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Collagen II antibodies define an acute onset RA phenotype linked to cellular effects of anti-collagen immune complexes

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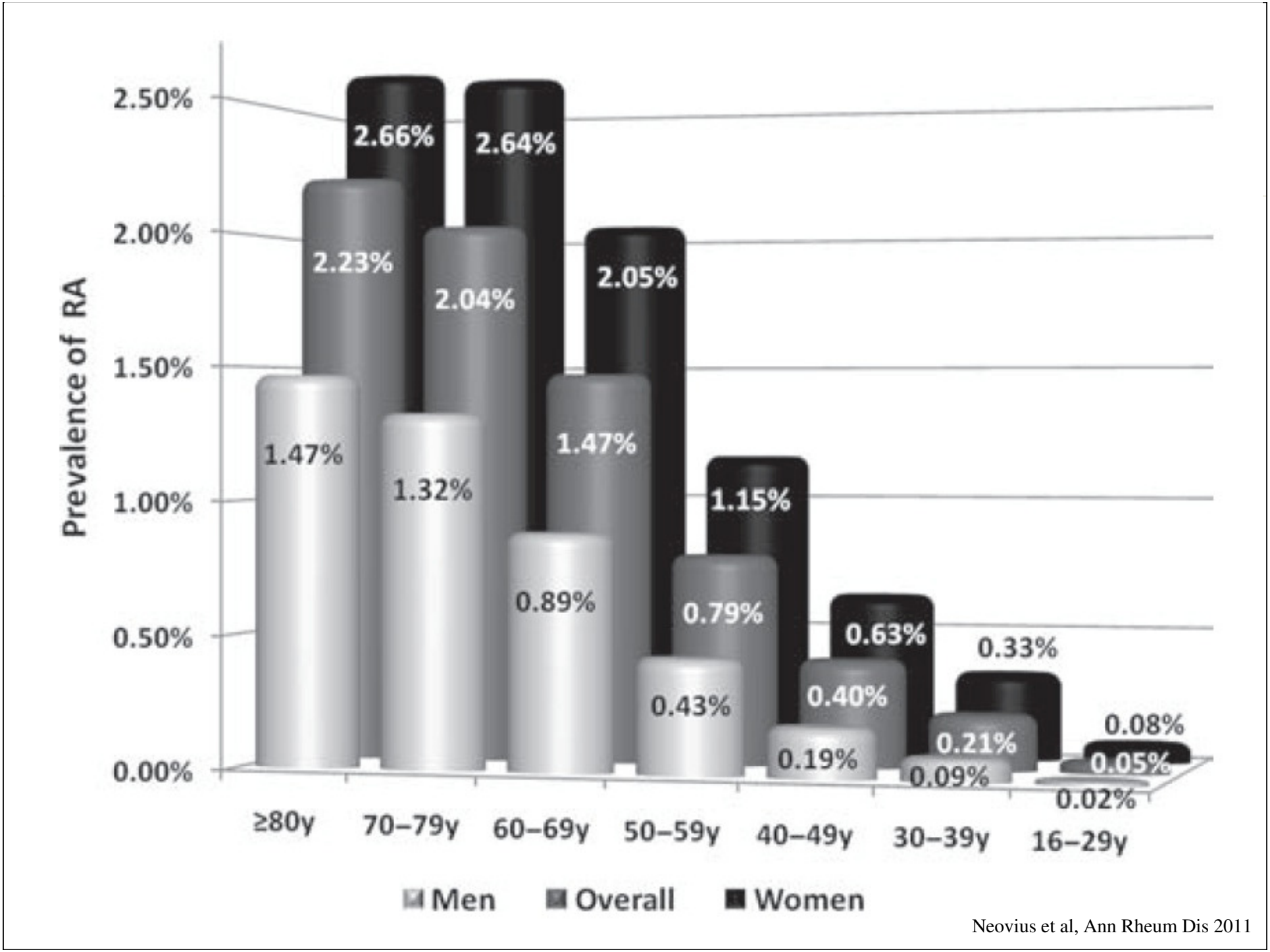
Rheumatoid arthritis (RA)

- A chronic articular and systemic inflammatory disease
- 0.5-0.7% prevalence
- Highest insidence at age 40-65
- Mostly females 3:1



Neovius et al, Ann Rheum Dis 2011

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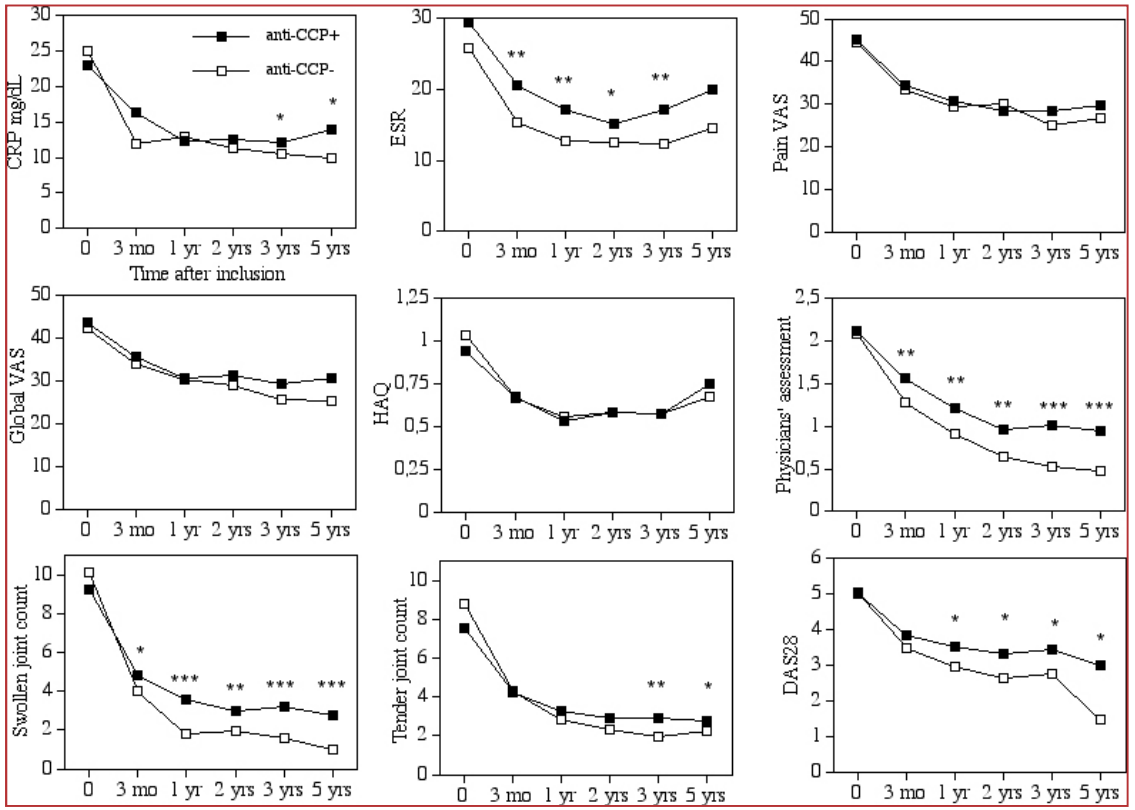
Seropositve RA. Rheumatoid factor (RF) and anti-citrulline antibodies (ACPA) with worse prognosis



Ann Rheum Dis 2005

ACPA associate with HLA DR4/1/10 (shared epitope)
ACPA associate with smoking

Antibodies against collagen type II

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- Collagen II (CII) is a major joint cartilage antigen
- Anti-CII in 3-27 (6-9)% of RA patients
- Exposure of CII protein in acute joint inflammation

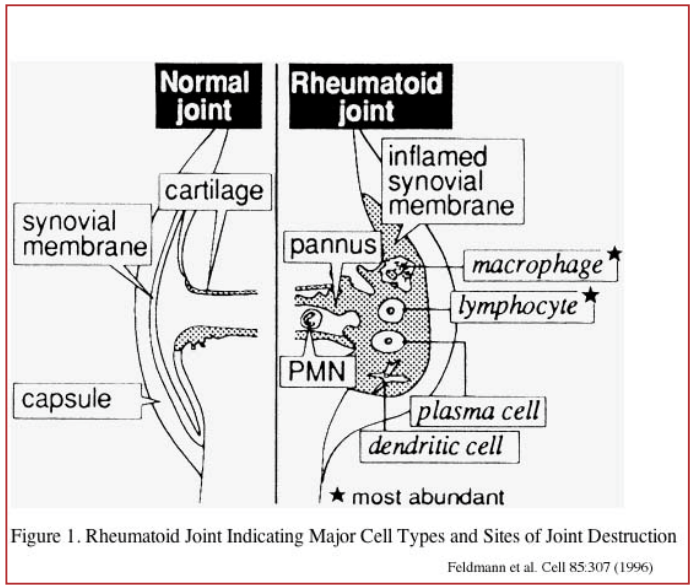
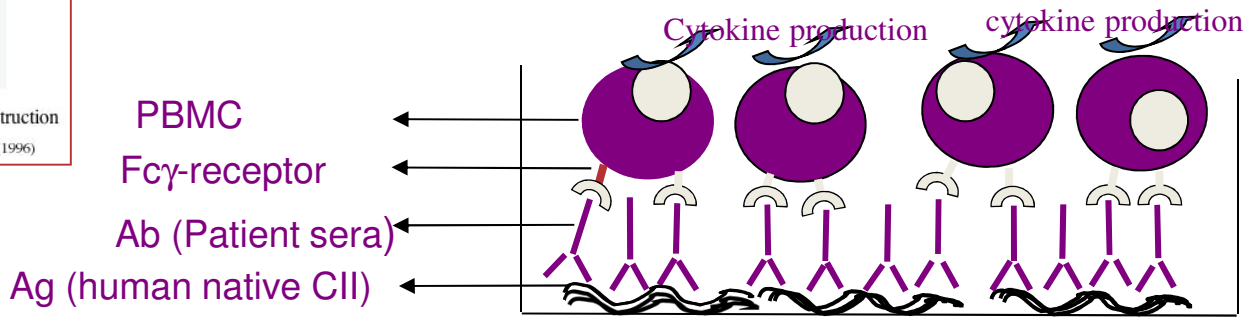


Figure 1. Rheumatoid Joint Indicating Major Cell Types and Sites of Joint Destruction

Feldmann et al. Cell 85:307 (1996)

Model I:



Mullazehi et al. Arthritis Rheum 2006;54:1759-71

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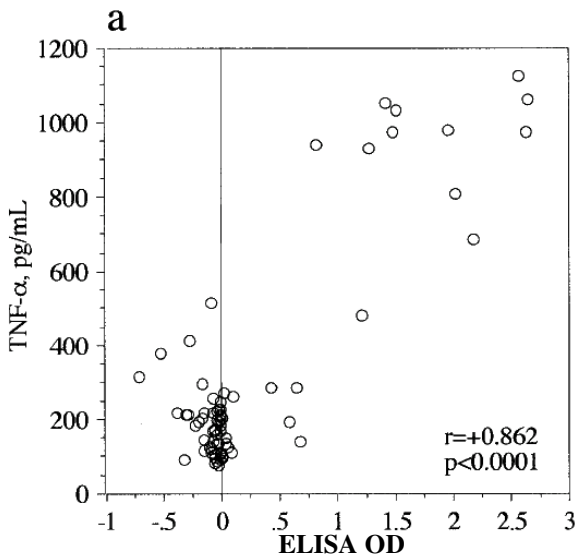
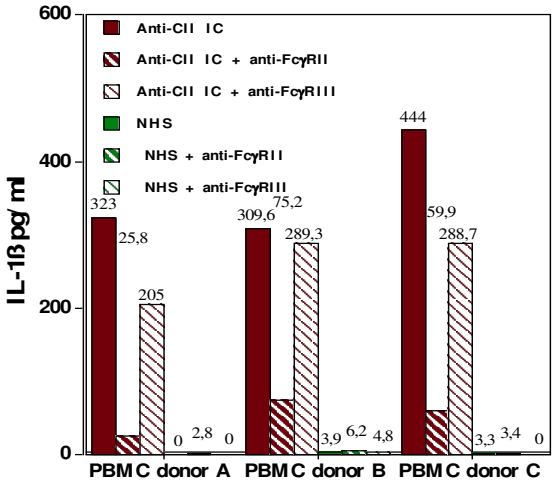
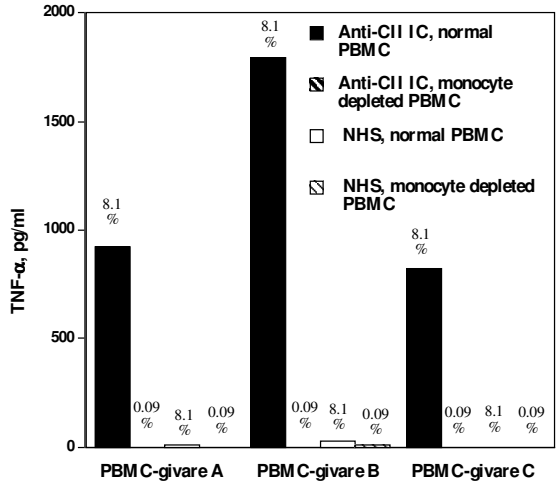
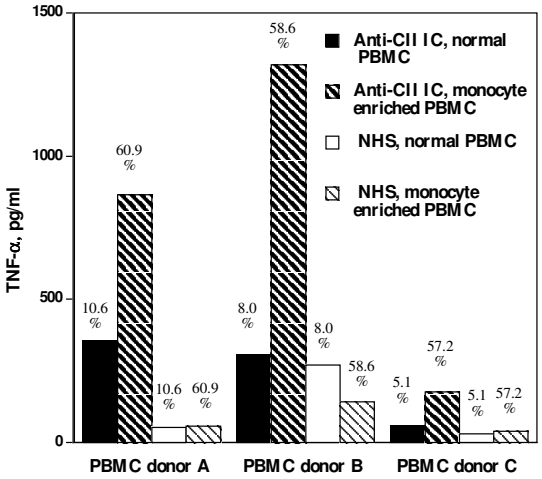
Anti-CII containing IC induce inflammatory cytokines from monocytes via FcγRIIa in a dose-dependent manner









