

MATTERS ARISING

Coffee consumption, RF, and the risk of RA

Stress is one of the factors that can trigger the onset of rheumatoid arthritis (RA). People working under deadline pressure, and people characterised as hard driving, "type A" personalities may be most likely to experience stress. These are the same people who may consume large quantities of coffee in order to stay at peak performance for longer periods of time. Possibly, therefore, the correlation reported by Heliövaara *et al*¹ between coffee consumption and RA may, in part, be due to the association between stress and RA.

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1 Heliövaara M, Aho K, Knekt P, Impivaara O, Reunanen A, Aromaa A. Coffee consumption, rheumatoid factor, and the risk of rheumatoid arthritis. *Ann Rheum Dis* 2000;59:631-5.

Authors' reply

The plausible hypothesis presented by Dr Glaser prompted us to complement our earlier results with a further analysis of data from the Finnish surveys.

Using information derived from the Mini-Finland Health Survey,¹ we studied stress and type A behaviour pattern for their associations with coffee consumption and the occurrence of rheumatoid factor (RF). In this survey we asked the participants about having been exposed to hurried or tight work schedules in their current occupation and in the previous occupation of longest duration. The Jenkins Activity Survey AB scale scores were computed from a standard questionnaire.^{2,3}

Table 1 Age and sex adjusted odds ratio (with 95% confidence interval (CI)) of rheumatoid factor (RF) positivity (sensitised sheep cell agglutination titre 128) for hurried or tight work schedules and for the type A behaviour pattern among participants without clinical arthritis in the Mini-Finland Health Survey

Variable, category	Number of subjects examined	Number of RF positive cases	Odds ratio	95% CI
Hurried or tight work schedule				
None	3240	37	1.00	
Mild	2793	30	0.96	0.59 to 1.58
Severe	785	2	0.22	0.05 to 0.93
Quintile of AB behaviour pattern score				
I (type B)	799	7	1.00	
II	803	8	1.14	0.41 to 3.16
III	811	11	1.56	0.60 to 4.04
IV	802	6	0.87	0.29 to 2.59
V (type A)	602	6	0.85	0.28 to 2.53

Table 2 Relative risk* (with 95% confidence interval (CI)) of developing rheumatoid factor positive rheumatoid arthritis for different stress symptoms among 52 260 participants of the Mobile Clinic Health Examination Survey

Symptom	Number of subjects with each symptom	Number of incident cases	Relative risk	95% CI
Nervousness	7 725	55	0.95	0.71 to 1.27
Fatigue	10 091	74	1.01	0.78 to 1.32
Sweating	8 828	48	0.72	0.53 to 0.97
Heart pounding	8 509	68	1.12	0.85 to 1.47
Headache	5 544	46	1.10	0.81 to 1.51
Number of symptoms†	52 260	343	0.97	0.85 to 1.12

*Adjusted for age, sex, and smoking history.

†Continuous variable; relative risk per one symptom.

Contrary to the hypothesis, there was a negative association between hurried or tight work schedules and the occurrence of RF (table 1). No significant association was seen between type A behaviour and RF. Coffee consumption showed only weak associations with work hurries ($r=0.035$, $p=0.004$) or the AB scale score ($r=0.001$, $p=0.54$).

We also studied a set of five stress related symptoms for their prediction of RF positive rheumatoid arthritis (RA) in the Mobile Clinic Health Examination Survey.⁴ In the baseline questionnaire, the subjects were asked: Have you lately suffered from nervousness? ...continuous fatigue? ...excessive sweating? ...heart pounding? ...continuous headache? Similar self reported complaints in a standard symptom inventory are likely to reflect anxiety, depression, and somatisation.⁵

No positive association was found between stress symptoms and RA risk, and again, contrary to the hypothesis, there was a negative association between excessive sweating and future RA (table 2). This unexpected finding may be due to either some unknown factor or to chance alone. It is not known whether there are joint determinants for sweating and RA, such as changes in sex hormones, or whether early Sjögren's syndrome might precede the onset of arthritis in the long term.

