Table S1: Univariate and multivariate Cox proportional hazard models comparing RF/ACPA high/low positive vs negative

|                      | NOAR                  | Leiden EAC             |
|----------------------|-----------------------|------------------------|
|                      | Unadjusted            | Age & sex adjusted     | Multivariate* | Unadjusted | Age & sex adjusted | Multivariate* |
| RF/ACPA negative     | HR 0.85 95% CI 0.61-1.18 | HR 0.81 95% CI 0.59-1.10 | HR 0.80 95% CI 0.57-1.13 | HR 2.38 95% CI 1.67-3.39 | HR 1.89 95% CI 1.13-2.70 | HR 1.92 95% CI 1.30-2.80 |
| RF/ACPA low positive | HR 1.51 95% CI 1.29-1.77 | HR 1.44 95% CI 1.21-1.70 | HR 1.44 95% CI 1.11-1.86 | HR 1.63 95% CI 1.26-2.12 | HR 1.42 95% CI 1.06-1.91 |
| RF/ACPA high positive| HR 0.70 95% CI 0.60-0.81 | HR 0.77 95% CI 0.65-0.91 | - - - - - - | 0.73 95% CI 0.57-0.92 | 0.72 95% CI 0.54-0.94 |
| Female gender        | HR 1.10 95% CI 1.09-1.11 | HR 1.11 95% CI 1.10-1.12 | - - - - - - | 1.10 95% CI 1.09-1.11 | 1.10 95% CI 1.09-1.12 |
| Age at onset         | HR 0.98 95% CI 0.81-1.18 | HR 1.68 95% CI 1.34-2.10 | - - - - - - | 0.95 95% CI 0.93-1.00 |
| Smoking              | HR 1.003 95% CI 1.002-1.005 | HR 1.006 95% CI 1.001-1.011 | - - - - - - | - - - - - - |
| Ever                 |                       |                        |               |                        |                        |
| Current              |                       |                        |               |                        |                        |
| Inclusion year       |                       |                        |               |                        |                        |

HR, hazard ratio; CI, confidence interval; RF, rheumatoid factor; ACPA, anti-citrullinated peptide antibodies; inflammatory marker = C-reactive protein in NOAR, = erythrocyte sedimentation rate in EAC
*adjusted for age at symptom onset, sex, baseline smoking status, year of inclusion in cohort & inflammatory marker
|                | NOAR Unadjusted | NOAR Age & sex adjusted | NOAR Multivariate* | Leiden EAC Unadjusted | Leiden EAC Age & sex adjusted | Leiden EAC Multivariate* |
|----------------|-----------------|-------------------------|-------------------|-----------------------|-------------------------------|-------------------------|
| RF negative    | ref             | ref                     | ref               | ref                   | ref                           | ref                     |
| RF low positive| 0.90 (0.68-1.20)| 0.81 (0.62-1.06)        | 0.80 (0.59-1.07)  | 2.13 (1.55-2.91)      | 1.67 (1.21-2.29)              | 1.62 (1.16-2.26)        |
| RF high positive| 1.67 (1.41-1.97)| 1.54 (1.29-1.83)        | 1.49 (1.23-1.80)  | 1.75 (1.33-2.31)      | 1.92 (1.46-2.53)              | 1.63 (1.19-2.24)        |
| Female gender  | -               | 0.71 (0.62-0.83)        | 0.78 (0.66-0.92)  | -                     | 0.75 (0.59-0.95)              | 0.73 (0.56-0.97)        |
| Age at onset   | -               | 1.10 (1.09-1.11)        | 1.11 (1.10-1.12)  | -                     | 1.10 (1.09-1.11)              | 1.11 (1.09-1.12)        |
| Smoking Never  | -               | -                       | -                 | -                     | -                             | -                       |
| Previous       | 0.98 (0.81-1.19)| -                       | -                 | -                     | -                             | -                       |
| Current        | 1.66 (1.33-2.08)| -                       | -                 | -                     | -                             | -                       |
| Inclusion year | -               | -                       | -                 | -                     | -                             | -                       |
| Inflammatory marker | 1.003 (1.002-1.005) | -                       | -                 | -                     | -                             | -                       |
| ACPA negative  | ref             | ref                     | ref               | ref                   | ref                           | ref                     |
| ACPA low positive| 1.05 (0.69-1.60)| 1.16 (0.80-1.68)        | 1.38 (0.98-1.97)  | 1.65 (1.00-2.72)      | 2.52 (1.52-4.18)              | 2.21 (1.31-3.72)        |
| ACPA high positive| 1.49 (1.24-1.79)| 1.41 (1.15-1.72)        | 1.38 (1.11-1.71)  | 1.17 (0.90-1.52)      | 1.45 (1.11-1.90)              | 1.25 (0.93-1.69)        |
| Female gender  | -               | 0.71 (0.60-0.84)        | 0.81 (0.67-0.98)  | -                     | 0.71 (0.55-0.91)              | 0.73 (0.55-0.97)        |
| Age at onset   | -               | 1.10 (1.09-1.11)        | 1.11 (1.10-1.12)  | -                     | 1.10 (1.09-1.11)              | 1.10 (1.09-1.12)        |
| Smoking Never  | -               | -                       | -                 | -                     | -                             | -                       |
| Previous       | 1.00 (0.81-1.24)| -                       | -                 | -                     | -                             | -                       |
| Current        | 1.80 (1.40-2.31)| -                       | -                 | -                     | -                             | -                       |
| Inclusion year | -               | -                       | -                 | -                     | -                             | -                       |
| Inflammatory marker | 1.003 (1.001-1.005) | -                       | -                 | -                     | -                             | -                       |