Mullazehi et al. Arthritis Rheum 2006;54:1759-71

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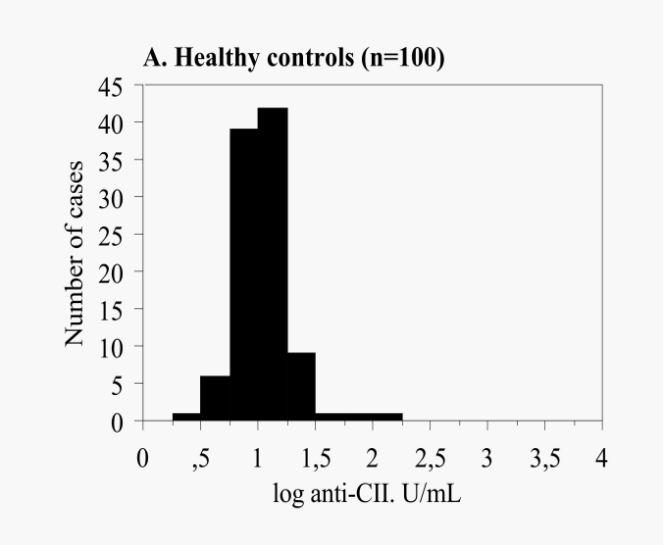
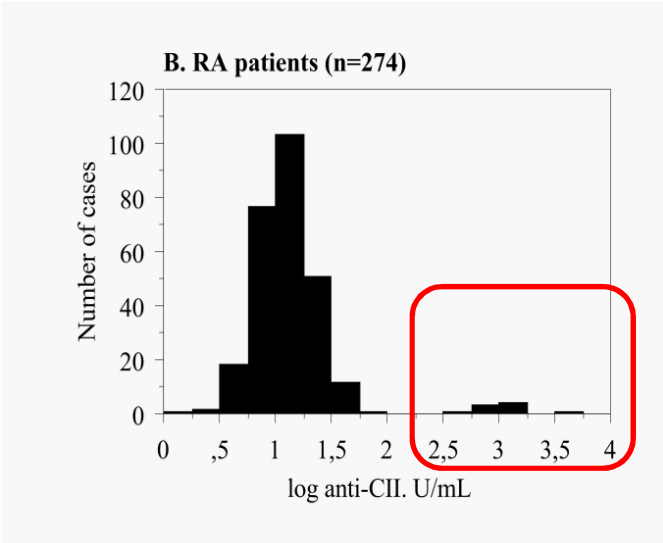
Dichotomous appearance of anti-CII in early RA

- 24 of 274 early RA patients anti-CII positive (8.8%)





Mullazehi et al. Ann Rheum Dis 2007;66:537

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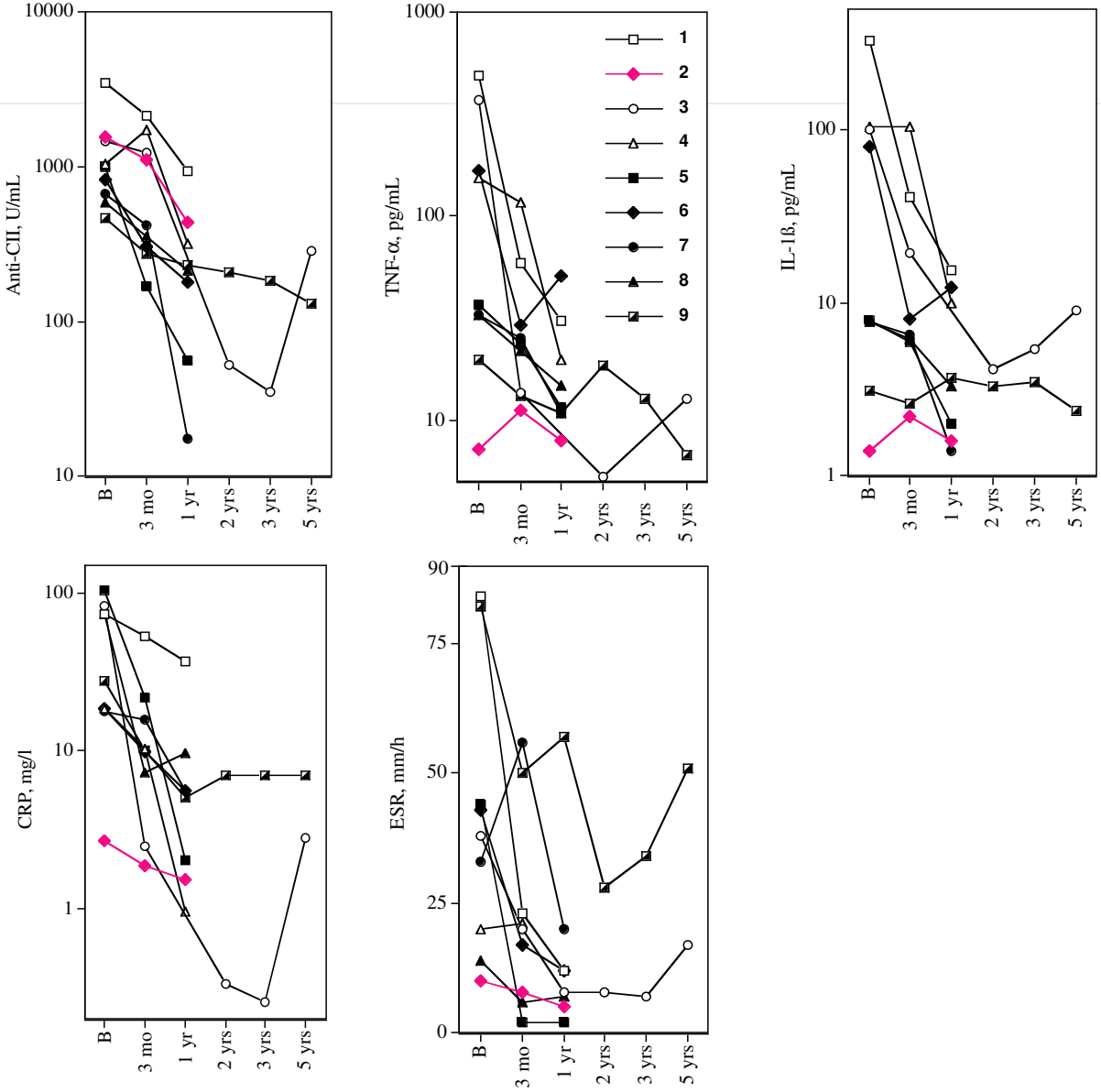
Anti-CII associate with IC-induced cytokine production and with changes in CRP and ESR



Mullazehi et al. Ann Rheum Dis 2007;66:537

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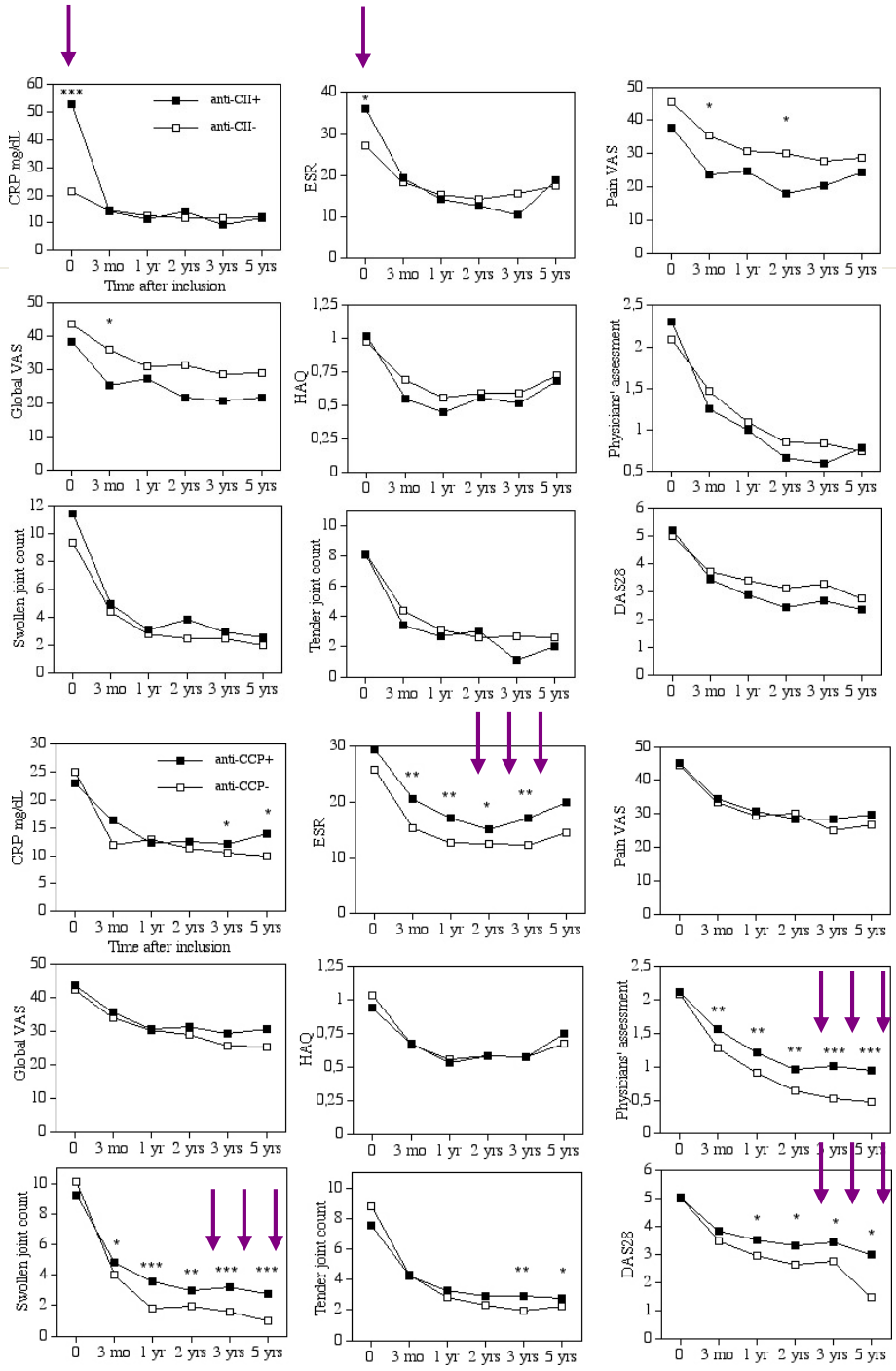

Anti-CII, early inflammation

(Mullazehi et al,Ann Rheum Dis 2007)

Anti-CCP, late inflammation

(Rönnelid et al.Ann Rheum Dis 2005)

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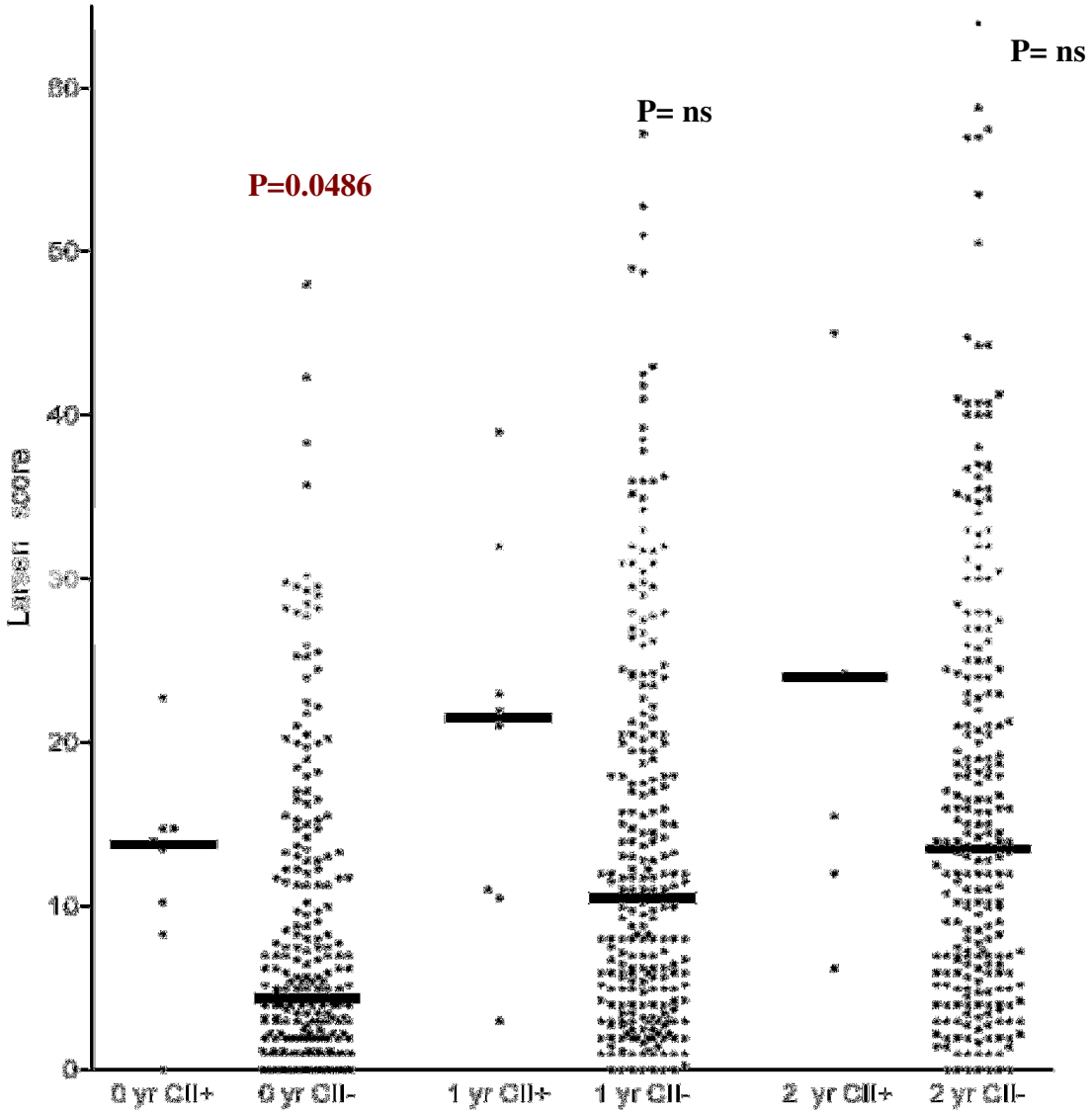
Anti-CII associate with early erosions in RA