These results do not support the contention that the associations between coffee consumption and RF and RA are attributable to stress. However, we have no survey data on stressful life events that in particular have been supposed to act as a precipitating factor for RA.⁶ Moreover, many determinants of RA presumably are still unknown. Both the letter by Dr Glaser and the results of our complementary analyses indicate the need for advanced epidemiological studies.

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Teaching rheumatology in primary care

I agree with Hosie¹ that each group in primary care "has different needs at different times and educational activities must be sufficiently flexible to deliver what is needed at the appropriate time."

Over the past decade I have been teaching rheumatology to trainees in general practice in a district general hospital and over the past four years in a teaching hospital in the east end of London.

Trainees find it more useful if musculoskeletal problems are discussed by region as they present in real life rather than as individual diseases. For example, the differential diagnosis of pain in the elbow includes medial and lateral epicondylitis, olecranon bursitis (traumatic, inflammatory, or crystal induced, but is not to be confused with tophi, rheumatoid nodules, or xanthomas), osteoarthritis, a loose body, and inflammatory synovitis.

Musculoskeletal diseases are discussed as conditions presenting with mainly problems of arms, legs or spine. Each of the three regions is discussed in a two hour session. After one hour's tutorial, four to five relevant cases are presented to illustrate the conditions discussed.

For established general practitioners we have started "teach and treat" sessions. This programme is funded for a year by the local primary care group. The rheumatologist visits a local multi-doctor practice every fortnight for a two and a half hour session. The general practitioners present six to eight patients that they would have referred to the hospital. The patients are examined and treatment is discussed and if a procedure is required, it is given at the same time.

So far 14 practices have enrolled in the programme and three sessions have been completed. The response has been encouraging. Eighteen patients (10 female, 8 male) with an age range of 30-76 years (average 57.5) have been seen. The case mix included shoulder problems (five), symptomatic osteoarthritis of various joints (four), recent onset inflammatory polyarthritis (four), soft tissue lesions (three), and back problems (two). Ten procedures have been performed.

Each session is being audited and appraised by the local doctors. Upon completion of the

first round of sessions, we should have a better idea of the case mix and the difficulties the local general practitioners face. The final audit would help in further developing the training of local trainees (in general practice) and in the continuing professional development of general practitioners.

Another added advantage is the improvement in communication between primary and secondary care and a better understanding of each other's problems. On the other hand, better awareness of musculoskeletal problems may lead to a paradoxical increase in the number of referrals. However, it should lead to a better patient care.

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Authors' reply

I agree with Dr Ali Jawad that teaching of general practitioners and general practitioner registrars is best done within primary care itself, reflecting the mix of musculoskeletal problems that present within the community.

Various groups around the country are putting in place teaching similar to that described and, in particular, the Primary Care Rheumatology Society is setting up a series of meetings led by society members looking at common problems presenting to GPs.

Our first round of training meetings is based on shoulder problems and the initial meetings have been greeted with enthusiasm by participating GPs. We hope to expand this programme to include other regional problems, osteoporosis, and inflammatory arthritis. I think that the main benefit of teaching in this way is that it produces positive practical outcomes for examination techniques, treatment options, and the demonstration and practice of practical procedures, such as steroid injections.

Education for GPs, which is perceived to be generated from within primary care, with consultant input as appropriate, seems to be well received by GPs.

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LETTERS TO THE EDITOR

Magnitude of the genetic component in juvenile idiopathic arthritis

Genetic factors undoubtedly play a part at least in some forms of juvenile idiopathic arthritis (JIA). Yet it is commonly believed that the risk to a sibling of a patient with JIA is not particularly strong as shown by the rarity of reported multicase families.¹

Multicase JIA families have been traced systematically at the Rheumatism Foundation Hospital in Heinola, Finland, over a period of 15 years. A total of 41 families with 88 affected siblings (34 boys, 54 girls) were found fulfilling the Durban criteria for JIA.² In 60 (68%) of these 88 patients the disease was pauciarticular and, in most instances, it ran a mild course. The mean age at JIA diagnosis was 4.6 years.

Over the same period, eight sets of MZ twins were found; two twin pairs were concordant for JIA.

