Traditional cardiovascular risk factors measured prior to the onset of inflammatory polyarthritis

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Background. Cardiovascular mortality is increased in patients with seropositive inflammatory polyarthritis (IP). We tested the hypothesis that the increased risk of cardiovascular disease (CVD) can be explained by elevated traditional CVD risk factor levels in persons prior to development of IP.

Methods. In a population-based, prospective nested case–control study, 25,600 people aged 45–75 yr participated in a health survey, including standard CVD risk factor assessment, between the years 1993 and 1997. There were 91 incident IP cases (one-third were seropositive at presentation) identified during follow-up to the end of July 2001. Baseline CVD risk factors in the IP cases were compared with those in two age/gender-matched controls.

Results. Current smokers had an odds ratio of 2.0 (95% CI 1.0–4.0) for IP. Other risk factors, including total and LDL cholesterol, systolic and diastolic blood pressure and obesity, did not differ significantly between cases and controls. Importantly, in combination, using a standard coronary disease risk score, these factors only had a modest association with future IP, and no association when analysis was restricted to the smaller number of cases who were seropositive.

Conclusion. Of the traditional cardiovascular risk factors, only smoking increases CVD risk prior to the onset of IP. Therefore the increased CVD observed in these patients is likely to be a consequence of factors operating after the onset of the arthritis.

KEY WORDS: Cardiovascular risk factors, Inflammatory polyarthritis, smoking, rheumatoid factor.
a population-based cohort study in which, at the baseline survey in 1993–97, a number of traditional cardiovascular risk factors were measured. The cohort was followed prospectively to examine the incidence of a number of major diseases, including coronary disease [29].

We examined the hypothesis that traditional coronary disease risk factors are also associated with an increased risk of development of IP, which may explain the substantial cardiac disease risk in patients with IP.

Participants and methods

Design

The design was a prospective, population-based, nested case–control study. Participants recruited by EPIC-Norfolk were followed up and new cases of IP identified. Each such case was matched with two controls and their baseline coronary disease risk factors were compared.

EPIC baseline survey

This has been described elsewhere [29]. Briefly, 25,633 men and women aged between 45 and 75 yr, identified from primary care age–sex registers within Norfolk between 1993 and 1997, participated in a prospective study on health and lifestyle and chronic disease which included a health check examination during which cardiovascular disease risk factors were assessed. Smoking history was obtained by questionnaire. Dates of stopping and starting smoking were recorded as well as the number of cigarettes smoked daily. Participants were categorised as ‘current’, ‘ex-smokers’ and ‘non-smokers’ at the time of the questionnaire ‘ever smoking’ being defined as at least one cigarette a day for at least 1 yr. The numbers of pack-years were also estimated for each decade of life. The history of diabetes was obtained by self-report. Height was measured to the nearest millimetre without shoes. Weight was measured without shoes in light clothing to the nearest 200 g using digital scales. Blood pressure was measured after the participant had sat for 3 min and two measurements were taken of both diastolic and systolic BP and the mean calculated. A non-fasting blood sample was obtained and the following lipids measured: total cholesterol, HDL cholesterol and triglyceride. Friedewald’s formula was used to estimate LDL cholesterol [30].

Ascertainment of inflammatory polyarthritis

The subjects who participated in EPIC-Norfolk were also part of the target population for ascertainment of new-onset IP cases arising within Norfolk (NOAR). This study has also been described in detail elsewhere [28]. In brief, any adult presenting to their primary care physician with swelling of two or more joints lasting at least 4 weeks is notified to NOAR for standardized evaluation that includes a detailed history, structured joint examination and RF estimation. The American College of Rheumatology (ACR) 1987 classification criteria for RA [31] are applied at baseline and at yearly intervals subsequently.