Mullazehi M et al, Arthritis Res Ther 2012

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Model II:

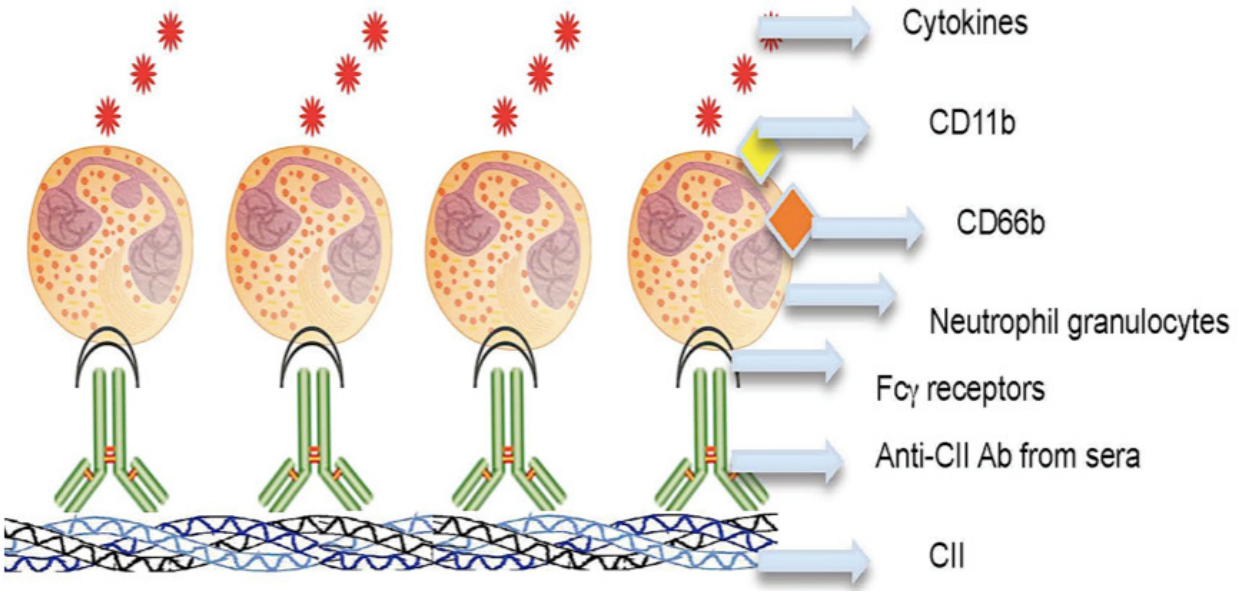

Table 2 Association between, on one hand, *in vitro* granulocyte responses, PBMC responses and baseline antibody levels and, on the other, baseline inflammatory markers, Larsen score and changes in Larsen score during the first 2 years after RA diagnosis

	Baseline CRP	Baseline ESR	Baseline Larsen score	1-year Larsen score	2-year Larsen score	Δ Larsen score 1 – 0 years	Δ Larsen score 2 – 0 years	Δ Larsen score 2 – 1 years
CD16 (PMN)	35/16.5 (0.08)	35.5/19.5 (0.26)	**14.4/5.5 (0.024)**	**22.5/11.0 (0.034)**	**24.0/31.1 (0.046)**	7.3/3.0 (0.08)	9.0/6.3 (0.88)	3.0/2.3 (0.27)
CD66b (PMN)	**49/14 (0.004)**	33/19 (0.063)	13.5/6.0 (0.15)	22.0/11.0 (0.071)	24.0/13.2 (0.059)	**7.5/2.6 (0.017)**	**10.4/5.2 (0.016)**	**5.1/2.3 (0.012)**
MPO (PMN)	14/18 (0.6)	19/21 (0.61)	5.4/7.0 (0.69)	17.0/11.0 (0.99)	17.7/13.2 (0.97)	6.9/2.8 (0.27)	9.6/5.3 (0.41)	2.5/2.3 (0.37)
TNFα (PBMC)	28/17 (0.18)	**43/19 (0.049)**	9.3/6.3 (0.57)	11.6/11.8 (0.75)	15.3/13.2 (0.52)	5.6/3.0 (0.50)	9.4/5.3 (0.43)	2.9/2.3 (0.48)
Anti-CII	**36.5/14 (0.012)**	29/19 (0.10)	11.5/6.3 (0.75)	16.0/11.0 (0.44)	15.0/13.5 (0.44)	4.3/3.6 (0.21)	8.1/5.3 (0.22)	2.6/2.3 (0.29)

Manivel VA et al. Arthritis Res Ther. 2015

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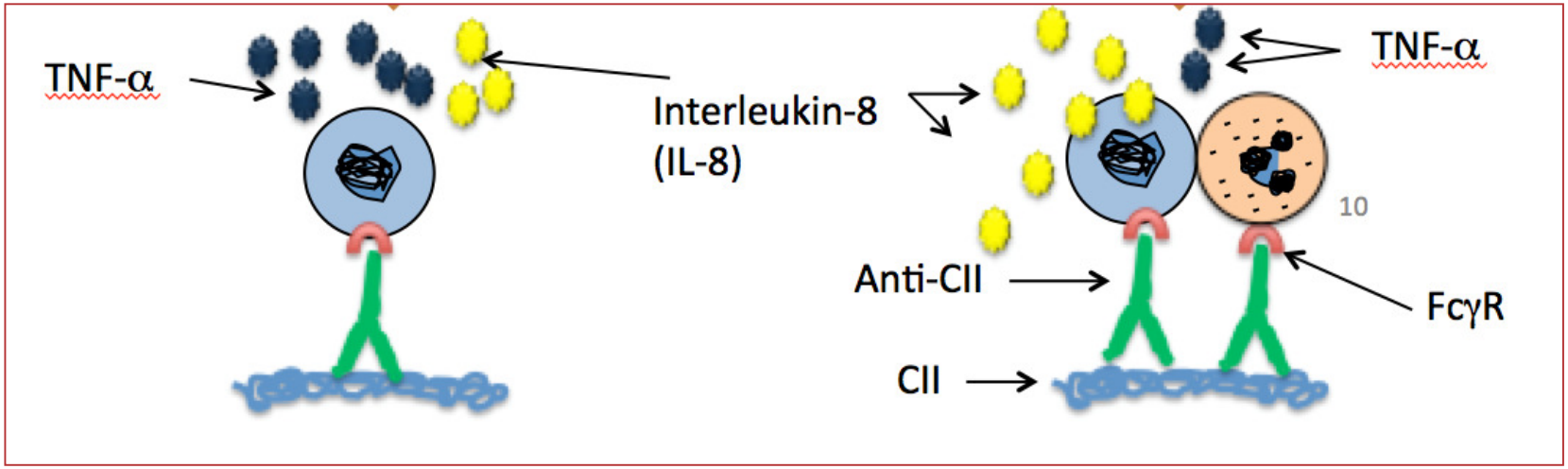
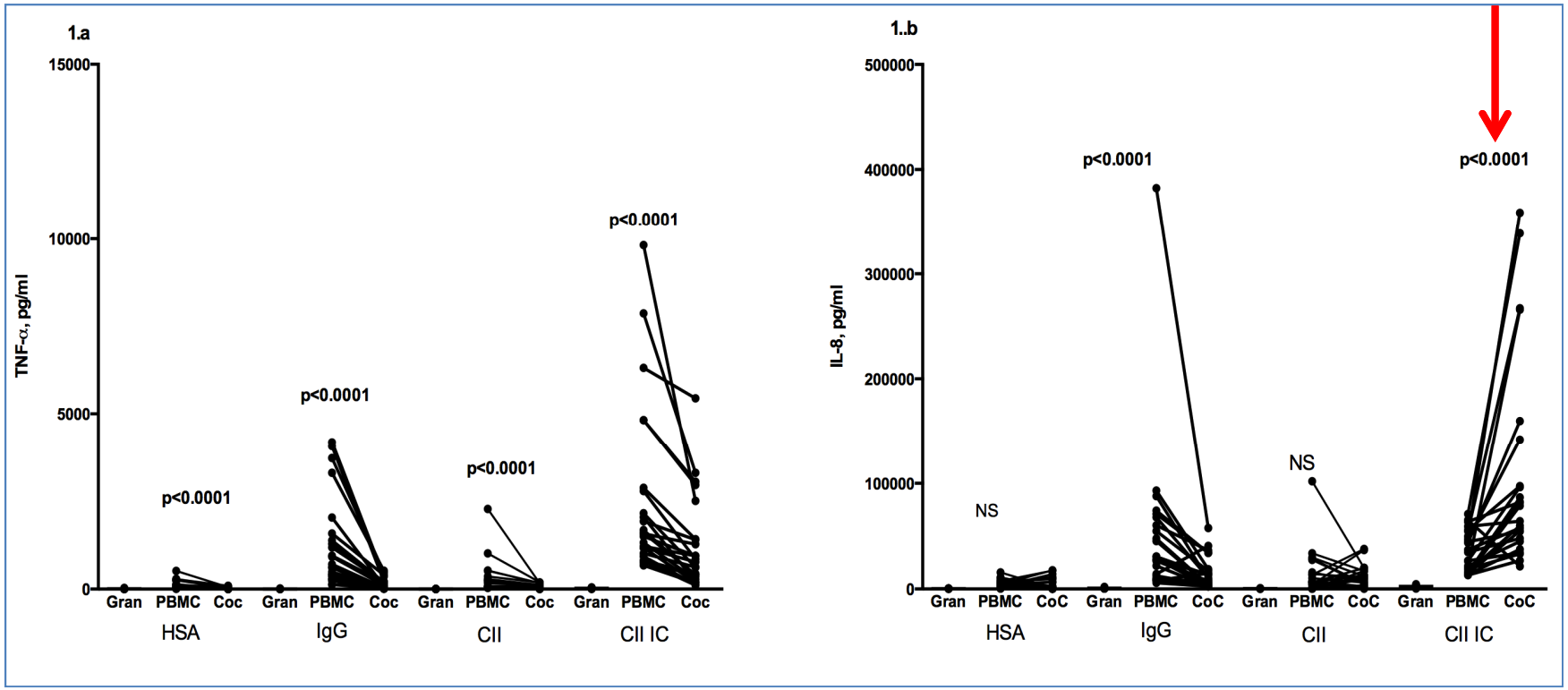
Model III:



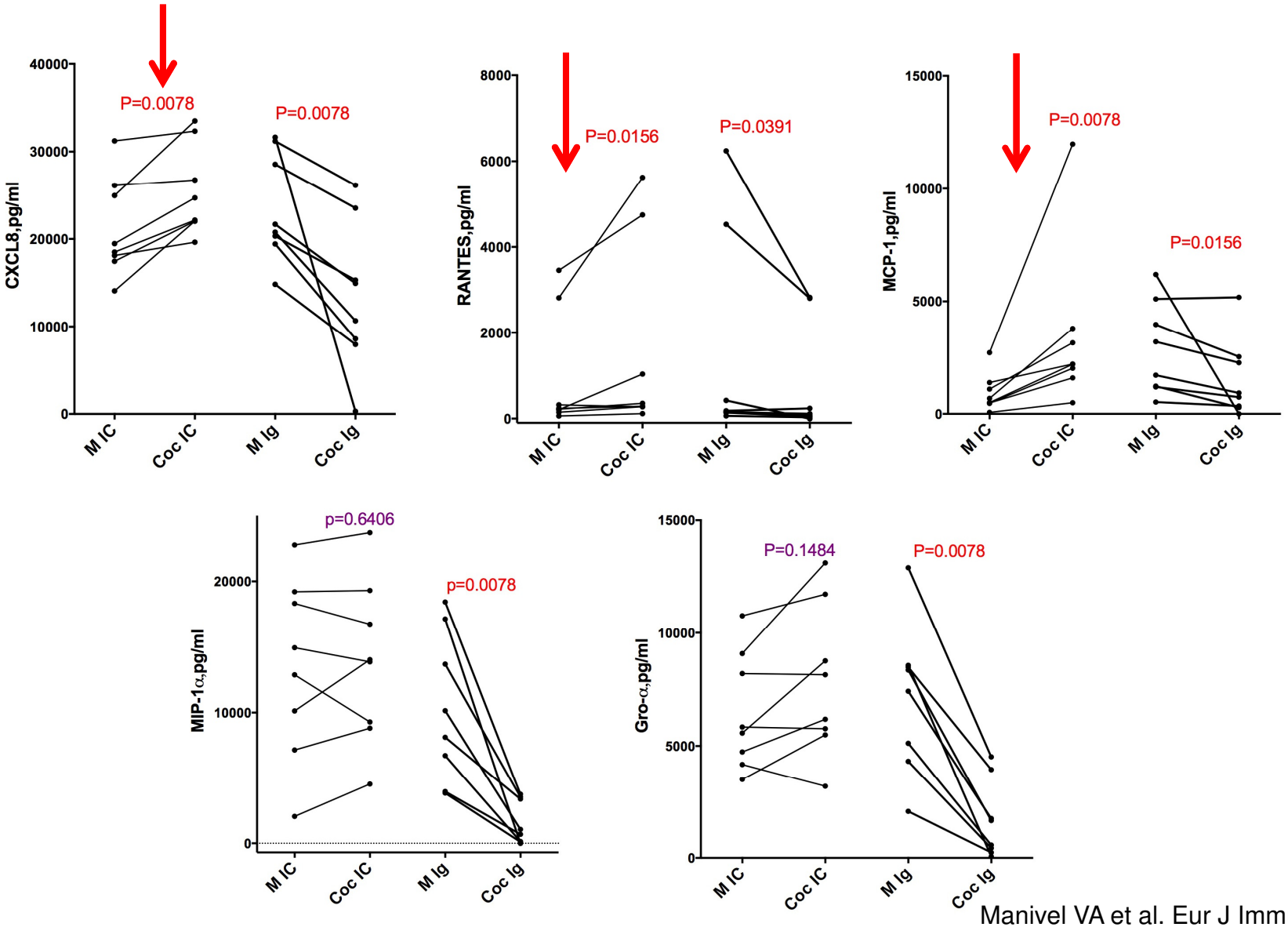
Manivel VA et al. Eur J Immunol. 2016

CXCL8 but not TNFα is up-regulated in anti-CII-IC-stimulated co-cultures.



