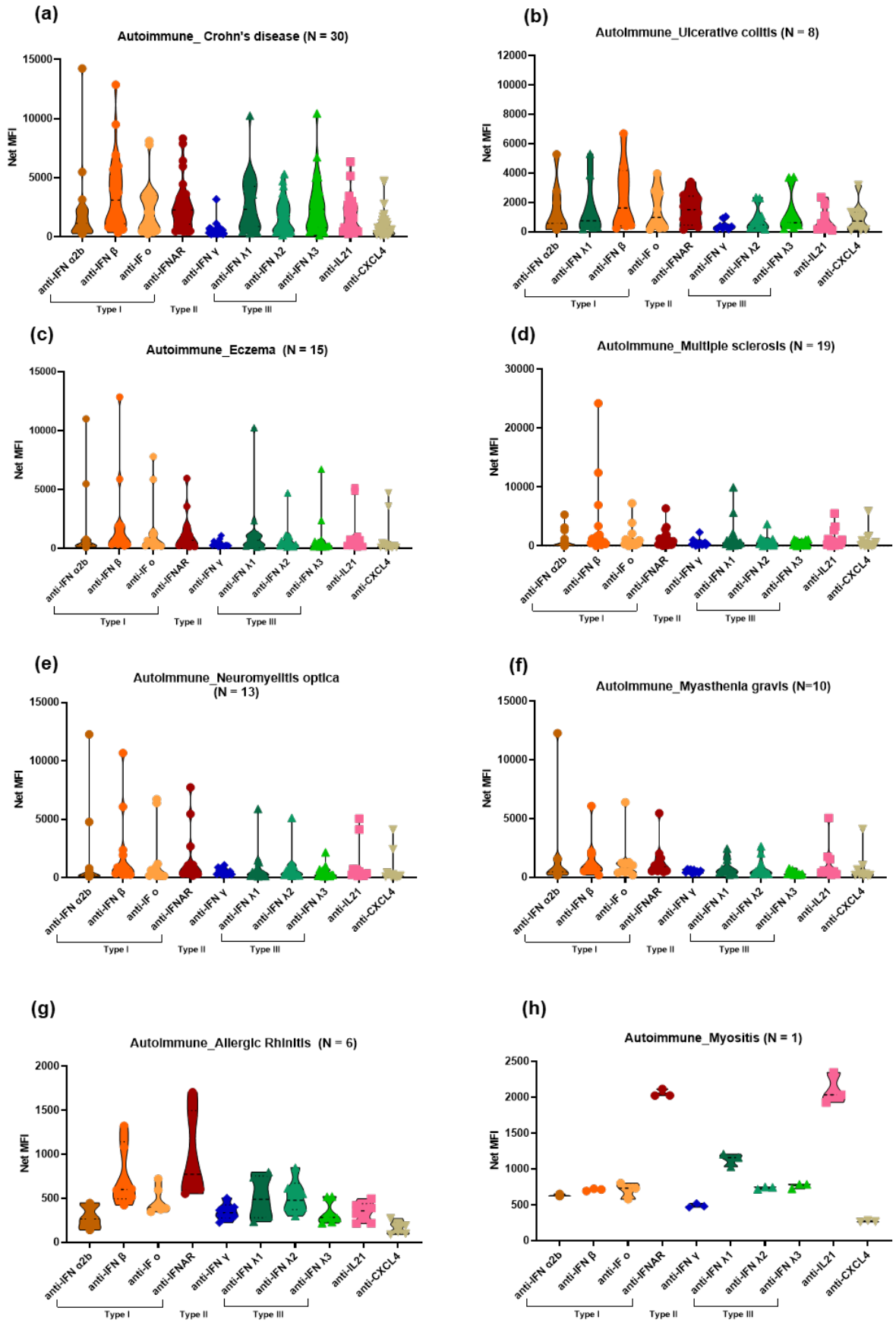
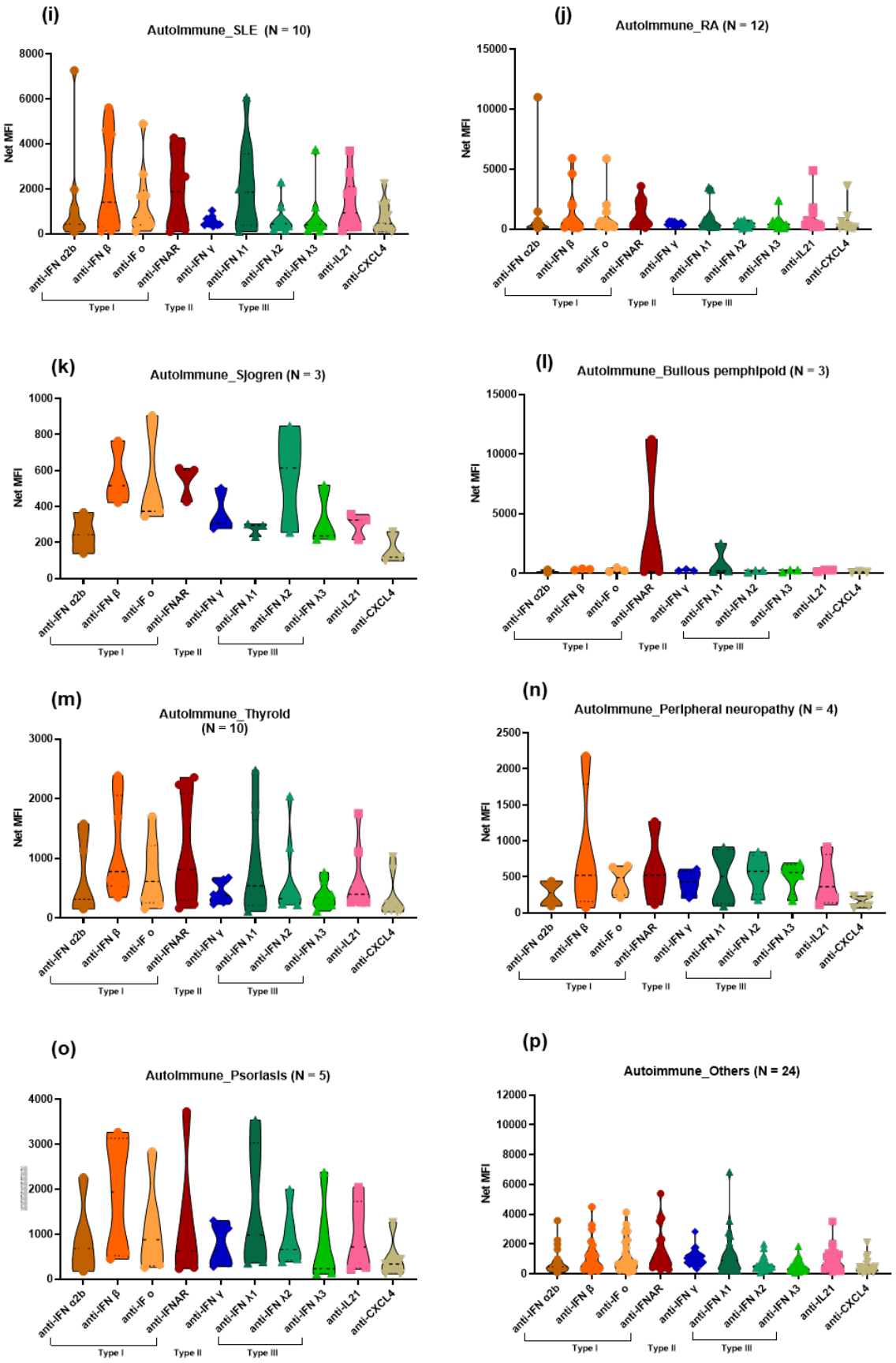