HR, hazard ratio; CI, confidence interval; RF, rheumatoid factor; ACPA, anti-citrullinated peptide antibodies; inflammatory marker = C-reactive protein in NOAR, = erythrocyte sedimentation rate in EAC

*adjusted for age at symptom onset, sex, baseline smoking status, year of inclusion in cohort & inflammatory marker
|                  | NOAR Total EIA population | 2010 ACR/EULAR positive cohort | Leiden EAC Total EIA population | 2010 ACR/EULAR positive cohort |
|------------------|---------------------------|--------------------------------|-------------------------------|-------------------------------|
| **RF:**          |                           |                                 |                               |                               |
| **Unadjusted †** | RF second tertile 0.92    | 0.69-1.23                      | 1.37                          | 0.96-1.94                     |
|                  | RF third tertile 1.39     | 0.19-1.63                      | 1.91                          | 1.47-2.49                     |
|                  | **Age & sex adjusted †** | RF second tertile 0.83         | 0.62-1.10                     | 1.49                          | 1.05-2.12                     |
|                  | RF third tertile 1.25     | 1.07-1.47                      | 1.86                          | 1.43-2.42                     |
|                  | **Multivariate †**       | RF second tertile 1.16         | 0.85-1.59                     | 1.53                          | 1.05-2.22                     |
|                  | RF third tertile 1.29     | 1.09-1.52                      | 1.66                          | 1.23-2.23                     |
| **ACPA:**        |                           |                                 |                               |                               |
| **Unadjusted §** | ACPA second tertile 1.04  | 0.85-1.27                      | 1.22                          | 0.89-1.68                     |
|                  | ACPA third tertile 1.29   | 1.06-1.57                      | 1.26                          | 0.91-1.73                     |
|                  | **Age & sex adjusted §** | ACPA second tertile 0.95       | 0.77-1.16                     | 1.58                          | 1.15-2.18                     |
|                  | ACPA third tertile 1.18   | 0.97-1.44                      | 1.77                          | 1.28-2.46                     |
|                  | **Multivariate §**       | ACPA second tertile 1.00       | 0.81-1.25                     | 1.21                          | 0.84-1.74                     |
|                  | ACPA third tertile 1.19   | 0.97-1.46                      | 1.30                          | 0.90-1.87                     |