The incidence of JIA in Finland is 14/100 000 in the paediatric population.³ This corresponds to about 150 cases a year. Because the mean age at diagnosis was 7 years, the total number of cases of JIA in the paediatric population is about 1200, and the prevalence of the disease is about 1 per 1000, in a population of 1.2 million under 16 years of age in the country. The incidence and prevalence figures are similar to those reported from other countries for which data are available.⁴ For instance, it has been estimated that in the United States with a population 50 times larger than that of Finland there are about 71 000 cases of JIA.¹

Over the 15 year period of study 2300 patients were seen at the paediatric department of the Rheumatism Foundation Hospital. Of these, about 90% had JIA. It can thus be estimated that the population of JIA cases from which all the recorded multicase families were derived amounted to about 2000. This corresponds to 60% of JIA cases in the country.

There are about four MZ births per 1000 in the population. Thus our eight MZ pairs indicated that most, if not all, such pairs had been traced in the study group. Considering the population prevalence of JIA (1 per 1000) the concordance rate of 25% implies a relative risk of about 250 for a MZ twin. In adult rheumatoid arthritis the risk was found to be nine.⁵

The average number of children in Finnish families is 1.8; 45% of families have only one child, 38% have two children, 13% have three children, and 4% four or more children. In adult rheumatoid arthritis the relative risk for a sibling is about three. In view of the population prevalence of JIA, this finding of 41 multicase families in the basic population of 2000 indicates that the relative risk in JIA is much higher.

These findings cannot perhaps be extended to other populations, though there is no reason to believe that this would not be the case. In any event, genome wide screening of Finnish patients offers a promise that new susceptibility loci outside the HLA region may be found.

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A case of rheumatoid meningitis positive for perinuclear antineutrophil cytoplasmic antibody

Rheumatoid meningitis (RM) is a pachymeningitis rarely occurring in rheumatoid arthritis (RA). The pathophysiology of RM is not clear, though a diffuse vasculitis in the dura mater has been shown in some patients.¹ Here we present a patient with RM who had a raised serum level of perinuclear antineutrophil cytoplasmic antibody (P-ANCA), which is known to be associated with vasculitic diseases.

A 72 year old woman was admitted to our hospital because of headache. Twenty two years before she had been diagnosed as having RA and treated with non-steroidal anti-inflammatory drugs, without complete remission. Seven months before admission, polyarthralgia deteriorated and a numbness of the hands and feet and a low grade fever occurred, and she lost 10 kg in 2 months. She was given prednisolone 15 mg/day and her symptoms disappeared in a few weeks; the dose of prednisolone was tapered to 5 mg/day over three months. Five weeks before admission a left temporal headache occurred and gradually worsened; then she was admitted to the hospital. On physical examination, there were paraesthesia in the hands and feet, but no meningeal signs, papilloedema, visual field defects, cranial nerve palsies, ataxia or pathological reflexes were present. In laboratory studies, urine analysis and blood chemistry were normal. Table 1 shows the serological findings. Analysis of cerebrospinal fluid was normal and multiple cultures were negative for micro-organisms. Magnetic resonance imaging (MRI) of the brain disclosed a diffusely thickened dura mater along the left cerebral hemisphere and the cerebellar tentorium was enhanced after gadolinium pentetic acid (Gd-DTPA) administration (figs 1A and B). Biopsy of the dura mater was refused by the patient. After various causes of pachymeningitis²⁻⁴ such as sarcoidosis, Wegener's granulomatosis, malignant lymphoma, and a number of infectious diseases were excluded, a diagnosis of RM was made. The dose of prednisolone was increased to 50 mg/day, and the headache disappeared in two weeks. Raised levels of rheumatoid factor (2390 fell to 153 IU/ml) and P-ANCA (65 fell to <10 EU) gradually normalised in eight weeks. Brain MRI performed three months later showed no dural thickening (figs 1C and D).