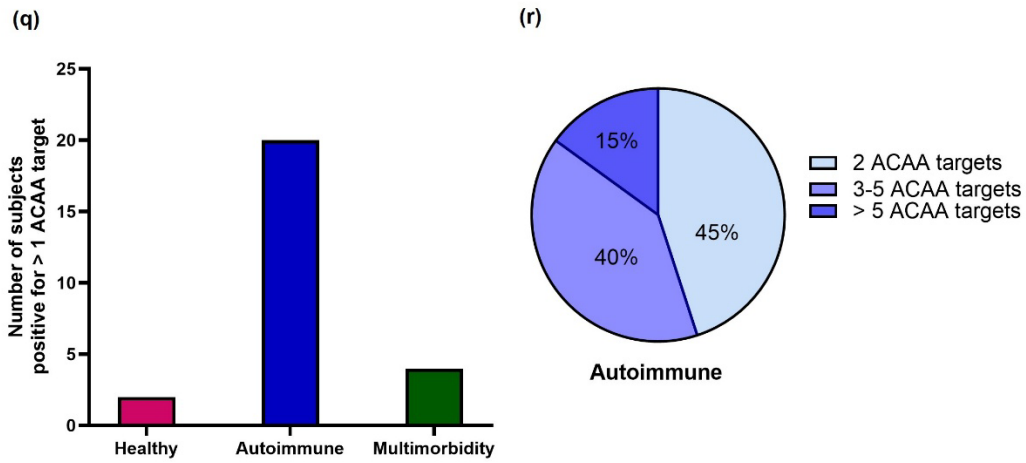
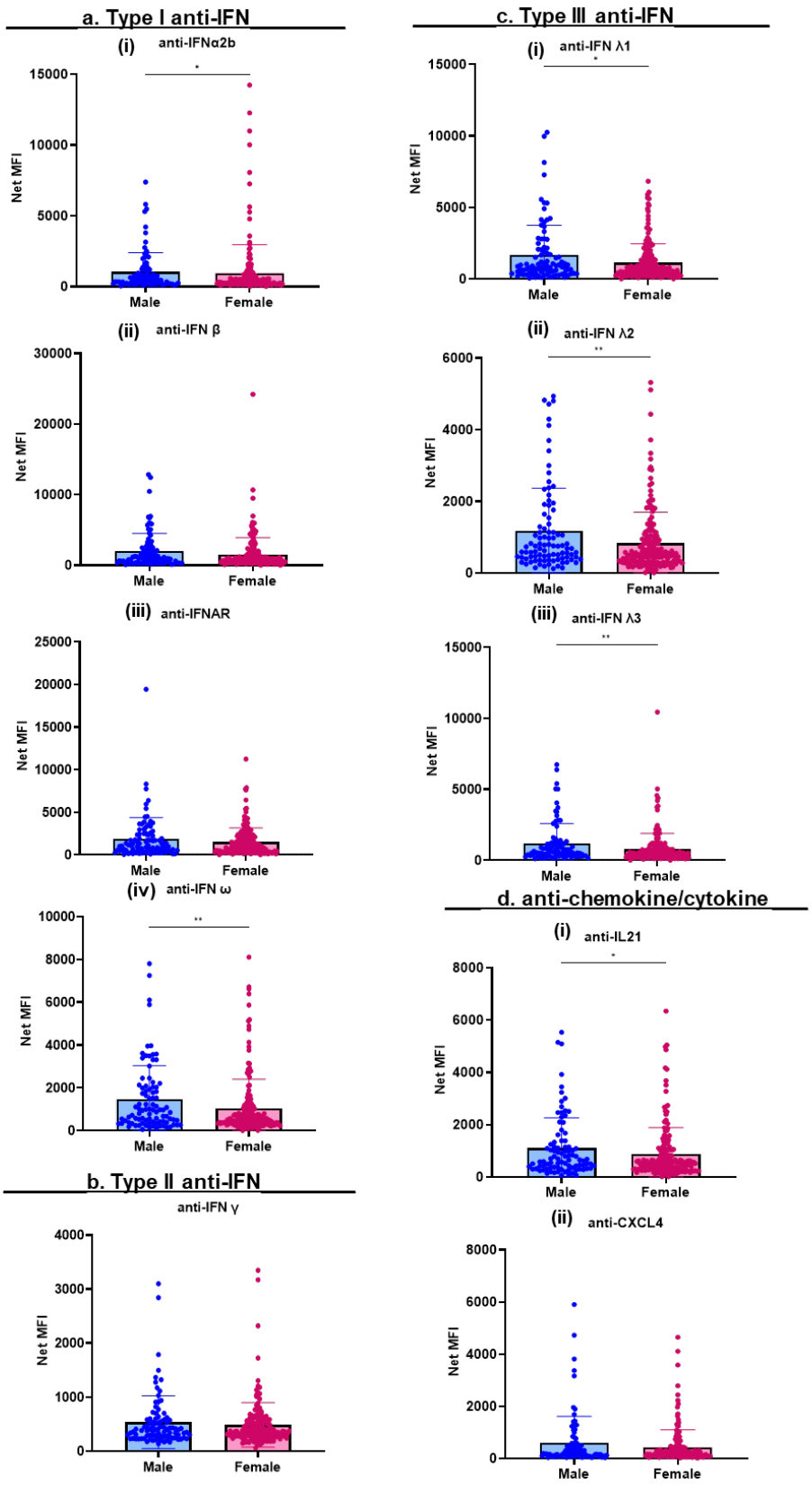