Analysis

The EPIC and NOAR databases were merged using date of birth and other demographic details as the identifiers to link subjects who had previously participated in the EPIC baseline assessment and then subsequently entered NOAR as a case of IP. Each case identified was matched to two EPIC participants who had not developed IP. Matching was done on gender, date of birth (to within 3 yr of the case year of birth) and date of EPIC assessment (to within 3 months of the case assessment date). The coronary disease risk factors mentioned above were assessed as continuous variables, though cigarette smoking was analysed in three ways: (i) by ever, never or current status; (ii) by dividing current smokers into those with heavy smoking (> 20 pack-years) and those with less smoking; and (iii) by treating pack-years as a continuous variable. Body mass index (BMI) was calculated as weight in kilograms divided by height in metres squared and was analysed as both a continuous variable and as a categorical variable according to WHO definitions of overweight and obesity [32]. The cardiovascular risk factors were also pooled to derive a coronary disease risk prediction score [33] based on the Framingham equation, which calculates the percentage likelihood of a cardiovascular event over a 10-yr period. Using the cardiac risk assessor computer program [34], we derived the 10-yr coronary heart disease event risk as a percentage based on gender, age, systolic and diastolic BP, current smoking status, serum total cholesterol, HDL cholesterol and self-report of diabetes. Current guidelines suggest that people with a 10-yr coronary risk score in excess of 15% should be defined as high-risk patients and those with a score in excess of 30% should be urgently targeted for risk reduction interventions. The calculated percentage 10-yr coronary risk was initially treated as a continuous variable, and was then dichotomized by dividing the subjects into those with high coronary risk (10-yr risk > 15%) and those without (10 yr risk ≤ 15%).

The matched triplets were maintained for analysis, and univariate conditional logistic regression was used to determine the association between the development of IP and individual risk factors. The risk factors in combination were examined by assessing the association between IP and the coronary risk prediction score. Subjects recruited to both NOAR and EPIC gave informed consent to participation in these respective studies. Both studies were approved by the local research ethics committee.

Results

A total of 91 cases of IP had developed in the EPIC Norfolk cohort by August 2001. Of these, 63 (69.2%) were female. The mean age at symptom onset was 62.8 yr (s.d. 9.8 yr). At the NOAR baseline visit, 34 (37%) of subjects were classified as having RA by ACR criteria and 29 (of the 87 with available sera) (33.3%) were RF-positive. The median interval between EPIC assessment and onset of IP, defined as the first observation by the patient of joint swelling, was 28.4 months [interquartile range (IQR) 11.7, 41.3].

The distribution of coronary disease risk factors for the incident cases and their matched controls is shown in Table 1. The data for triglycerides and pack-years of smoking were not normally distributed and are displayed as medians and IQRs. The cases were well matched to the controls for gender and age, as expected. Self-reported diabetes was rare, but more common in the cases than the controls. A higher proportion (20.9%) of the cases were current smokers compared with the controls (11.6%), and not only were the cases more likely to smoke but they were also more likely to be heavy smokers. Thus, smoking more than 20 pack-years was reported by 62% of the ever-smoking cases compared with 40% of the ever-smoking controls. There was little difference observed in the distributions of serum lipid concentrations, systolic or diastolic BP or BMI between the two groups. BMI was analysed both as a continuous variable and using arbitrary cut-off points. Thus, using the WHO criteria for hypertension, there were 41 (45%) cases and 78 (43%) controls with systolic BP > 140 mmHg, and there were 22 (24%) cases and 78 (25%) controls with diastolic blood pressure > 90 mmHg. Similarly, using the WHO criteria for hypercholesterolaemia, there were 63 (75%) cases and 131 (78%) controls with cholesterol > 5.2 mmol/l.

As shown in Table 1, there was a very modest increase in the 10-yr percentage cardiovascular disease risk in the cases compared to the controls. Comparison was then made between the individual
risk factors in the cases and controls, maintaining matching. The results of this univariate conditional logistic regression are shown in Table 2. As the cases and controls were matched for age and gender, no further adjustment for these variables was made. Data are presented for the 91 case-control triplets and separately by gender, although the number of male triplets (a total of 28) was relatively small. As expected, the major difference was in relation to cigarette smoking. This is most marked in males, with male ever-smokers having a fourfold increase in risk of developing IP. This was mainly explained by an increased risk in those with more than 20 pack-years of smoking. There was also an increased risk associated with diabetes in both men and women, although, with small numbers, confidence intervals were wide. Despite the influence of smoking, the 10-yr cardiovascular disease risk score showed very little difference between the cases and the controls. Thus, each 1% increase in this score was associated with a non-significant 2% increase in IP risk. Stratifying subjects into high and low coronary risk (10-yr risk >15%) resulted in almost a twofold increase in IP risk, but the confidence intervals included unity.

