Cardiovascular disease and psychological morbidity among rheumatoid arthritis patients

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Objectives. To examine whether patients with rheumatoid arthritis (RA) with co-morbid cardiovascular disease (CVD) have different psychological morbidity (and psychosocial risk factors for it) compared with RA patients without co-morbid CVD.

Methods. Patients with RA and co-morbid CVD ($n=44$; hypertension alone for $n=27$) were compared with RA patients without CVD ($n=110$). Differences in psychological morbidity (depression and anxiety) and psychosocial risk factors for this (arthritis self-efficacy, acceptance, social support and optimism) were examined while controlling statistically for medical and demographic covariates.

Results. Groups did not differ on RA duration, RA activity, marital status or socioeconomic status, but RA patients with co-morbid CVD were older, less likely to be female and less likely to be in employment than those without CVD. RA patients with co-morbid CVD had significantly higher depression and were more likely to score above cut-offs for depression than RA patients without CVD. No differences existed in anxiety, although anxiety appeared to be more common than depression. Low optimism was identified as a possible psychosocial risk factor for depression.

Conclusions. RA patients with co-morbid CVD have higher depression than RA patients without CVD; low optimism is a potentially modifiable risk factor that may mediate this difference. RA patients with co-morbid CVD may benefit from systematic screening for depression and targeted intervention if necessary.

KEY WORDS: Comorbidity, Depression, Anxiety, Optimism, Work status.

Patients with rheumatoid arthritis (RA) suffer from depression or anxiety more frequently than the general population [1, 2]. Depressed individuals, in general, have greater functional disability and higher mortality from suicide and other causes [3]. When people with RA commit suicide the method tends to be violent and decisive [4], but suicide is not the main cause of higher mortality in RA. The commonest cause of death in RA is ischaemic heart disease (IHD) [5], which is more prevalent in RA patients than in the general population. The reasons for this are yet to be fully explained.

Depression predicts mortality following myocardial infarction [6]. Furthermore, having more than one chronic physical illness may be a risk factor for depression [7] but this has not yet been investigated specifically for psychological morbidity among RA patients in relation to co-morbid cardiovascular disease (CVD). In the present study we include hypertension in the definition of CVD, but we acknowledge that in other contexts hypertension may be classified only as a risk factor for more severe CVD.

There are several risk factors for psychological morbidity in RA patients that include RA duration, RA activity, demographics and psychosocial factors. RA duration, RA activity or age relate to depression and anxiety in some studies [8–13] but not others [1, 14]. Younger people with longstanding RA are the most likely to be depressed [15] and also to have worse cardiovascular outcome [5]. Compared with healthy individuals, people with RA are more likely to be divorced, unemployed and to have lower socioeconomic status (SES) [15, 16]. Being out of employment predicts depression in the general population [17], and may be important in RA. Being unmarried is also a possible risk factor for depression in RA patients, perhaps through lack of social support [18]. Although the evidence is not unanimous, notable demographic differences in psychological morbidity have been found among RA patients and should be controlled for.

Several psychosocial resources also relate to psychological morbidity in RA: findings are again not unanimous, but strong evidence implicates arthritis self-efficacy, coping, social support and generalized outcome expectancy (optimism/pessimism). RA patients with higher arthritis self-efficacy show greater decreases in depression and anxiety up to 5 yr later than those with lower self-efficacy [11, 19, 20]. Coping by acceptance of RA also predicts adjustment 6 months later [21], whereas passive pain coping predicts depression 1 yr later [10]. RA patients receiving more emotional support show decreases in depression over 6 months, whereas those with less support do not [9]. Optimistic RA patients show an improvement in composite psychological well-being over the next year, whereas those who are less optimistic do not [8, 11].

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Extrapolating the scant findings on psychological morbidity in people with multiple physical morbidities, we predicted that RA patients with co-morbid CVD would show more depression and anxiety than RA patients without CVD. We also investigated whether any such difference relates to the above medical, demographic or psychosocial risk factors for psychological morbidity in RA patients.

**Methods**

**Procedure and participants**

A sample of 154 White patients with RA satisfying the 1987 revised American College of Rheumatology criteria [22] were recruited as part of a larger study from out-patient clinics of the Dudley Group of Hospitals and South Birmingham Hospitals (formerly City Hospital, Birmingham) NHS Trusts, where Local Research Ethics Committee approval was granted. Written informed consent was obtained from all participants. Particular focus was put on including participants in the early stages of the disease to investigate differences by duration. Within the sample, 44 cases (29%) had confirmed co-morbid CVD, in line with recent research [5], although no stratified sampling for this was carried out. Hypertension was the most common form of co-morbid CVD, occurring alone in 27 cases (61%) and in combination with other CVD in eight cases (18%). The characteristics of the total sample, as well as those of the groups with versus without co-morbid CVD, are shown in Table 1.