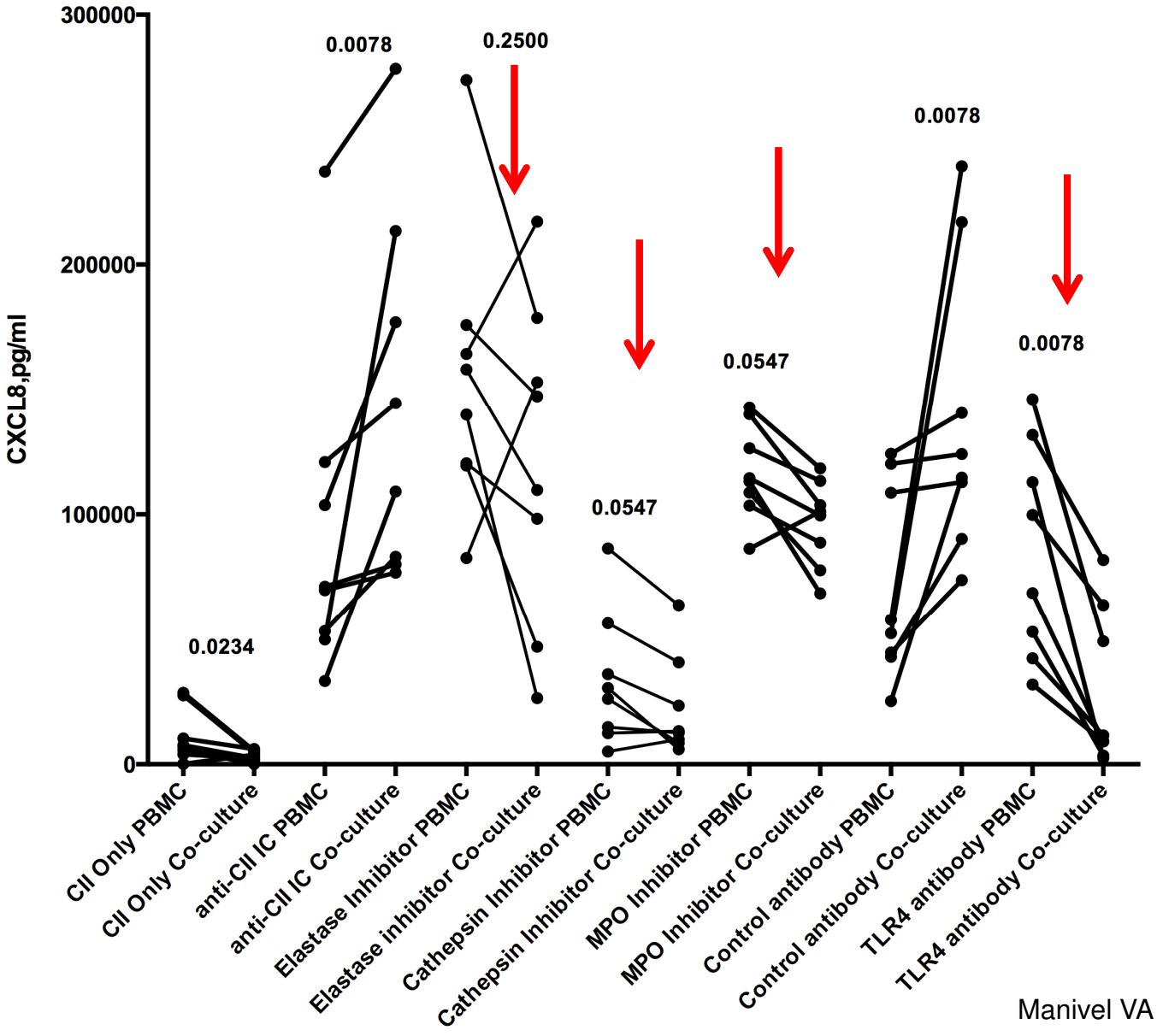
Manivel VA et al. Eur J Immunol. 2016

Many chemokines are upregulated in anti-CII IC-stimulated co-cultures

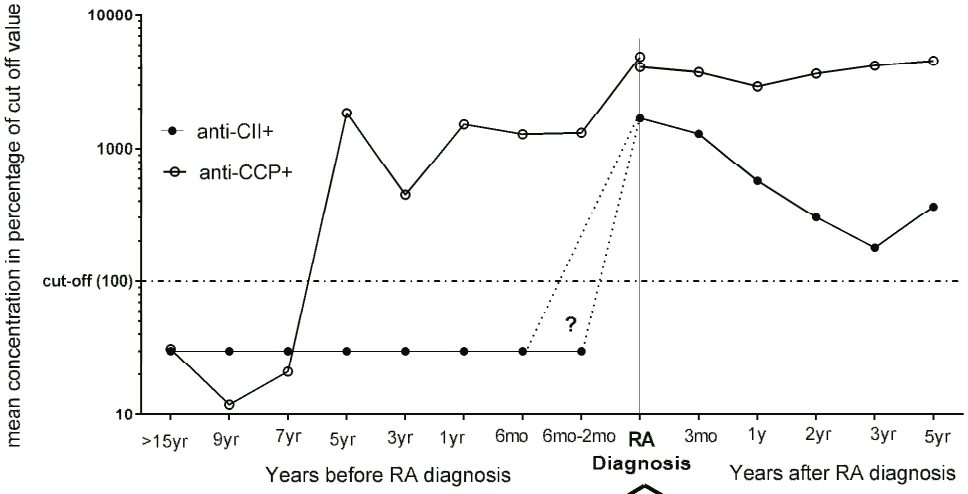


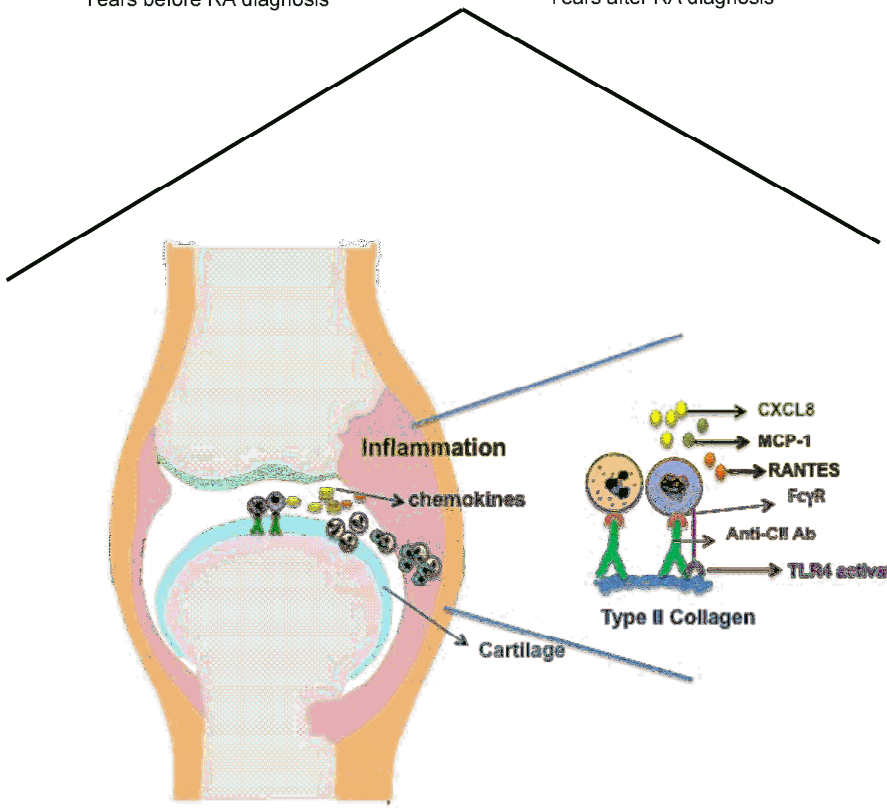
Manivel VA et al. Eur J Immunol. 2016

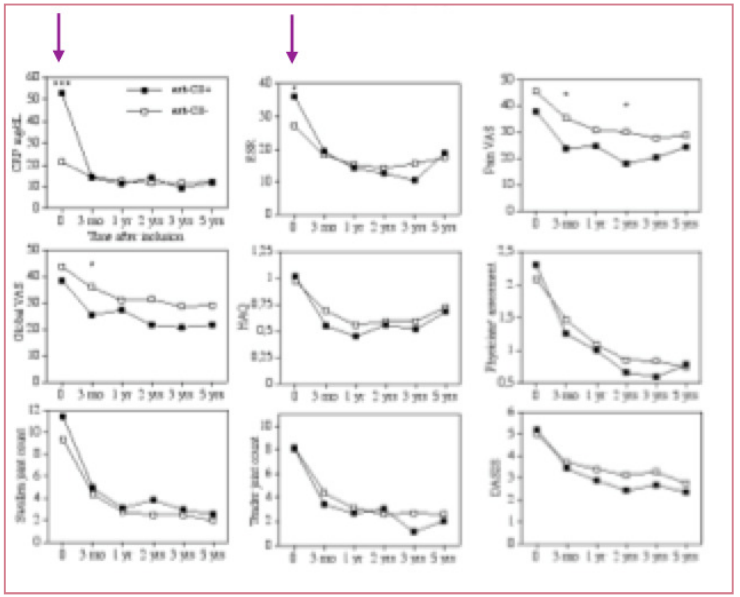
CXCL-8 enhancement in co-cultures depends on a.) TLR4 b.) granulocyte enzymes.



Manivel VA et al. Eur J Immunol. 2016



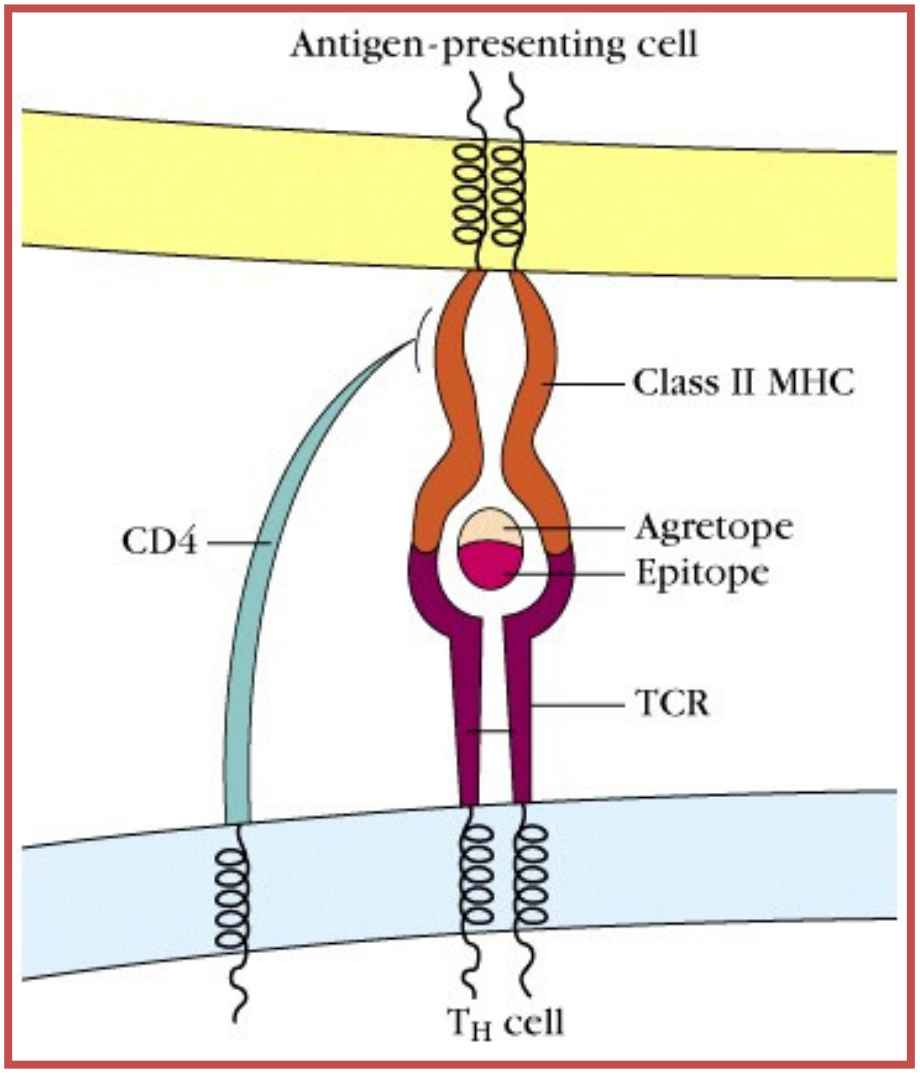




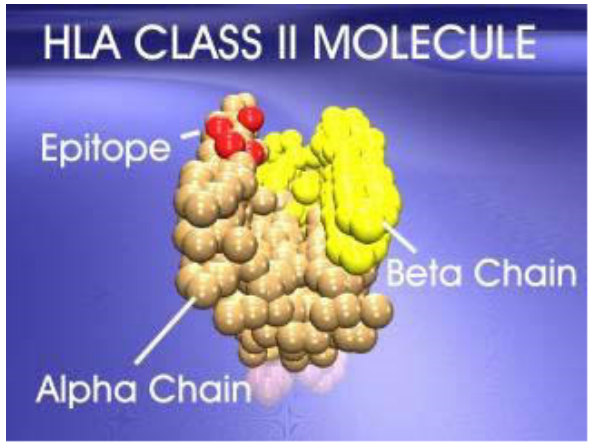
Manivel VA et al. Eur J Immunol. 2016

Epidemiological Investigations in Rheumatoid Arthritis (EIRA)

- A Swedish study.
- The World's largest case-control study for RA
- Currently (Jan. 2017) 4100 RA patients (cases) and 6500 controls (referents), individually matched for age, sex and county.
- Extensive profiling for autoimmune serology, genetics and epidemiological risk factors.