The above analyses were conducted on the case group as a whole. We had previously demonstrated that the increased CVD mortality risk was restricted to those who were RF-positive. We therefore repeated all the above analyses on the smaller number of subjects who were RF-positive at baseline. The confidence intervals were wider but the results were even more consistent with a null effect. Thus, the OR (95% CI) associated with a 1% increase in the overall CVD score was actually 1.0 (0.9–1.1). Similarly, the OR (95% CI) associated with having a 10-yr CVD risk greater than 15% was also 1.0 (0.3–3.7).

Finally, we did not observe a statistically significant association between obesity and the subsequent development of IP, although there was a trend towards increased obesity prior to IP onset in women but not in men. The previous, though cross-sectional, case-control study of NOAR patients found that obesity (BMI >30) was associated with IP and RA [16]. One possible explanation for the lack of consistency between these study findings might be that obesity is a risk factor for IP only if it is present in the period just prior to the onset of joint symptoms. A number of patients in the current study had their BMI assessed several years prior to the onset of IP. Thus, it is possible that some of these patients may have increased their weight during this intervening period. In order to investigate this, the time between the EPIC assessment and the onset of IP symptoms was divided into tertiles. When the analysis was repeated, stratified by the duration between the health examination and the onset of IP symptoms, we found that obesity was significantly associated with IP in those patients who developed their arthritis within 18 months of their EPIC health assessment and the onset of IP symptoms, we found that obesity was mainly explained by an increased risk in those with more than 20 pack-years of smoking. There was also an increased risk associated with diabetes in both men and women, although, with small numbers, confidence intervals were wide. Despite the influence of smoking, the 10-yr cardiovascular disease risk score showed very little difference between the cases and the controls. Thus, each 1% increase in this score was associated with a non-significant 2% increase in IP risk. Stratifying subjects into high and low coronary risk (10-yr risk >15%) resulted in almost a twofold increase in IP risk, but the confidence intervals included unity.

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<table>
<thead>
<tr>
<th>Variable</th>
<th>Risk comparator</th>
<th>OR (95% CI)</th>
<th>OR (95% CI)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lipids</strong></td>
<td></td>
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</tr>
<tr>
<td>HDL cholesterol</td>
<td>Per mmol/l</td>
<td>0.87 (0.42, 1.84)</td>
<td>0.75 (0.32, 1.74)</td>
<td>1.59 (0.31, 8.08)</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>Per mmol/l</td>
<td>0.85 (0.64, 1.14)</td>
<td>0.67 (0.47, 0.98)</td>
<td>1.31 (0.78, 2.21)</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>Per mmol/l</td>
<td>0.94 (0.73, 1.21)</td>
<td>0.75 (0.54, 1.04)</td>
<td>1.39 (0.89, 2.19)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>Per mmol/l</td>
<td>1.05 (0.80, 1.39)</td>
<td>1.03 (0.71, 1.49)</td>
<td>1.08 (0.72, 1.59)</td>
</tr>
<tr>
<td><strong>Smoking</strong></td>
<td></td>
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<tr>
<td>Ever smoked</td>
<td>Never smokers</td>
<td>1.41 (0.84, 2.35)</td>
<td>1.06 (0.58, 1.92)</td>
<td>4.00 (1.09, 14.6)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>Never smokers</td>
<td>2.00 (1.00, 4.03)</td>
<td>1.33 (0.60, 2.94)</td>
<td>11.60 (1.41, 95.9)</td>
</tr>
<tr>
<td>Quantity of smoking</td>
<td>Per 10 pack-years</td>
<td>1.17 (1.00, 1.37)</td>
<td>1.05 (0.82, 1.34)</td>
<td>1.26 (1.01, 1.58)</td>
</tr>
<tr>
<td><strong>Moderate smoking</strong></td>
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</tr>
<tr>
<td>(&lt;20 pack-years)</td>
<td>Non-smoker</td>
<td>0.87 (0.47, 1.64)</td>
<td>0.78 (0.37, 1.62)</td>
<td>1.60 (0.41, 6.26)</td>
</tr>
<tr>
<td>Heavy smoking</td>
<td>Non-smoker</td>
<td>2.37 (1.20, 4.65)</td>
<td>1.72 (0.74, 4.01)</td>
<td>5.07 (1.33, 19.3)</td>
</tr>
<tr>
<td><strong>BP</strong></td>
<td></td>
<td></td>
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<tr>
<td>Systolic BP</td>
<td>Per 10 mm Hg</td>
<td>1.03 (0.88, 1.19)</td>
<td>1.04 (0.86, 1.27)</td>
<td>0.98 (0.76, 1.27)</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>Per 10 mmHg</td>
<td>1.09 (0.86, 1.39)</td>
<td>1.02 (0.76, 1.37)</td>
<td>1.24 (0.83, 1.87)</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>Non-diabetic</td>
<td>2.68 (0.74, 9.68)</td>
<td>3.35 (0.59, 18.9)</td>
<td>2.00 (0.28, 14.2)</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
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<tr>
<td>BMI</td>
<td>Per kg/m²</td>
<td>1.00 (0.94, 1.06)</td>
<td>1.05 (0.97, 1.12)</td>
<td>0.88 (0.76, 1.01)</td>
</tr>
<tr>
<td>Overweight (BMI &gt;25)</td>
<td></td>
<td>0.88 (0.49, 1.60)</td>
<td>1.07 (0.54, 2.16)</td>
<td>0.51 (0.15, 1.67)</td>
</tr>
<tr>
<td>Obese (BMI &gt;30)</td>
<td>BMI &lt;25</td>
<td>1.09 (0.54, 2.19)</td>
<td>2.06 (0.87, 4.84)</td>
<td>0.25 (0.05, 1.11)</td>
</tr>
<tr>
<td><strong>CVD risk</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>*10-yr CVD</td>
<td>Per 1% risk</td>
<td>1.02 (0.96, 1.09)</td>
<td>1.02 (0.94, 1.09)</td>
<td>1.03 (0.95, 1.11)</td>
</tr>
<tr>
<td>*High CVD</td>
<td>Risk &lt;15%</td>
<td>1.90 (0.89, 4.04)</td>
<td>1.56 (0.57, 4.27)</td>
<td>2.32 (0.69, 7.73)</td>
</tr>
</tbody>
</table>