(a)
Autoimmune_ Crohn's disease (N = 30)
Net MFI
15000
10000
5000
0
anti-IFN α2b
anti-IFN β
anti-IF o
anti-IFNAR
anti-IFN γ
anti-IFN λ1
anti-IFN λ2
anti-IFN λ3
anti-IL21
anti-CXCL4
Type I
Type II
Type III
(b)
Autoimmune_Ulcerative colitis (N = 8)
Net MFI
12000
10000
8000
6000
4000
2000
0
anti-IFN α2b
anti-IFN λ1
anti-IFN β
anti-IF o
anti-IFNAR
anti-IFN γ
anti-IFN λ2
anti-IFN λ3
anti-IL21
anti-CXCL4
Type I
Type II
Type III
(c)
Autoimmune_Eczema (N = 15)
Net MFI
15000
10000
5000
0
anti-IFN α2b
anti-IFN β
anti-IF o
anti-IFNAR
anti-IFN γ
anti-IFN λ1
anti-IFN λ2
anti-IFN λ3
anti-IL21
anti-CXCL4
Type I
Type II
Type III
(d)
Autoimmune_Multiple sclerosis (N = 19)
Net MFI
30000
20000
10000
0
anti-IFN α2b
anti-IFN β
anti-IF o
anti-IFNAR
anti-IFN γ
anti-IFN λ1
anti-IFN λ2
anti-IFN λ3
anti-IL21
anti-CXCL4
Type I
Type II
Type III
(e)
Autoimmune_Neuromyelitis optica
(N = 13)
Net MFI
15000
10000
5000
0
anti-IFN α2b
anti-IFN β
anti-IF o
anti-IFNAR
anti-IFN γ
anti-IFN λ1
anti-IFN λ2
anti-IFN λ3
anti-IL21
anti-CXCL4
Type I
Type II
Type III
(f)
Autoimmune_Myasthenia gravis (N=10)
Net MFI
15000
10000
5000
0
anti-IFN α2b
anti-IFN β
anti-IF o
anti-IFNAR
anti-IFN γ
anti-IFN λ1
anti-IFN λ2
anti-IFN λ3
anti-IL21
anti-CXCL4
Type I
Type II
Type III
(g)
Autoimmune_Allergic Rhinitis (N = 6)
Net MFI
2000
1500
1000
500
0
anti-IFN α2b
anti-IFN β
anti-IF o
anti-IFNAR
anti-IFN γ
anti-IFN λ1
anti-IFN λ2
anti-IFN λ3
anti-IL21
anti-CXCL4
Type I
Type II
Type III
(h)
Autoimmune_Myositis (N = 1)
Net MFI
2500
2000
1500
1000
500
0
anti-IFN α2b
anti-IFN β
anti-IF o
anti-IFNAR
anti-IFN γ
anti-IFN λ1
anti-IFN λ2
anti-IFN λ3
anti-IL21
anti-CXCL4
Type I
Type II
Type III