The Shared Epitope (SE) - a group of HLA molecules with similar structure in an important part of the molecule



SE: mainly HLA-DRB1*01, *04, *10 alleles

ACPA associate with SE but negatively with *03

PRESS RELEASE

Smoking is a major preventable risk factor for rheumatoid arthritis: estimations of risks after various exposures to cigarette smoke

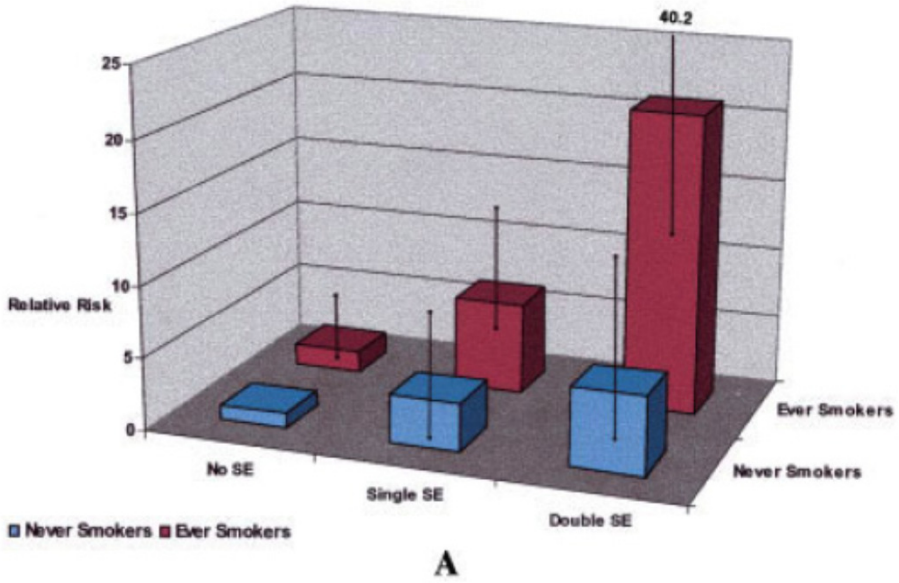
Henrik Källberg,[1] Bo Ding,[1] Leonid Padyukov,[2] Camilla Bengtsson,[1] Johan Rönnelid,[3] Lars Klareskog,[2] Lars Alfredsson.[1,4] EIRA Study Group

Ann Rheum Dis 2010

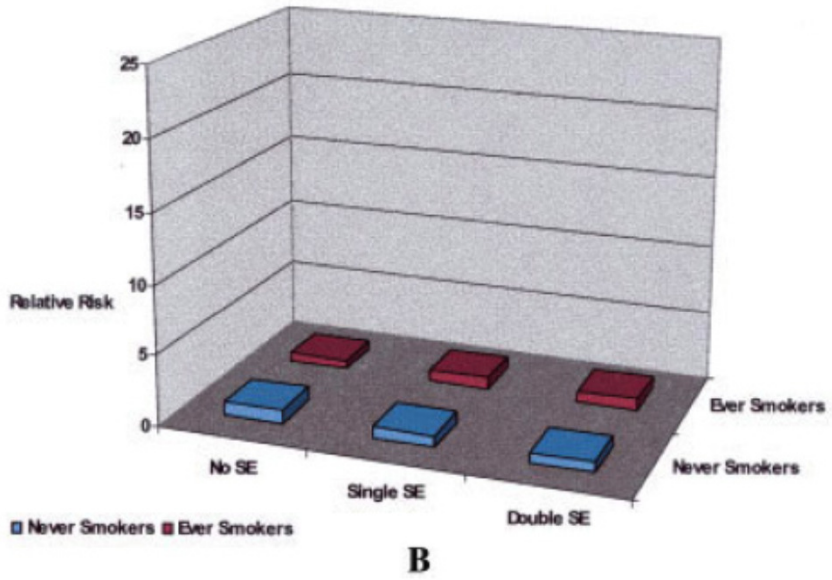
Excess fraction attributable to smoking:
Overall: 20%
ACPA positive RA: 35%
Shared epitope homozygous RA: 55%

ACPA-positive RA - a distinct disease phenotype assoc. with HLA and smoking:

Anti-CCP positive RA



Anti-CCP negative RA



Klareskog et al. Arthritis Rheum 2006;54:38

The Swedish Rheumatology Quality Register: optimisation of rheumatic disease assessments using register-enriched data

J.K. Eriksson, J. Askling, E.V. Arkema

Clin Exp Rheumatol 2014

- Started in 1995 by the Swedish Rheumatology Society.
- Used to improve care. Fully integrated in health care.
- Originally only for RA, now also other diagnoses.
- We have linked EIRA data to SRQ data (n=773).
- HLA + smoking data available for 1476 patients.

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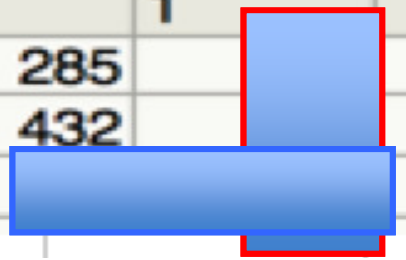
Anti-CII and anti-CCP2 Assocation to disease outcome measures

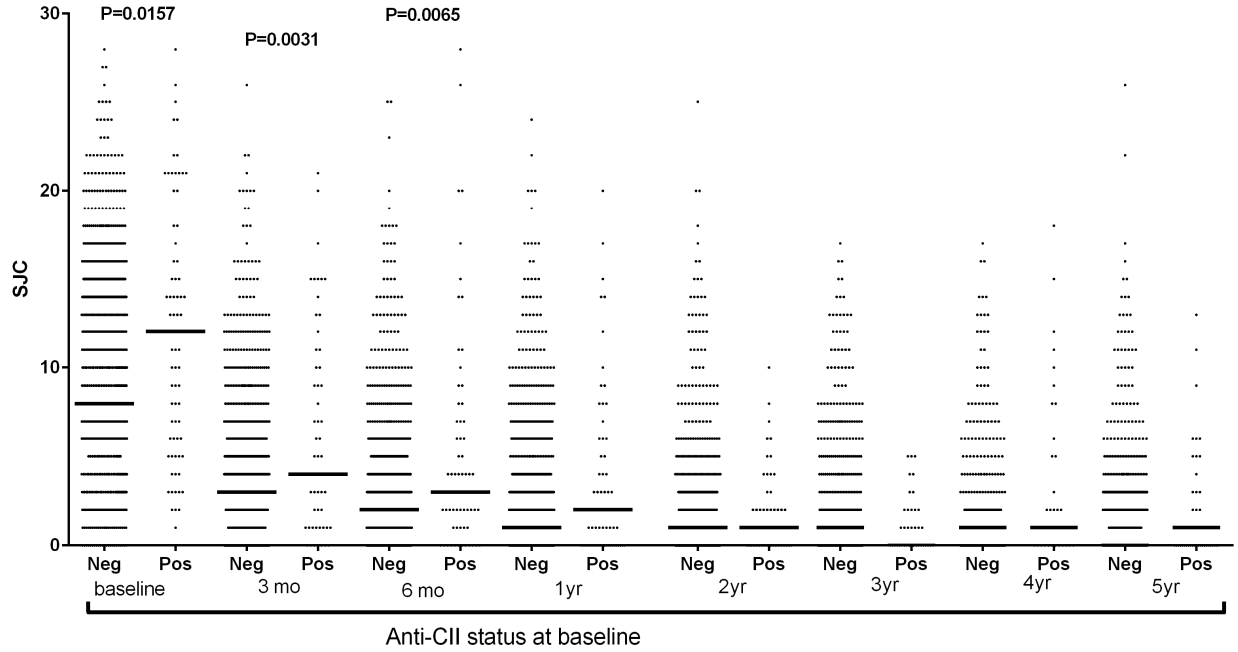
CCP2 pos(1)/ neg((0) based on EIRA data

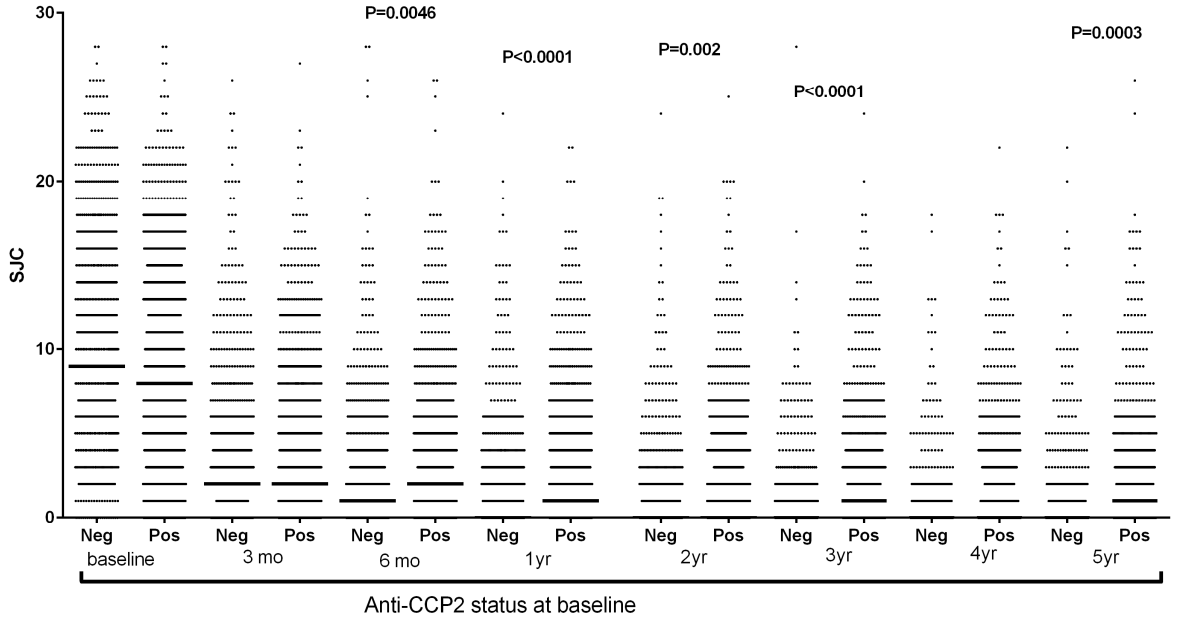
Anti-CII +/- (cutoff 29) false pos excluded