Table 1 Blood count and serological findings

Variable	Value
White blood cells (/l)	16.6 ×10 ⁹
Stab (%)	7.0
Segmented (%)	75.5
Lymphocytes (%)	7.5
Monocytes (%)	6.5
Eosinophils (%)	3.0
Basophils (%)	0.5
Haemoglobin (g/l)	8.8
Platelets (×10 ¹⁰ /l)	49.2
Erythrocyte sedimentation rate (mm/1st h)	134
Angiotensin converting enzyme (IU/l)	8.3*
Adenosine deaminase (IU/l)	8.0*
C reactive protein (mg/l)	148
IgG (g/l)	13.45
IgA (g/l)	6.45
IgM (g/l)	4.27
C3 (g/l)	1.2
C4 (g/l)	0.1
CH ₅₀ (arb unit)	41.5
Antinuclear antibody (titre)	<20×
Rheumatoid factor (IU/ml)†	2390
P-ANCA‡ (EU)	65
C-ANCA¶ (EU)	<10
STS**	(-)
2,5AS activity†† (pmol/l)	<200*
Anti-hepatitis C virus	(-)
Anti-HTLV-1‡‡	(-)
Anti-cytomegalovirus	(-)
Anti-Epstein-Barr virus (IgG)	(-)
Tumour markers	
CEA (µg/l)	2.2*
CA-125 (U/ml)	13*
Ferritin (µg/l)	274

*These values are within the normal limit.

†Detected by a kit (RF, Eiken Ltd, Tokyo, Japan) using a latex agglutination method. Cut off value is <10 IU/ml.

‡P-ANCA = perinuclear antineutrophil cytoplasmic antibody; detected by an enzyme linked immunosorbent assay kit (MPO-ANC, Nipro Ltd, Osaka, Japan) using myeloperoxidase. Cut off value is <10 EU. The sensitivity and specificity for the crescent forming nephritis and/or focal necrotising nephritis are 76.4 and 87.4%, respectively. Possibility of the interference by various factors, including rheumatoid factor (<500 IU/ml), chylomicron, glutathione (<500 mg/l), anti-dsDNA antibodies, and C-ANCA, has been excluded. 10 to 20 EU is a grey zone in RA.

¶C-ANCA detected by an enzyme linked immunosorbent assay kit (PR3-ANC, Nipro Ltd) using protein. Cut off value is <10 EU.

**Serological test for syphilis.

††2',5'-Oligoadenylate synthetase activity, which rises in non-specific viral infections.

‡‡Human T cell leukaemia virus 1.

Recent development of MRI has helped the diagnosis of RM greatly.⁵ Because enhancement of MRI by administration of Gd-DTPA implies disruption of the blood-brain barrier,⁶ it was suspected that this case was complicated by RM.

Although it has been reported that some neurological complications in RA are related to vasculitis,^{6,7} there have been some investigators who could not show the existence of vasculitis in patients with RM.⁸ Demonstration of vasculitis in RM may depend on the phase and extent of the pathological changes of RM.

P-ANCA is often detected in systemic vasculitic diseases, such as polyarteritis nodosa and pauci-immune necrotising crescentic glomerulonephritis,⁹ but it has been reported that the sensitivity and specificity of P-ANCA for vasculitis are not high. Because vasculitis occurs in rheumatic diseases, which are often mediated by immune complexes, P-ANCA in this case may result from non-specific polyclonal B cell activation. On the other hand, it has also been reported that the frequency of vasculitic involvement was significantly high