**Measures**

Duration of RA, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) level and rheumatoid factor (RF) status were recorded from hospital records. Known co-morbid CVD was defined as the presence of hypertension, angina (or IHD), peripheral vascular disease, congestive heart failure or cerebrovascular disease diagnosed (and/or treated) by a physician, confirmed previous myocardial infarction, cerebrovascular accident, acute peripheral ischaemic episode or revascularization procedure, as stated in written hospital records and ICD codes from the hospitals’ information systems. These were checked against medications listed in hospital records and primary care repeat prescriptions.

SES was ascribed from job descriptions as manual or non-manual using standard occupational tables [23].

Depression and anxiety were measured using the two subscales of the Hospital Anxiety and Depression Scale (HADS) [24]. Cases of depression or anxiety can be identified using the cut-off scores of ≥8 or >10; scores of 0–7 are considered ‘normal’; scores of 8–10 denote ‘possible’ cases; scores of >10 suggest ‘probable’ cases. The cut-off of 10 was used in the present study as it is the most comparable to psychiatric ratings [24].

Functional disability was self-reported on the British Health Assessment Questionnaire (HAQ) [25]. Pain and fatigue were measured on 100 mm visual analogue scales (VASs).

Self-efficacy was assessed on the subscales for pain management (fatigue and mood) (ASES) [24].

Table 1. Descriptive statistics of psychological morbidity and its risk factors in rheumatoid arthritis by presence/absence of comorbid cardiovascular disease

<table>
<thead>
<tr>
<th>Variable</th>
<th>Direction of scoring</th>
<th>Total sample (n = 154) (%)</th>
<th>Participants without co-morbid CVD (n = 110) (%)</th>
<th>Participants with confirmed co-morbid CVD (n = 44) (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-reported cardiovascular co-morbidity</td>
<td></td>
<td>9</td>
<td>2</td>
<td>27</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension considered a symptom of RA</td>
<td></td>
<td>18</td>
<td>16</td>
<td>24</td>
<td>0.29</td>
</tr>
<tr>
<td>Sex (female)</td>
<td></td>
<td>73</td>
<td>78</td>
<td>61</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Married or living as such</td>
<td></td>
<td>78</td>
<td>81</td>
<td>70</td>
<td>0.16</td>
</tr>
<tr>
<td>Manual SES</td>
<td></td>
<td>35</td>
<td>35</td>
<td>35</td>
<td>0.99</td>
</tr>
<tr>
<td>In employment</td>
<td></td>
<td>28</td>
<td>35</td>
<td>10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RF positive</td>
<td></td>
<td>61</td>
<td>61</td>
<td>64</td>
<td>0.72</td>
</tr>
<tr>
<td>RA duration:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early</td>
<td></td>
<td>35.7</td>
<td>39.1</td>
<td>27.2</td>
<td>0.16</td>
</tr>
<tr>
<td>Intermediate</td>
<td></td>
<td>33.8</td>
<td>32.7</td>
<td>36.4</td>
<td></td>
</tr>
<tr>
<td>Established</td>
<td></td>
<td>30.5</td>
<td>28.2</td>
<td>36.4</td>
<td></td>
</tr>
<tr>
<td>Other physical co-morbidity</td>
<td></td>
<td>71</td>
<td>70</td>
<td>75</td>
<td>0.53</td>
</tr>
<tr>
<td>Probable anxiety (HADS &gt;10)</td>
<td></td>
<td>29</td>
<td>29</td>
<td>29</td>
<td>1.00</td>
</tr>
<tr>
<td>Probable depression (HADS &gt;10)</td>
<td></td>
<td>16</td>
<td>11</td>
<td>26</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