(i)
Autoimmune_SLE (N = 10)
(j)
Autoimmune_RA (N = 12)
(k)
Autoimmune_Sjogren (N = 3)
(l)
Autoimmune_Bullous pemphigoid (N = 3)
(m)
Autoimmune_Thyroid (N = 10)
(n)
Autoimmune_Peripheral neuropathy (N = 4)
(o)
Autoimmune_Psoriasis (N = 5)
(p)
Autoimmune_Others (N = 24)
Net MFI
anti-IFN α2b
anti-IFN β
anti-IF ο
anti-IFNAR
anti-IFN γ
anti-IFN λ1
anti-IFN λ2
anti-IFN λ3
anti-IL21
anti-CXCL4
Type I
Type II
Type III



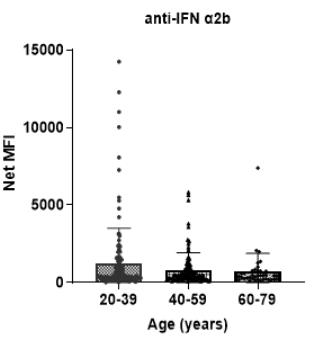
Supplementary figure 1: An autoimmune disease-specific representation of the anti-cytokine autoantibody levels. The autoimmune group was stratified based on the various conditions presented by the individuals. Truncated box-violin plots were employed to display the net MFI autoantibody levels across the different targets evaluated in the magnetic-bead based Luminex assay. The plots are represented as follows: (a-p) Each graph represents one specific anti-cytokine autoantibody target. All data is represented as mean± S.E.M for 3 technical replicate experiments. (q)- The bar graphs represent the number of subjects across the 3 different subsets, that display net MFI values above the defined threshold values for more than 1 ACAA target. (q-r)The pie chart focuses on the autoimmune group and is divided into percentage of subjects which display net MFI values above the defined threshold values for 2, 3-5 and >5 ACAA targets respectively. The percentage values for each group is reflected on the pie chart.