Count	0	1	
0	285		305
1	432		468
			773



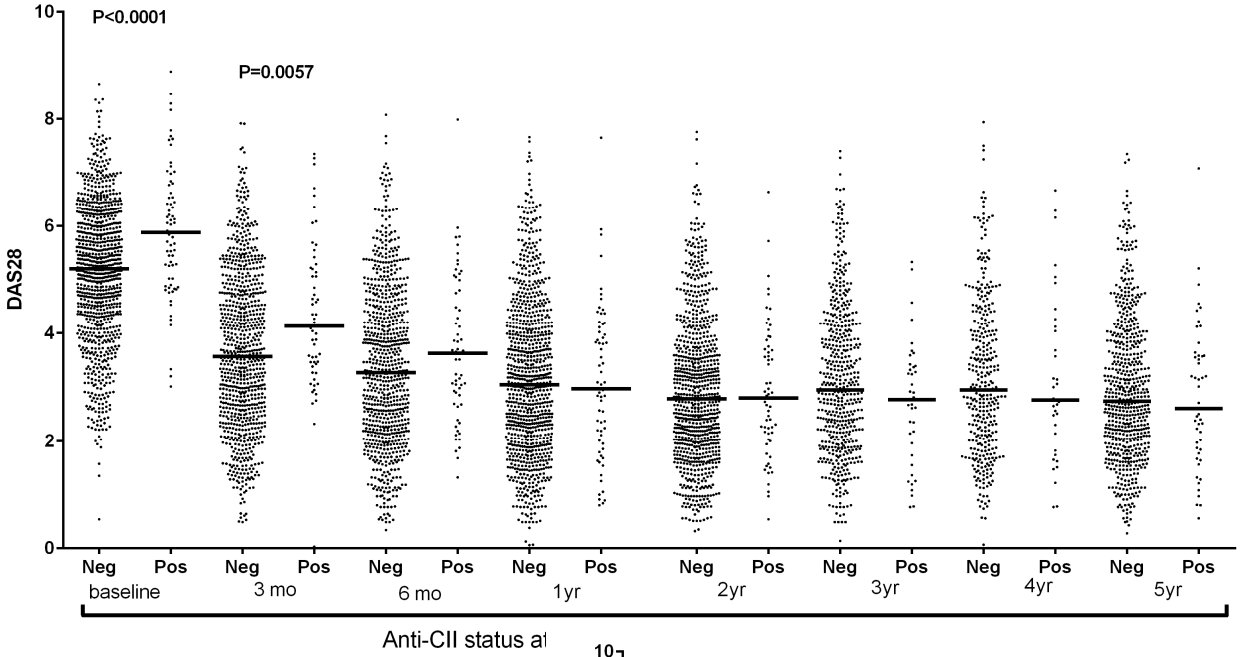
SJC

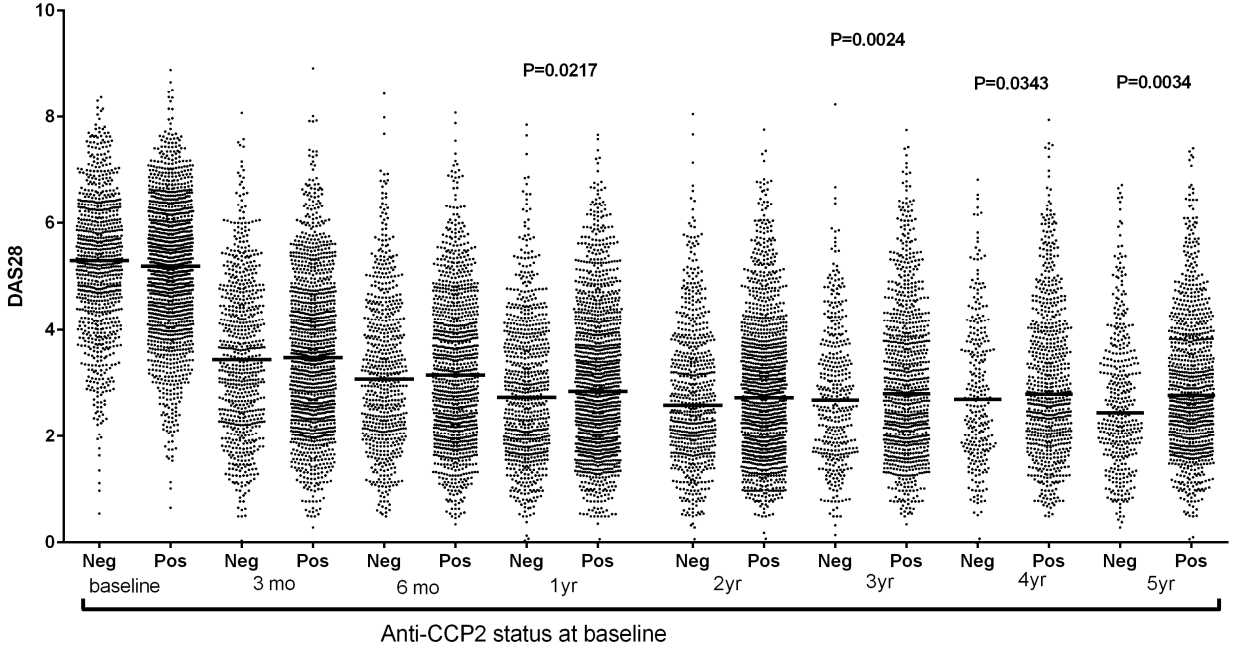




Manivel VA et al. Ann Rheum Dis. 2017;76:1529

DAS28





Manivel VA et al. Ann Rheum Dis. 2017;76:1529

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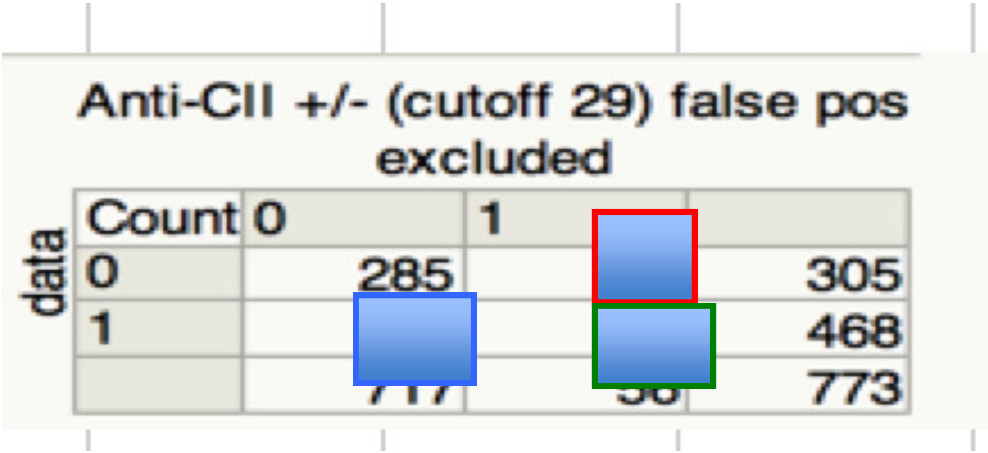
Anti-CII vs anti-CCP individual reactivities and double positive



Variable	Median double -	Median anti-CCP only +	Median anti-CII only +	Median anti-DB +	Anti-CCP only p	anti-CII only p	Double pos p
crp_0	11.5	16	31.5	31	0.0003	0.0002	<0.0001
crp_3	8	9	12	15	0.0023	0.0028	0.0356
crp_6	8	9	10	18	0.0098	0.0217	<0.0001
crp_12	8	8	7	10	0.0187	0.4074	0.0242
crp_24	7	8	7	11.31	0.0069	0.7158	0.0214
crp_36	7	7	4.5	9	0.0201	0.0689	0.1553
crp_48	4	7	4	5	0.003	0.993	0.2067
crp_60	5	6	4	8.5	0.0285	0.1562	0.0042
esr_0	20	27	38	41	<0.0001	0.0057	<0.0001
esr_3	10	16	13	24.5	<0.0001	0.627	<0.0001
esr_6	10	13	10	20	0.0011	0.8962	0.0002
esr_12	10	14	8	16	<0.0001	0.2334	0.0007
esr_24	11	12	8	15	0.0351	0.2046	0.0716
esr_36	10	14	9	17	0.0006	0.1641	0.1191
esr_48	11	16.5	10	14	0.008	0.6684	0.3414
esr_60	12	15	8	15	0.0039	0.0107	0.4832
sjc_0	9	8	12.5	10	0.3044	0.0094	0.4849
sjc_3	2	3	4	4	0.1803	0.0286	0.0137
sjc_6	1	2	2	3.5	0.0133	0.0438	0.005
sjc_12	0	1	2	2	<0.0001	0.2162	0.0079
sjc_24	0	1	0	1	0.004	0.8665	0.0193
sjc_36	0	1	0	0	<0.0001	0.7398	0.5592
sjc_48	0	1	1	1	0.1558	0.4832	0.1326
sjc_60	0	1	0	1	0.0005	0.6476	0.0255
tjc_0	8	7	9	10	0.0507	0.3287	0.2184
tjc_3	2	2	4	3	0.2769	0.198	0.8287
tjc_6	2	2	1.5	2	0.8609	0.6959	0.6709
tjc_12	1	1	1	1	0.7637	0.9806	0.3739
tjc_24	1	1	1	1	0.3927	0.6795	0.3084
tjc_36	0	1	0	1	0.0387	0.4851	0.688
tjc_48	1	1	0	1	0.7175	0.2582	0.877
tjc_60	0	1	0.5	1	0.1168	0.955	0.4795
das28_0	5.19	5.21	5.87	5.78	0.6974	0.0124	0.0012
das28_3	3.6	3.52	3.58	4.24	0.6942	0.2602	0.0107
das28_6	3.17	3.27	2.85	3.77	0.4274	0.609	0.0135
das28_12	2.92	3.06	2.19	3.08	0.0451	0.3007	0.2391
das28_24	2.73	2.81	2.38	3.07	0.2976	0.4362	0.1166
das28_36	2.56	3.07	2.27	2.89	0.0008	0.1776	0.5288
das28_48	2.6	3.09	2.72	2.99	0.0691	0.913	0.4416
das28_60	2.42	2.95	2.07	3.16	0.0018	0.1548	0.354

Anti-CII and anti-CCP predict opposite changes in outcomes

	CCP- CII-	CCP- **CII+**	**CCP+** CII-	**CCP+ CII+**	Total p	Anti-CII p	Anti-CCP p	interaction
CRP Δ 3 mo	-9,47	-24,35	-12,72	-22,36	0,045	0,01	0,8945	0,5803
CRP Δ 6 mo	-10,39	-29,17	-15,3	-25,45	0,016	0,0053	0,9089	0,4046
CRP Δ 12 mo	-10,11	-34,72	-14,96	-23,84	0,008	0,0021	0,5792	0,1479
CRP Δ 24 mo	-14,32	-32,5	-18,18	-30,91	0,0177	0,0036	0,8305	0,6061
CRP Δ 36 mo	-12,45	-43,7	-16,07	-32,42	0,0079	0,0007	0,5847	0,2879
CRP Δ 48 mo	-14,78	-28	-23,26	-42,72	0,072	0,0731	0,2027	0,7311
CRP Δ 60 mo	-15,51	-38,93	-22,49	-29,54	0,0668	0,0257	0,8596	0,2301
SJC Δ 3 mo	-5,89	-6,71	-5,17	-4,52	0,2651	0,9271	0,1054	0,4165
SJC Δ 6 mo	-7,11	-8,61	-6,04	-6,3	0,0825	0,3453	0,0689	0,5041
SJC Δ 12 mo	-8,05	-11,05	-6,43	-7,32	0,0003	0,0305	0,0031	0,242
SJC Δ 24 mo	-8,49	-13,56	-7,16	-8,19	<0.0001	0,001	0,0003	0,0296
SJC Δ 36 mo	-9,02	-14,45	-6,7	-8,5	<0.0001	0,0029	0,0007	0,1329
SJC Δ 48 mo	-8,28	-10,63	-7,49	-8,58	0,5046	0,2547	0,3442	0,6784
SJC Δ 60 mo	-8,86	-13,79	-7,17	-8,15	0,0006	0,0106	0,0015	0,0875
DAS28CRP Δ 3 mo	-1,37	-1,47	-1,29	-1,37	0,8864	0,6741	0,6873	0,9525
DAS28CRP Δ 6 mo	-1,62	-2,33	-1,53	-1,89	0,0718	0,0152	0,2244	0,4341
DAS28CRP Δ 12 mo	-1,97	-2,83	-1,68	-2,25	0,0005	0,0014	0,0499	0,5187
DAS28CRP Δ 24 mo	-2,15	-3,2	-1,98	-2,37	0,0038	0,0017	0,0337	0,1733
DAS28CRP Δ 36 mo	-2,32	-3,74	-1,81	-2,6	<0.0001	0,0005	0,0085	0,3152
DAS28CRP Δ 48 mo	-2,4	-3,09	-2,05	-2,84	0,1116	0,0647	0,4615	0,9052
DAS28CRP Δ 60 mo	-2,39	-3,56	-2,03	-2,56	0,0013	0,0029	0,0164	0,261

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DEVELOPMENT AND VALIDATION OF THE EUROPEAN LEAGUE AGAINST RHEUMATISM RESPONSE CRITERIA FOR RHEUMATOID ARTHRITIS

Comparison with the Preliminary American College of Rheumatology and the World Health Organization/International League Against Rheumatism Criteria