*Complete data for calculating CVD score in 82 cases and 162 controls.
was only demonstrated in women; the small number of males prevented further subanalysis.

Discussion

This study has confirmed that cigarette smoking is associated with an increased risk of the development of IP. This result has been observed before within NOAR [16], but the present study was prospective whereas the previous report was based on retrospective recall. The population of cases included in this report is different from that in the previous study. We have also shown for the first time that serum lipid levels and BP are not increased prior to the onset of IP.

The major conclusion with regard to the study hypothesis is that standard cardiovascular risk factors are not (with the exception of cigarette smoking) increased prior to the onset of IP; and that the overall risk profile of subjects destined to develop IP is modest. Therefore, the excess CVD mortality in these patients must be explained by other factors.

This study had a number of strengths. The coronary disease risk factors were ascertained prospectively and not subject to recall error or problems with retrospective assessment. The questions on smoking and diabetes were based on self-report and not subject to further individual validation in this study. The validity of such self-reports for these variables is considered acceptable in large epidemiological studies and any misclassification, given the prospective nature of the study, would have been random between the future cases and ‘non-cases’. Cases were ascertained from a population base and controls from the same population and so there are unlikely to be any selection factors that could have contributed to obtaining the results shown. Data on the occurrence of IP were obtained in real time using standardized techniques and do not rely, as is the case in other prospective studies, on subjects’ self-report.

However, there are a number of limitations. Despite the large size of the EPIC cohort, which recruited over 25,000 subjects, only 91 participants developed IP during follow-up, of whom only 28 were male. This reflects the overall low population incidence of the disease and hence the difficulty in undertaking sufficiently large studies to obtain sufficient incident cases for analysis. The confidence intervals around the key estimates, particularly the confidence intervals were so wide as to preclude useful comment. Therefore, the excess CVD mortality in these patients must be explained by other factors.