HR, hazard ratio; CI, confidence interval; RF, rheumatoid factor; ACPA, anti-citrullinated protein antibodies; inflammatory marker = C-reactive protein in NOAR, = erythrocyte sedimentation rate in EAC
†RF first tertile was used as a reference group; §ACPA first tertile was used as a reference group
*adjusted for age at symptom onset, sex, baseline smoking status, year of inclusion in cohort & inflammatory marker
|                                   | NOAR                  | Leiden EAC             |
|-----------------------------------|-----------------------|------------------------|
|                                   | Unadjusted            | Age & sex adjusted     | Multivariate* |
|                                   | HR        | 95% CI    | HR        | 95% CI    | HR        | 95% CI    | HR        | 95% CI    |
| Both antibodies negative          | ref        | 1.11      | 0.83-1.49 | 1.05      | 0.78-1.41 | 1.11      | 0.82-1.51 | 1.88      | 1.29-2.74 |
| RF positive                       | 1.11      | 0.83-1.49 | 1.05      | 0.78-1.41 | 1.11      | 0.82-1.51 | 1.88      | 1.29-2.74 |
| ACPA positive                     | 1.27      | 0.94-1.73 | 1.40      | 1.03-1.91 | 1.35      | 0.98-1.88 | 0.63      | 0.32-1.23 |
| Both antibodies positive          | 1.51      | 1.23-1.84 | 1.38      | 1.11-1.72 | 1.35      | 1.09-1.68 | 1.59      | 1.21-2.09 |
| Female gender                     | -         | -         | 0.72      | 0.61-0.85 | 0.81      | 0.67-0.98 | -         | -         |
| Age at onset                      | -         | -         | 1.11      | 1.10-1.12 | 1.11      | 1.10-1.12 | -         | -         |
| Smoking Never                     | -         | -         | -         | -         | ref       | -         | -         | -         |
| Previous                          | -         | -         | -         | -         | -         | 1.00      | 0.81-1.24 | 1.00      | 0.70-1.42 |
| Current                           | -         | -         | -         | -         | -         | 1.76      | 1.37-2.27 | 1.82      | 1.31-2.51 |
| Inclusion year                    | -         | -         | -         | -         | -         | -         | -         | -         |
| Inflammatory marker               | -         | -         | -         | -         | -         | -         | 1.003     | 1.002-1.005 | 1.005    | 1.000-1.010 |

HR, hazard ratio; CI, confidence interval, inflammatory marker = C-reactive protein in NOAR, = erythrocyte sedimentation rate in EAC
*adjusted for age at symptom onset, sex, baseline smoking status, year of inclusion in cohort & inflammatory marker
| Variable                      | HR   | 95% CI       | FMI  |
|-------------------------------|------|--------------|------|
| Both antibodies negative      | ref  | -            | -    |
| RF positive                   | 1.12 | 0.83-1.52    | 0.153|
| ACPA positive                 | 1.31 | 0.95-1.83    | 0.198|
| Both antibodies positive      | 1.38 | 1.13-1.68    | 0.101|
| Female gender                 | 0.76 | 0.65-0.90    | 0.002|
| Age at onset                  | 1.11 | 1.10-1.12    | 0.005|
| Smoking Never                 | ref  | -            | -    |
| Ever                          | 0.97 | 0.80-1.18    | 0.001|
| Current                       | 1.65 | 1.32-2.07    | 0.003|
| Inclusion year                | 0.96 | 0.94-0.98    | 0.002|
| Inflammatory marker           | 1.003| 1.002-1.005  | 0.004|

HR, hazard ratio; CI, confidence interval; FMI, fraction of missing information; inflammatory marker = C-reactive protein in NOAR

*adjusted for age at symptom onset, sex, baseline smoking status, year of inclusion in cohort & inflammatory marker