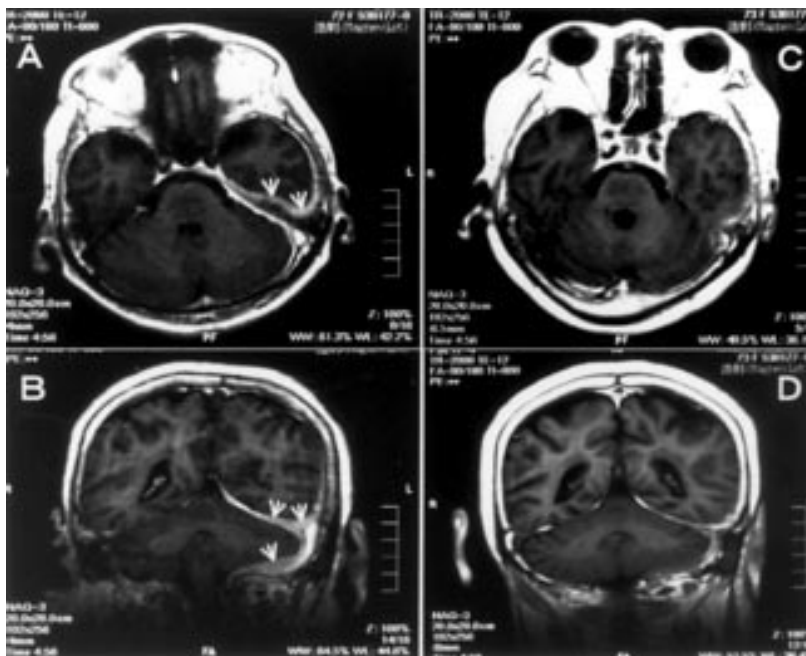


Figure 1 Magnetic resonance imaging after administration of gadolinium on admission (A, B) and six months after treatment (C, D). T₁ weighted images are shown. Arrows represent the thickened dura mater along the left cerebral hemisphere and the cerebellar tentorium. (A, C) Horizontal section; (B, D) coronal section.

in a P-ANCA positive subgroup of patients with RA.¹⁰ However, the number of the cases in which pachymeningitis is shown by MRI or pathological analysis are few, and the serum P-ANCA was determined and followed up in the clinical course. Therefore, accumulation of cases of RM in which serum P-ANCA is determined may be helpful in understanding the pathogenesis of RM and the histochemical analysis of this antibody in the dura mater.

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Increased frequency of HLA-DRB1*0401 in patients with RA and bronchiectasis

Lung disease is one of the extra-articular manifestations of rheumatoid arthritis (RA) and includes pleuritis, parenchymal nodules, interstitial fibrosis, and obstructive airway disease.¹ Increased risk of pulmonary infection and bronchiectasis (BC) are also seen.^{1,2} An association between RA and BC has been reported in some series of patients with RA, with an estimated prevalence of 5%.^{1,2} With the use of high resolution computed tomography (CT), this prevalence has been found to be higher, ranging from 6 to 50%.³ It has been claimed that the severity of the polyarthritis is similar in patients with and without BC.⁴ However, some authors noted a severe disease in patients with RA with BC when the polyarthritis preceded the lung disease.⁵ Additionally, patients with RA with BC had a reduced five year survival rate compared with those without BC.⁶ Secondary Sjögren's syndrome, recurrent pulmonary infections, and genetic background have been proposed to explain the relation between these two conditions.² In this way, RA with BC has been found to be associated with HLA-DR1 and DQB1*0601.⁷ The association between RA and HLA-DRB1* alleles expressing the shared epitope (SE) (DRB1*0101, *0102,

Table 1 HLA-DRB1* frequencies in patients with rheumatoid arthritis (RA) with or without bronchiectasis (BC) and in healthy controls (HC)

	RA with BC (%)	RA without BC (%)	HC (%)	p Value‡
No	23	23	104	
DRB1*01	6 (26)	9 (39)	20 (19)	0.12
DRB1*04	10 (43)	10 (43)	18 (17)	0.003
SE†	15 (65)	14 (61)	37 (36)	0.007
DRB1*0401	9 (39)¶	4 (17)**	6 (6)	<0.0001
DRB1*0101	6 (26)	9 (39)	19 (18)	0.09
or *0404	2 (9)	2 (9)	3 (3)	0.3
or *0405	0 (0)	0 (0)	3 (3)	0.5
or *0408	1 (4)	2 (9)	1 (1)	0.1
or *1001	1 (4)	0 (0)	4 (4)	0.6

†SE = alleles encompassing the shared epitope: DRB1*0101, *0401, *0404, *0405, *0408, *1001.

‡ χ^2 Test between the three groups; ¶ χ^2 test with Yates's correction between RA with BC and HC; p=0.00003 (OR 10.5; CI: 2.84 to 40.21); ** χ^2 test with Yates's correction between RA without BC and HC; p=0.15.

*0401, *0404, *0405, *0408, *1001, *1402 alleles) is well established. The presence of these alleles in RA has been reported to be associated with disease severity, and particularly with extra-articular manifestations, such as vasculitis or subcutaneous nodules.^{8,9} Whether RA with BC is associated with the SE or not has not been previously examined. Thus in this study we determined the HLA-DRB1* alleles in patients with RA with and without BC (RA/BC+ and RA/BC-, respectively) with a special emphasis on the expression of the SE.