A. M. VAN GESTEL, M. L. L. PREVOO, M. A. VAN 'T HOF, M. H. VAN RIJSWIJK, L. B. A. VAN DE PUTTE, and P. L. C. M. VAN RIEL

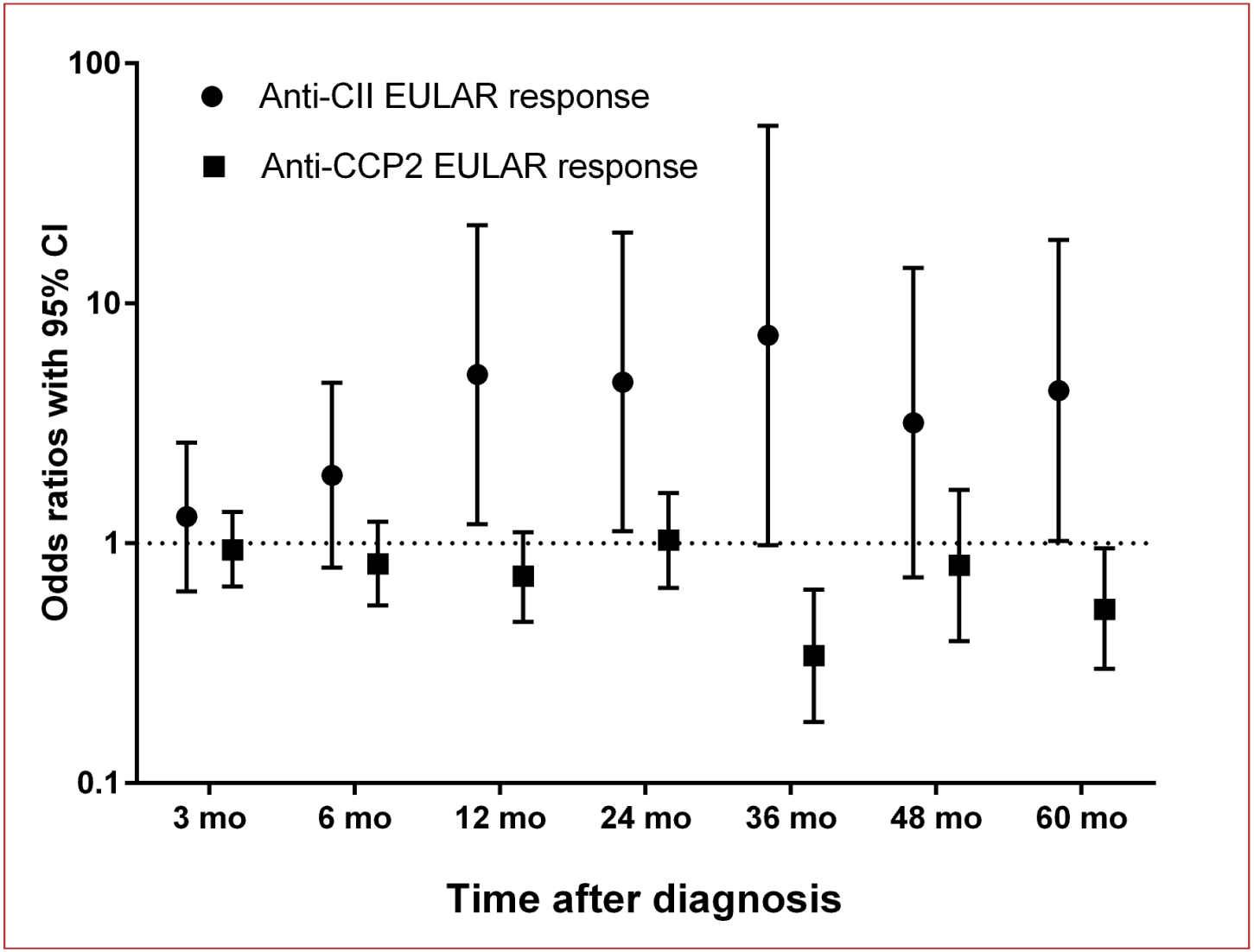
Arthritis Rheum 1996

EULAR response criteria

Comparing the DAS28 from one patient on two different time points, it is possible to define improvement or response. The EULAR response criteria are defined as follows:

DAS28 improvement → / Present DAS28↓	> 1.2	> 0.6 and ≤ 1.2	≤ 0.6
≤ 3.2	good response	moderate response	no response
> 3.2 and ≤ 5.1	moderate response	moderate response	no response
> 5.1	moderate response	no response	no response

Both the thresholds for high and low disease activity and remission and the abovementioned improvement criteria should give you a feel how to interpret your DAS28 scores.



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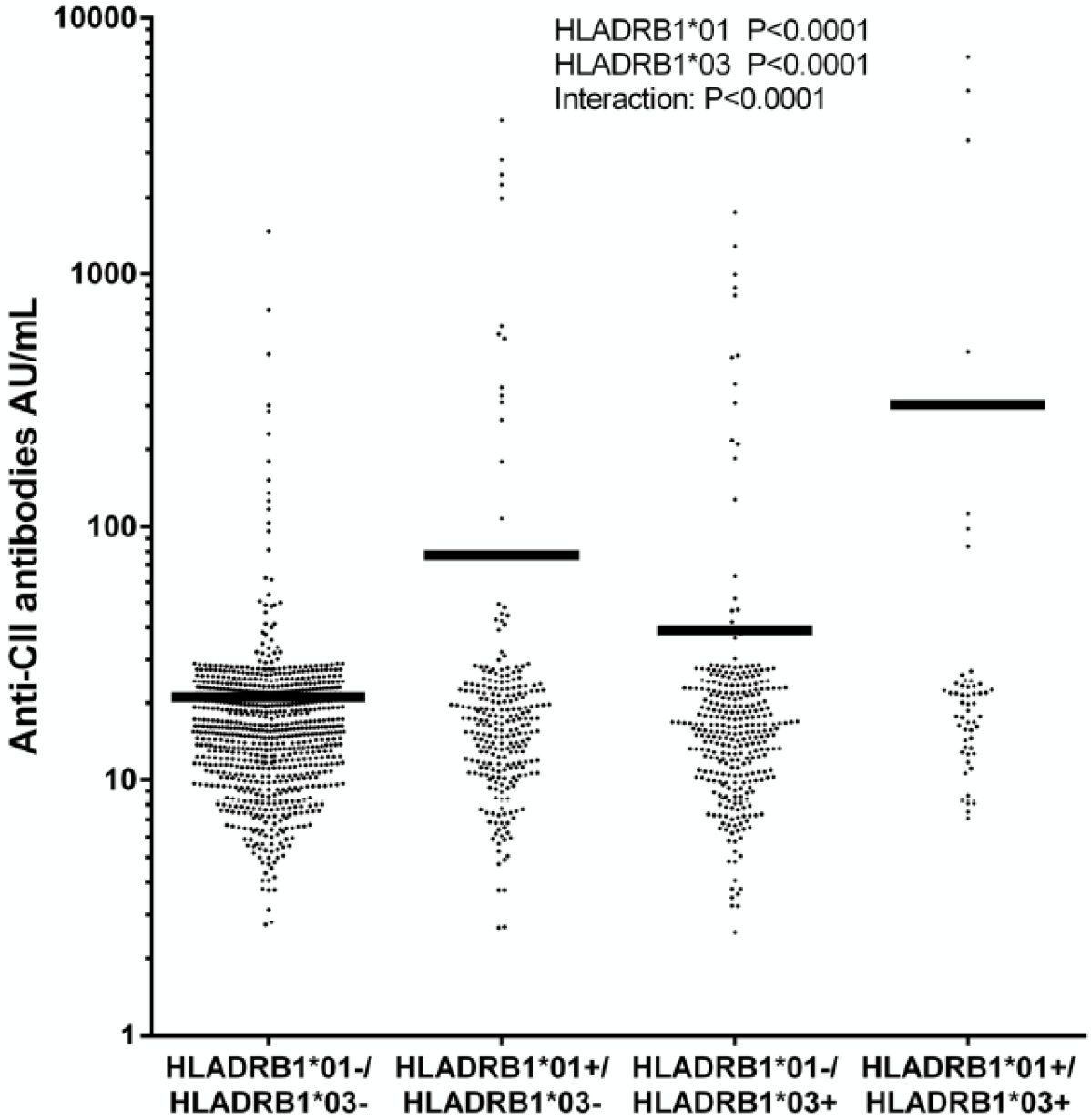
HLA DRB1* analysis

Anti-CCP2 25AU/ml	Anti-CCP2 pos with/without genotype	Anti-CCP2 neg with/without genotype	OR(CI_{low}-CI_{high})	p value
DRB1*03	138/717	182/439	0.46(0.36-0.6)	<0.0001
DRB1*04	569/286	217/404	3.7(2.97-4.6)	<0.0001

Anti-CII 29AU/ml	Anti-CII pos with/without genotype	Anti-CII neg with/without genotype	OR(CI_{low}-CI_{high})	p value
DRB1*03	33/64	287/1092	1.96(1.26-3.05)	0.0023
DRB1*04	40/57	746/633	0.6(0.39-0.9)	0.0141

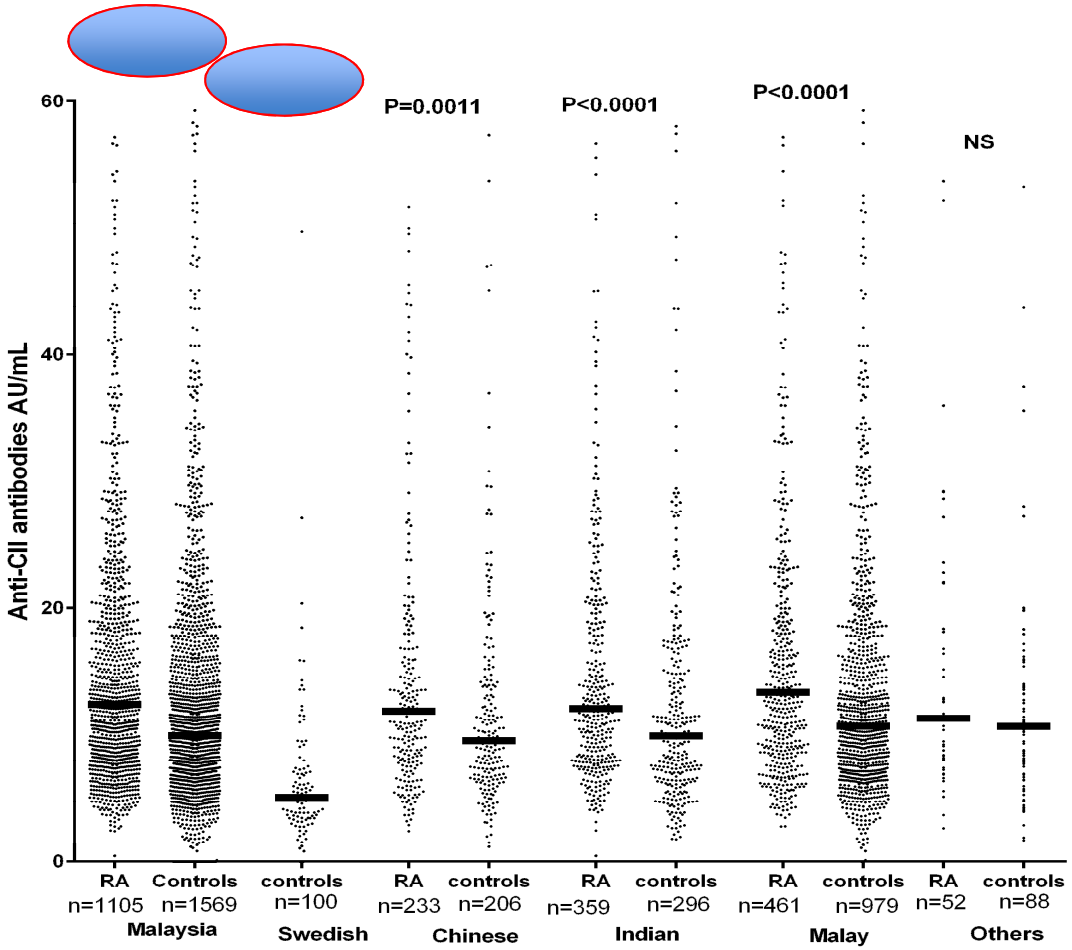
Anti-CII 200AU/ml	Anti-CII pos with/without genotype	Anti-CII neg with/without genotype	OR(CI_{low}-CI_{high})	p value
DRB1*01	15/18	375/1068	2.37(1.18-4.76)	0.0121
DRB1*03	16/17	304/1139	3.53(1.76-7.06)	0.0002
DRB1*04	5/28	781/662	0.15(0.06-0.39)	<0.0001



Compared to ACPA: inverse relation to DR3. And to smoking!

The Malaysian EIRA (MyEIRA) cohort

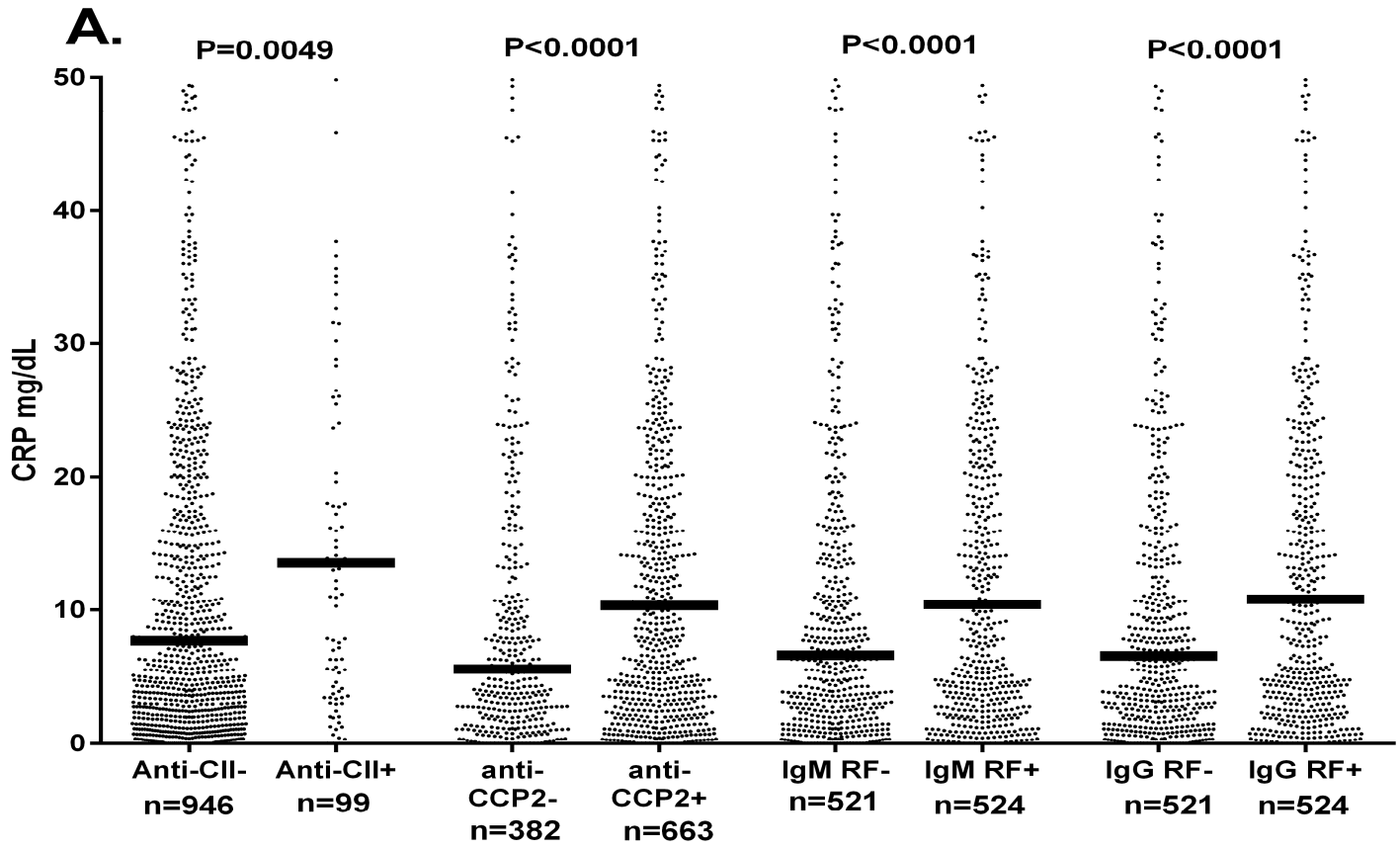
1260 patients,1569 healthy controls
three different ethnicities
Baseline CRP available in 1045 patients
No clinical follow-up data available