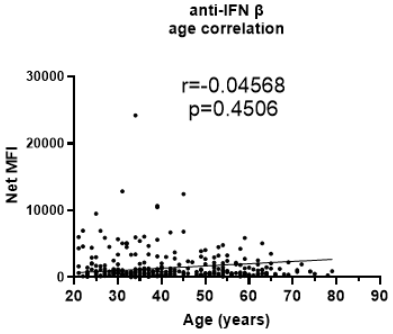


Supplementary figure 2: Assessment of sex as a demographic factor influencing autoantibody levels: The measured net MFI autoantibody levels for the cohort was distributed based on males vs females for each target on the anti-cytokine autoantibody panel. Dotplots were used to represent the comparison of net MFI levels between the 2 groups. a (i-Iv)- Type I anti- IFNs, b- Type II anti-IFN, c (i-iii)-Type III anti-IFNs and d (i and ii)-anti-cytokine/anti-chemokine. Each graph evaluates one specific anti-cytokine autoantibody. Each dot represents the net MFI value of one individual. The statistical evaluation was performed using the Mann-Whitney. All data is represented as mean± S.E.M for 3 technical replicate experiments.

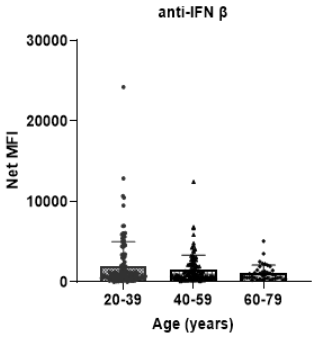
a. Type I anti-IFN

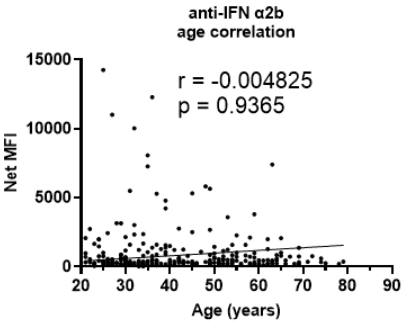
(i)



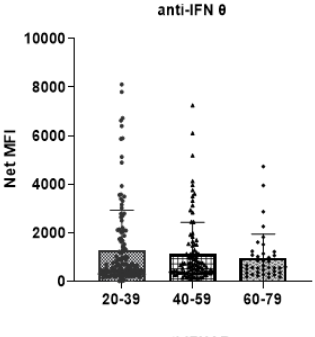


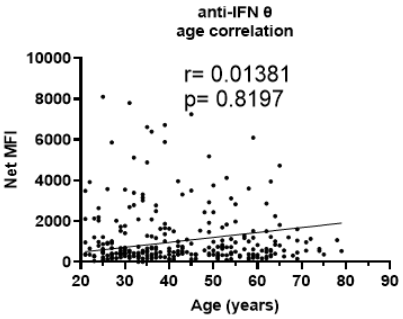
(ii)



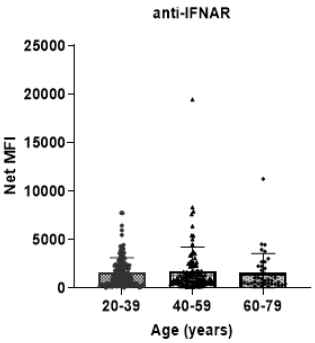


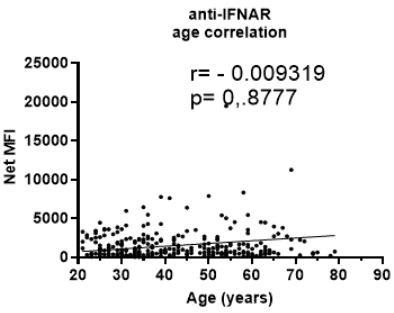
(iii)