This study, therefore, is concerned with factors associated with the onset of IP and is not about risk factors for cardiovascular disease per se. The fact that traditional CVD risk factors are not increased prior to the onset of IP does not mean that IP patients

<table>
<thead>
<tr>
<th>Months between EPIC assessment and IP onset</th>
<th>All</th>
<th></th>
<th>Females</th>
<th></th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>OR (95% CI)</td>
<td>n</td>
<td>OR (95% CI)</td>
<td>n</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>&lt;18</td>
<td>31</td>
<td>4.79 (1.17, 19.6)</td>
<td>24</td>
<td>9.88 (1.74, 56.0)</td>
<td>7</td>
</tr>
<tr>
<td>18–37</td>
<td>30</td>
<td>0.49 (0.14, 1.76)</td>
<td>21</td>
<td>0.75 (0.16, 3.44)</td>
<td>9</td>
</tr>
<tr>
<td>&gt;37</td>
<td>30</td>
<td>0.71 (0.21, 2.38)</td>
<td>18</td>
<td>1.29 (0.28, 5.83)</td>
<td>12</td>
</tr>
</tbody>
</table>

showed no difference in results, despite the smaller numbers. Thus, the observation within the NOAR cohort of increased CVD mortality in seropositive subjects cannot be explained by their premorbid cardiovascular risk.

Although smoking is a key risk factor for the development of IP, particularly in men, other factors have to be sought to explain the increased cardiovascular disease mortality in subjects with RA. Indeed, studies have failed to identify smoking as a predictor of CVD mortality in RA [4] and IP [7]. Traditional cardiovascular risk factors, although highly prevalent in clinic-based populations of established RA patients [38, 39], do not seem to explain the increased CVD event rates observed in RA compared with the general population [40]. It seems that there are other key factors that are responsible for promoting CVD in these patients.

Several novel CVD risk factors identified in the general population are of particular interest in RA. It has emerged in recent years that inflammation is an important marker of increased CVD risk in the general population. CRP levels have been found to be associated with the risk of developing coronary heart disease events in the general population [8, 10] and were also found to be associated with coronary death or myocardial infarction in patients with known CVD [41]. In RA populations, the amount of inflammation, as measured longitudinally by disease activity assessments, has been shown to predict all-cause mortality [14], and increased inflammatory cytokines [11] and elevated erythrocyte sedimentation rates [42] have both been associated with increased cardiovascular mortality. There are many other markers of inflammation common to atherosclerosis and RA; these include elevated levels of soluble adhesion molecules, macrophage activation, and T-cell and B-cell activation [43]. Therefore, it seems likely that, if coronary heart disease is an inflammatory disease, inflammatory comorbid conditions such as RA may potentiate atherosclerosis.

Other factors that may be important following the onset of IP include treatments. For example, drugs such as methotrexate and sulphasalazine may increase the homocysteine level [44], which has been recognized to be a novel risk factor for CVD [45]. Chronic NSAID use may potentiate hypertension. Use of ibuprofen seems to reduce the CVD-protective, antiplatelet effects of aspirin [46] and there are ongoing concerns about the CVD safety of the selective cyclooxygenase 2 inhibitors [47]. Corticosteroids have many potential adverse CVD side-effects [48], although their prolonged use was not found to be associated with increased CVD mortality in a study by Wållberg-Jonsson et al. [42].

Many of the data on coronary disease risk in subjects with RA relate to mortality, and it would be important to separate out those factors in the disease that predict coronary disease onset from those that predict mortality once arterial disease is present. However, we suggest that the increased CVD mortality observed in RA is more likely to be caused by factors that develop either with the inflammatory disease process or its treatment than by increased traditional CVD risk factors prior to disease onset.

This study, therefore, is concerned with factors associated with the onset of IP and is not about risk factors for cardiovascular disease per se. The fact that traditional CVD risk factors are not increased prior to the onset of IP does not mean that IP patients

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**TABLE 3. Conditional logistic regression, testing the strength of association between obesity and the risk of developing IP stratified by interval between EPIC assessment and onset of IP symptoms**
Cardiovascular risk factors measured before inflammatory polyarthritis

with elevated coronary heart disease risk scores are not candidates for primary interventions to reduce CVD risk. In fact, one could argue that RA may be an independent risk factor for coronary heart disease (similar to diabetes) and future work is required to investigate whether the presence or absence of RA should be factored in to future CVD risk assessment calculations.

Acknowledgements

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