Too Chun Lai, Manivel et al, unpublished

Autoantibody association to CRP

Baseline CRP was measured in 1045 RA patients



Too Chun Lai, Manivel et al, unpublished

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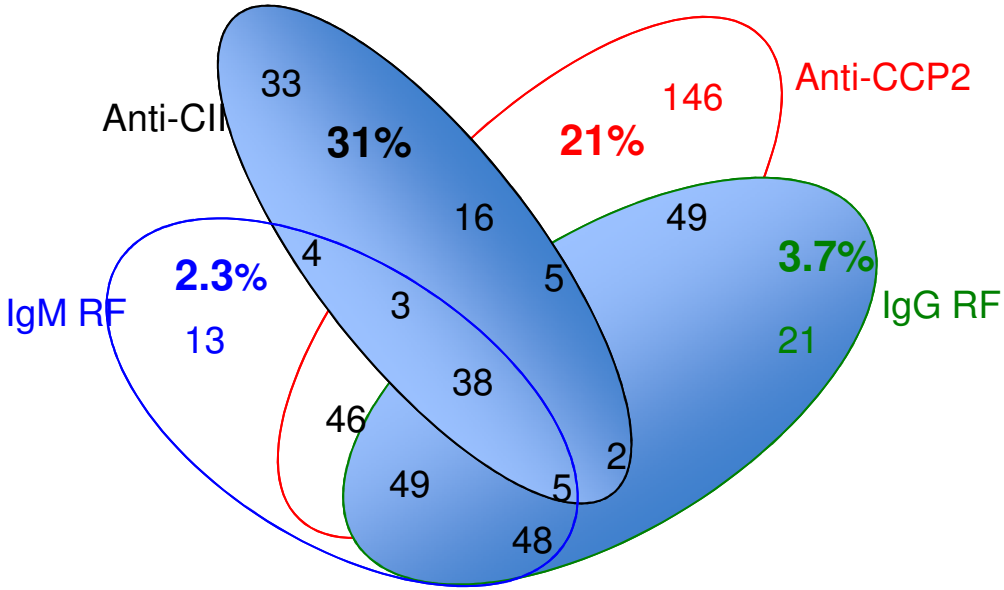
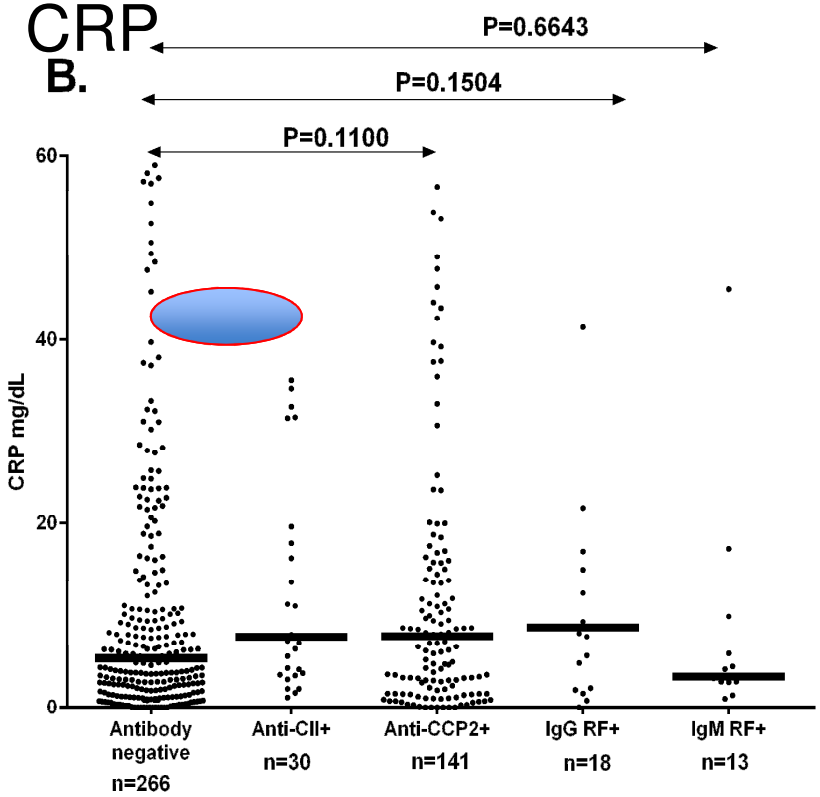
Co occurrence of autoantibodies



Anti-CII alone is associated with CRP



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Conclusions:

- Anti-CII positive RA patients have an acute onset phenotype, related to the cellular function of anti-CII-containing IC around the time of RA diagnosis.

- Anti-CII-containing IC stimulate PBMC-granulocyte cocultures to enhanced production of chemokines. This mechanism can attract inflammatory cells in early RA and depends on TLR4 and granulocyte enzymes.

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Conclusions cont.:

- Anti-CII seropositive RA represents a distinct phenotype, in many respects representing the converse to the clinical, genetic and smoking associations described for ACPA.

- Dual measurement of anti-CII and anti-CCP in early RA can distinguish groups with better and worse prognosis as compared to antibody-negative patients.

Spontaneous remission in “RA”?

Ann. rheum. Dis. (1957), **16**, 411.

COURSE AND PROGNOSIS IN RHEUMATOID ARTHRITIS*

BY

J. J. R. DUTHIE, P. E. BROWN, J. D. E. KNOX, AND M. THOMPSON

From the Rheumatic Unit, Northern General Hospital, Edinburgh

While in hospital the basic regimen of treatment consisted of rest in bed, the application of plaster splints to affected joints, maximum tolerable doses of aspirin, physiotherapy, and a graduated return to the optimum functional level attainable. Gold, Butazolidin, corticotrophin, and steroids were not used. Throughout the

run up to the time of admission. Patients admitted within one year of the onset of symptoms fared substantially better than those admitted at a later stage of the disease; the prognosis in males was better than in females; an acute onset followed by a rapidly progressive course in the early stages seemed to indicate a more benign form of the disease. Age at onset, the erythrocyte sedimentation

Disease Activity.—Table VI shows the distribution of patients in the three degrees of disease activity. The percentage rated as moderately active showed little variation during the period of observation, but there was a significant diminution in the very active group, with a corresponding increase in those considered to be inactive at the time of assessment.

TABLE VI

DISEASE ACTIVITY ON ADMISSION, DISCHARGE, FIRST ASSESSMENT, AND THIRD ASSESSMENT

Time of Estimation	No. of Cases	Disease Activity (per cent.)		
		Very Active	Moderately Active	Inactive
Admission	282	26·2	63·5	10·3
Discharge	282	5·0	59·2	35·8
First Assessment ..	282	3·5	65·6	30·9
Third Assessment ..	247	1·2	69·6	29·2

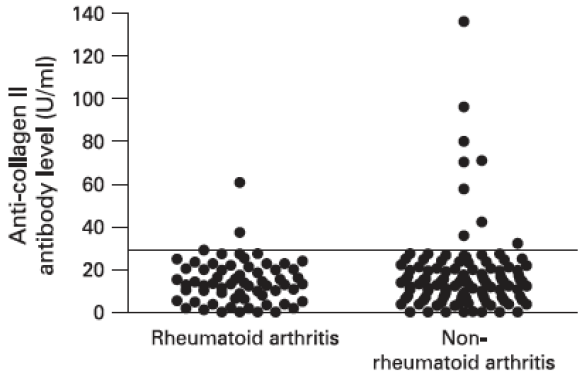


Figure 1 Anti-collagen II antibody levels in patients with very early synovitis divided according to final outcome (rheumatoid arthritis and non-rheumatoid arthritis).

Raza K et al ARD 2008

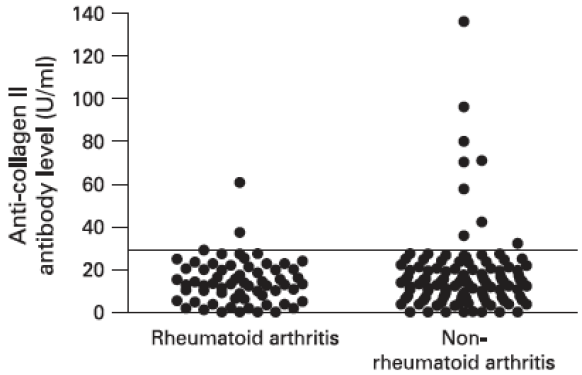
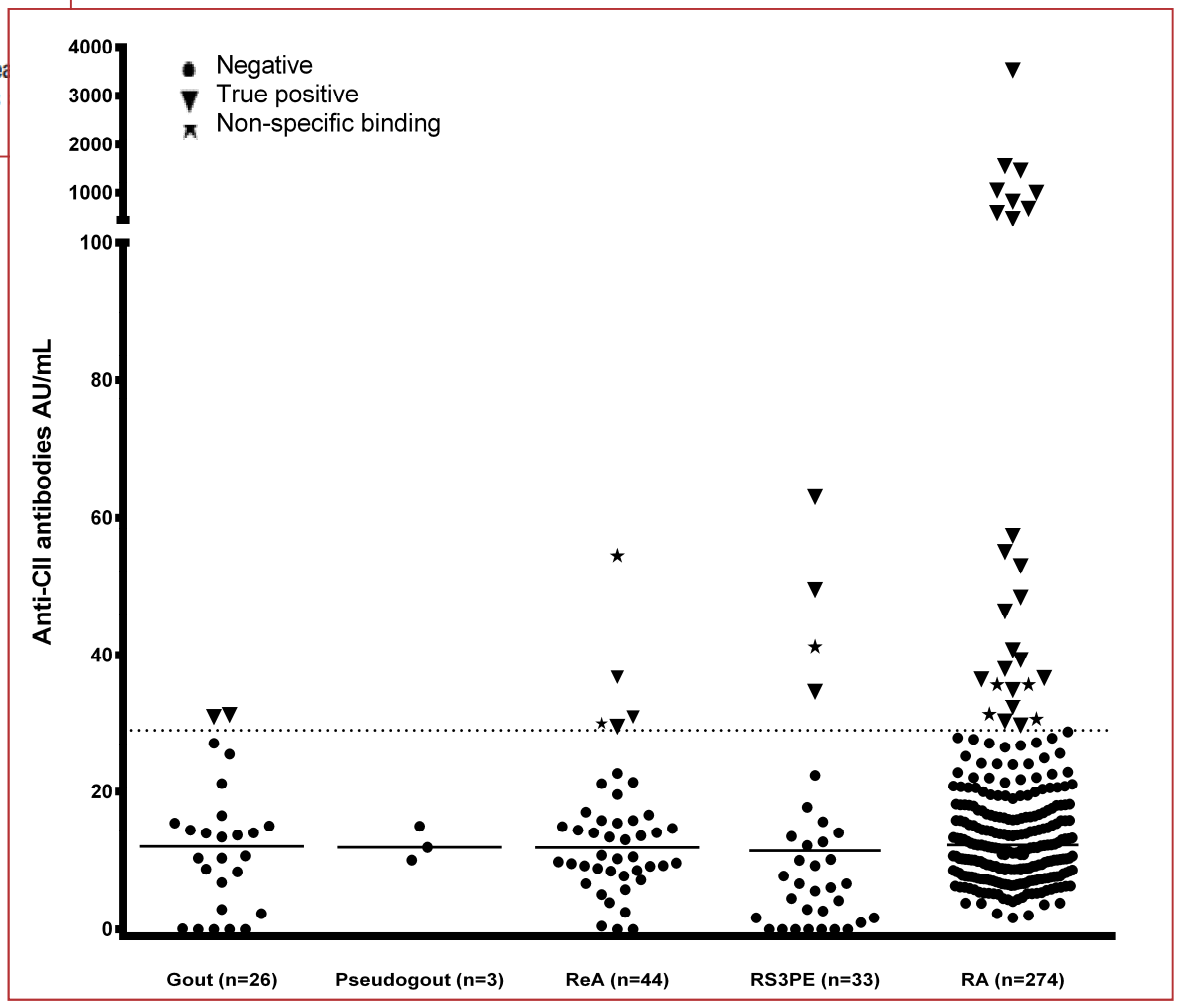


Figure 1 Anti-collagen II antibody levels in patients with very ea synovitis divided according to final outcome (rheumatoid arthritis non-rheumatoid arthritis).

Raza K et al ARD 2008



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