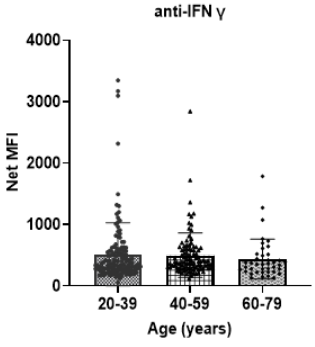


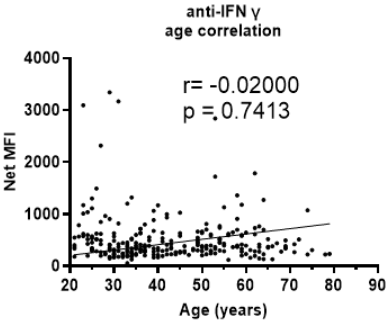
(iv)





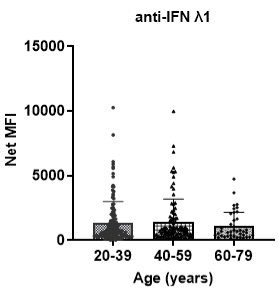
b. Type II anti-IFN

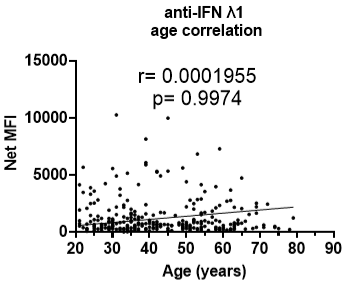




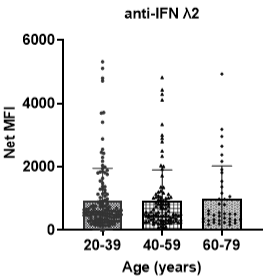
c. Type III anti-IFN

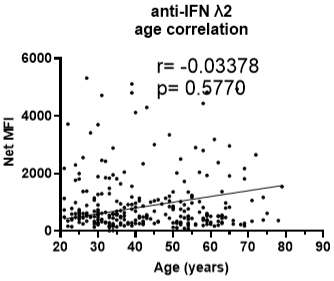
(i)



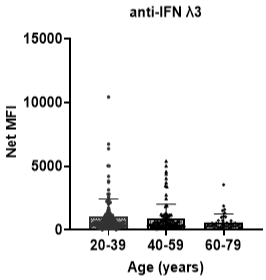


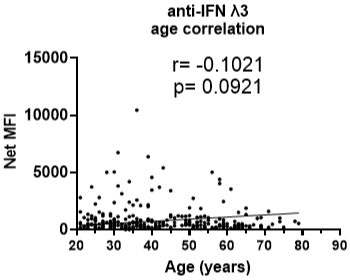
(ii)





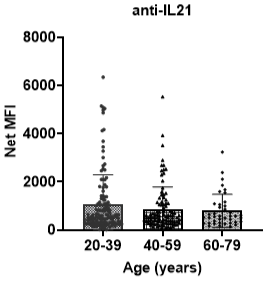
(iii)

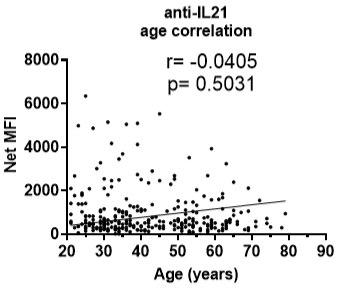




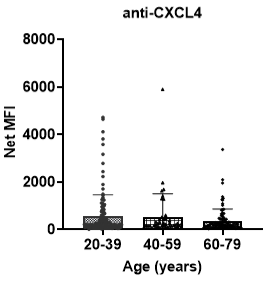
d. anti-chemokine/cytokine

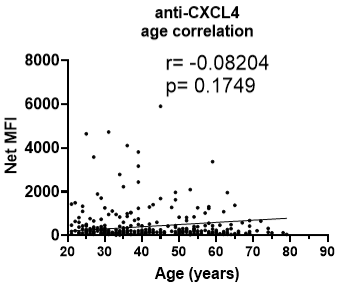
(i)