Between 1997 and 1998, 46 inpatients and outpatients fulfilling the 1987 American College of Rheumatology criteria for RA were included to determine the prevalence of BC. They all underwent high resolution CT of the chest. HLA-DRB1* typing was performed using the PCR-SSO method (people who typed as DRB1*01 and *04 had a subtyping for HLA-DRB1*0101 to *0104 and DRB1*0401 to *0422, respectively (PCR-SSP)). One hundred and four unrelated healthy subjects without any history of lung disease were used as controls for HLA-DRB1* comparisons.

The results of the clinical features, laboratory investigations, and CT findings of this series have been previously published.¹⁰ BC was found in 50% of patients. Most of them had not been previously diagnosed with BC before the study and were free of respiratory symptoms. No differences were found between patients with and without BC for age (RA/BC+ *v* RA/BC- 59.1 *v* 60.1 years), sex ratio (16 women and 7 men *v* 18 women and 5 men), disease duration (10.6 *v* 9.6 years), positivity for rheumatoid factors (91% *v* 91%), bony erosions, use of corticosteroids or immunosuppressive drugs, respiratory manifestations, or smoking. Additionally, extra-articular manifestations were present in eight RA/BC+ (35%) and six (26%) RA/BC- patients (χ^2 test between the two groups: p=0.7).

In eastern France, patients with RA express the SE with a significant prevalence of HLA-DRB1*0101, DRB1*0401, and DRB1*0404.¹¹ Similar findings were seen in this RA series, with a higher frequency of the SE and DRB1*0401 in the two RA groups than in the healthy controls (table 1). The SE

was expressed in 15/23 (65%) of RA/BC+ patients, 14/23 (61%) of RA/BC- patients, and 37/104 (36%) of controls (χ^2 test between the three groups: p=0.007). Analysing the DRB1*04 subtypes, we noted that the frequency of DRB1*0401 was significantly higher in the RA/BC+ group (39%) than in the RA/BC- (17%) and control (6%) groups (χ^2 test between the three groups: p<0.0001). However, when the frequency of DRB1*0401 was compared between the RA/BC+ and RA/BC- groups, the results did not reach significance (χ^2 test between the two groups: p=0.19). Moreover, the DRB1*0401 frequency was significantly higher in RA/BC+ patients than in controls (39% *v* 6%; χ^2 test between the two groups: p=0.00003; OR 10.5; CI 2.84 to 40.21), and, conversely, no difference was found between the RA group without BC and the controls (17% *v* 6%; χ^2 test between the two groups: p=0.15). Finally, the frequency of the other alleles expressing the SE (DRB1*0101, *0404, *0405, *0408, *1001) did not differ between the two RA groups and the controls (table 1).

Our data suggest that DRB1*0401, but not the other RA linked alleles, was significantly associated with patients with BC. A slight increase in the prevalence of this allele was also seen in the RA/BC+ group as compared with the other patients, but not significantly. This may be explained by the small number of patients in each group (n=23). The relation of the alleles encompassing the SE with disease severity is still discussed, but an association with certain DRB1*04 subtypes has been reported in patients originating from North America and northern Europe.^{8,9} In fact, DRB1*0401 and *0404 appear to be strongly associated with severe manifestations of the disease, such as nodules or vasculitis.⁸ In this study, patients with BC significantly expressed DRB1*0401. The coexistence of RA and BC has been associated with a poor prognosis and a more severe disease in some studies.^{5,6} Thus it is tempting to speculate that this might be related to the expression of the DRB1*0401 allele, as suggested by our results. Thus patients with RA expressing DRB1*0401 should be considered to have a higher risk of developing BC and these patients should be regarded with

caution and an awareness of the possibility of extra-articular manifestations and therefore, disease severity.

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CORRECTION

ARD supplement

The supplement "Advances in targeted therapies II", published at the same time as the November 2000 issue of the *Annals*, was mistakenly called supplement I. It should have been called supplement II. The EULAR supplement published in July was supplement I.