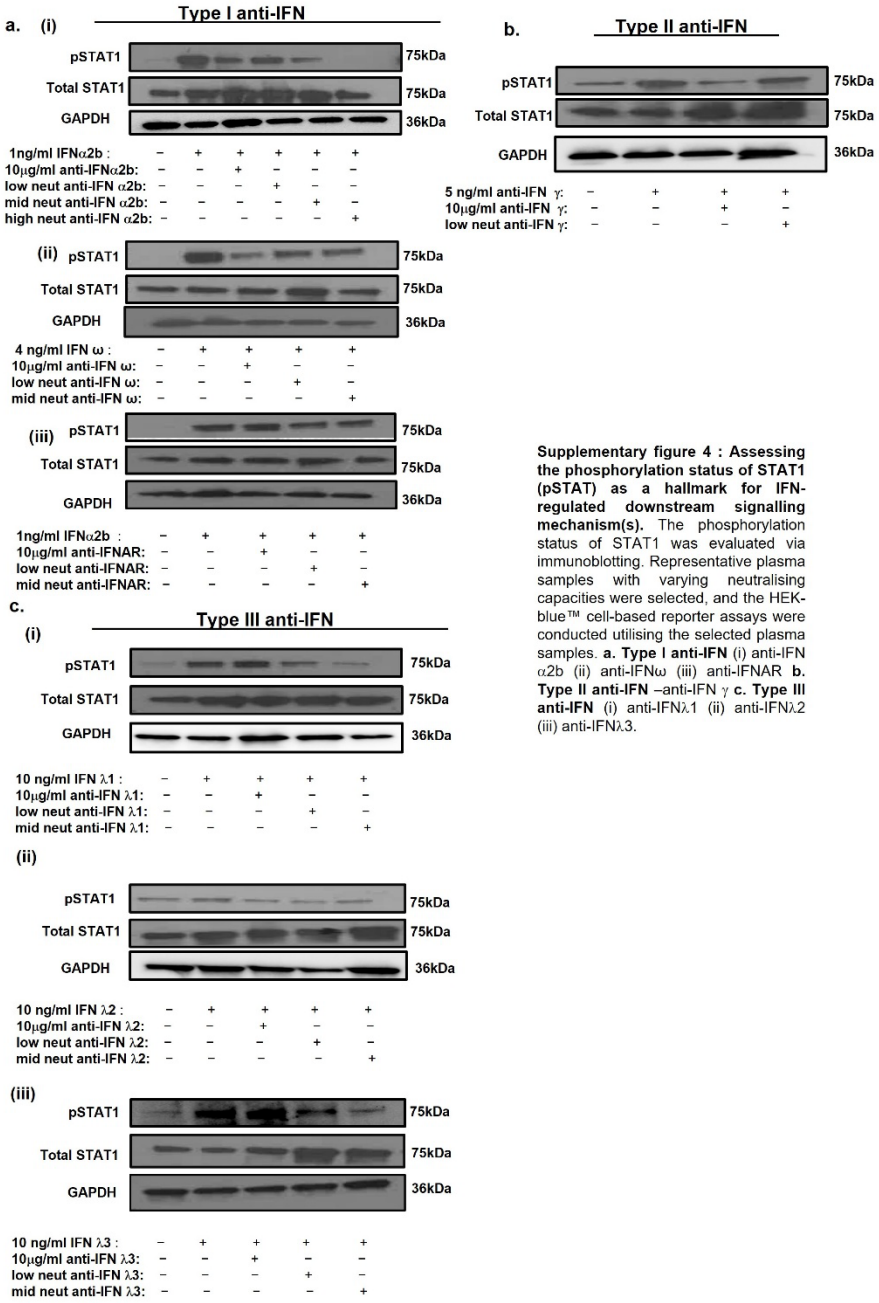


(ii)





Supplementary figure 3: Assessment of age as a demographic factor influencing autoantibody levels: The measured net MFI autoantibody levels for the cohort was distributed based on 3 major age groups; 20-39, 40-59 and 60-79, for each target on the anti-cytokine autoantibody panel. Dotplots were used to represent the comparison of net MFI levels within the age groups. a (i-Iv)- Type I anti- IFNs, b- Type II anti-IFN, c (i-iii)-Type III anti-IFNs and d (i and ii)- anti-cytokine/anti-chemokine. Each graph evaluates one specific anti-cytokine autoantibody. Each dot represents the net MFI value of one individual. The statistical evaluation was performed using the Kruskal-Wallis test followed by Dunn's test. Simple linear regression analyses were conducted, followed by a non-parametric spearman correlation analysis. Each graph evaluates one specific anti-cytokine autoantibody. Each dot represents the net MFI value of one individual. The spearman correlation r is indicated on each linear regression graph. All data is represented as mean± S.E.M for 3 technical replicate experiments.



Supplementary figure 4 : Assessing the phosphorylation status of STAT1 (pSTAT) as a hallmark for IFN-regulated downstream signalling mechanism(s). The phosphorylation status of STAT1 was evaluated via immunoblotting. Representative plasma samples with varying neutralising capacities were selected, and the HEK-blue™ cell-based reporter assays were conducted utilising the selected plasma samples. **a. Type I anti-IFN** (i) anti-IFN α2b (ii) anti-IFNω (iii) anti-IFNAR **b. Type II anti-IFN** –anti-IFN γ **c. Type III anti-IFN** (i) anti-IFNλ1 (ii) anti-IFNλ2 (iii) anti-IFNλ3.

Supplementary figure 4 : Assessing the phosphorylation status of STAT1 (pSTAT) as a hallmark for IFN-regulated downstream signalling mechanism(s). The phosphorylation status of STAT1 was evaluated via immunoblotting. Representative plasma samples with varying neutralising capacities were selected, and the HEK-blue™ cell-based reporter assays were conducted utilising the selected plasma samples. a. Type I anti-IFN (i) anti-IFN α2b (ii) anti-IFNω (iii) anti-IFNAR b. Type II anti-IFN –anti-IFN γ c. Type III anti-IFN (i) anti-IFNλ1 (ii) anti-IFNλ2 (iii) anti-IFNλ3.

	Net MFI threshold value
anti-IFN α2b	4720.46
anti-IFN β	5710.07
anti-IF o	4118.30
anti-IFNAR	6056.31
anti-IFN γ	1869.98
anti-IFN λ1	4541.81
anti-IFN λ2	3505.28
anti-IFN λ3	4358.37
anti-IL21	3209.20
anti-CXCL4	1847.49

Supplementary table 1: The average net MFI levels for each specific autoantibody target were calculated for all 3 groups representing the study cohort, and tabulated as shown above.

	Average Net MFI values		
	Healthy	Autoimmune	Multimorbidity
anti-IFN α2b	682.28	1151.80	1024.22
anti-IFN β	1205.67	2096.70	1441.52
anti-IF o	820.42	1350.31	1267.82
anti-IFNAR	1402.26	1714.70	1775.80
anti-IFN γ	433.44	588.86	364.38
anti-IFN λ1	918.76	1526.00	1371.89
anti-IFN λ2	793.41	926.21	1195.55
anti-IFN λ3	933.15	1004.77	629.83
anti-IL21	661.24	1080.84	1061.70
anti-CXCL4	345.92	646.80	333.78

Supplementary table 2: Net MFI threshold values for each autoantibody target was established by assigning the healthy individuals as a reference group and applying the following formula: (Net MFI threshold= Mean $_{\text{MFI healthy}}$ $\pm$ 3* Av. Std.dev $_{\text{MFI healthy}}$). The respective threshold values were then tabulated as shown above.

(Autoimmune)

Biomarker regulated	Type of ACAA displaying significant association				
IL-12B	anti-IFN β	anti-IFNλ2	anti-IFNλ3		
IL17A	anti-IFN α2b	anti-IFN ω	anti-IFNAR	anti-IFNλ1	anti-IL21
MCP3	anti-IFN β	anti-IFNλ1	anti-CXCL4		
CASP8	anti-IFN α2b	anti-IFN ω	anti-IFNAR	anti-IFNλ1	anti-IL21
GDNF	anti-IFNλ1				
TNF	anti-IFNAR				

Supplementary table 3: Significant associations between target biomarker and ACAA levels in the autoimmune group.

(Multimorbidity)

Biomarker regulated	Type of ACAA displaying significant association				
CCL20	anti-IFN α2b	anti-IFN ω			
CCL19	anti-IFN α2b	anti-IFN β	anti-IFN ω	anti-IFNλ1	anti-IL21
TNFRSF9	anti-IFN ω	anti-IFN γ	anti-CXCL4		
FGF23	anti-IL21				
MCP3	anti-IFN β				
SLAMF1	anti-IFN ω	anti-IL21			
FGF5	anti-IFNAR	anti-IFNλ1			
IL15RA	anti-IFNλ3				
GDNF	anti-IFNλ2	IL-21			
CDCP1	anti-IFN ω				
CXCL10	anti-CXCL4				
CCL25	anti-IFN ω	anti-CXCL4			

Supplementary table 4: Significant associations between target biomarker and ACAA levels in the multimorbidity group