**Mean (±s.d.)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (±s.d.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>56.34 (±15.05)</td>
</tr>
<tr>
<td>ESR</td>
<td>25.05 (±18.55)</td>
</tr>
<tr>
<td>CRP</td>
<td>16.86 (±16.83)</td>
</tr>
<tr>
<td>Pain (VAS)</td>
<td>38.06 (±24.41)</td>
</tr>
<tr>
<td>Fatigue (VAS)</td>
<td>47.41 (±27.99)</td>
</tr>
<tr>
<td>Functional disability (HAQ)</td>
<td>1.51 (±0.92)</td>
</tr>
<tr>
<td>Anxiety (HADS)</td>
<td>8.27 (±3.87)</td>
</tr>
<tr>
<td>Depression (HADS)</td>
<td>6.46 (±3.60)</td>
</tr>
<tr>
<td>Self-efficacy for pain (ASES)</td>
<td>5.06 (±1.94)</td>
</tr>
<tr>
<td>Self-efficacy for other symptoms (fatigue and mood) (ASES)</td>
<td>5.67 (±1.98)</td>
</tr>
<tr>
<td>Acceptance (AIS)</td>
<td>2.85 (±0.79)</td>
</tr>
<tr>
<td>Social support (SSS)</td>
<td>2.93 (±0.68)</td>
</tr>
<tr>
<td>Optimism (LOT)</td>
<td>9.38 (±3.43)</td>
</tr>
<tr>
<td>Pessimism (LOT)</td>
<td>7.64 (±3.30)</td>
</tr>
</tbody>
</table>
Social support was operationalized as helpfulness using the Social Support Survey (SSS) [28]. Optimism and pessimism were measured with the two separate subscales of the Life Orientation Test (LOT) [29–32]. Concerns that optimism/pessimism may overlap with HADS depression because of item 12 (looking forward with enjoyment to things) were briefly investigated. The Spearman’s correlations of the optimism and pessimism scores with this HADS item were moderate (\(\rho = -0.33, 0.20\), respectively) and not larger than with the other depression items (mean \(\rho = -0.31, 0.21\), respectively).

Knowledge of the distinction between RA and CVD was addressed using question 3 of the Patient Knowledge Questionnaire (PKQ) for RA [33]. Participants were also asked to list any co-morbid medical conditions they had in an open written question (‘Are you currently suffering from the effects of any illness other than rheumatoid arthritis, such as angina or a cold? If yes, please give brief details’).

Statistical analyses
Continuous variables were screened for normality. Only RA duration was skewed; mean duration was 7.29 yr (s.d. = 9.99) with significant positive skew. To avoid violation of parametric assumptions, the total sample was split into three groups: ‘early’ duration \(< 6\) months, \(n = 55\) (35.7%), ‘intermediate’ duration \([1 \text{ to } 7 \text{ yr, } n = 52\) (33.8%)] and ‘established’ duration \([> 7 \text{ yr, } n = 47\) (30.5%).

Differences between participants with versus without co-morbid CVD were initially investigated using independent sample \(t\)-tests for continuous variables (with group differences in means and Kendall’s point-biserial correlation \(\tau\) value reported), a \(\chi^2\) test for a trend for the one ordinal variable (disease duration grouping) and unordered \(\chi^2\) tests for nominal variables (with odds ratios and Cramér’s associative \(\phi\) value reported). Much like Pearson’s product–moment correlation \(r\) value, \(\tau\) and \(\phi\) give an effect size and direction, allowing easy comparison between coefficients [34]. Ninety-five per cent confidence intervals (CIs) are also reported.

Multivariate analyses made use of analyses of covariance (ANCOVAs) to test differences in depression between participants with versus without co-morbid CVD while controlling for relevant covariates identified in bivariate analyses. Partial correlation coefficients (\(r_p\)) were calculated to describe the direction and size of relationships, again controlling for relevant covariates.

Power calculations based on meaningful differences of 3 on the HADS (representing the difference between the two HADS case cut-off scores of 8 and 11) indicated that a total sample of 60 would be more than adequate at standard power (0.80) and significance (0.05) [34].

Results
Descriptive characteristics of the total sample of RA patients
As shown in Table 1, the majority of participants were female (73%), not in employment (72%), of non-manual SES (65%) and married or living as such (78%). Psychological morbidity levels (also in Table 1) were similar to previous studies [1, 2, 35]. Using case cut-off scores of \(> 10\) on the relevant HADS subscale, symptoms of depression or anxiety that suggested probable clinical cases were reported by 16 and 29% of participants, respectively.

Self-reported CVD and differences in disease knowledge in RA patients by the presence/absence of co-morbid CVD
Only 12 of the 44 participants (27%) with confirmed co-morbid CVD reported some form of CVD on the open question about other illnesses, but, as shown in Table 1, this was significantly more than those without CVD (2%; \(P < 0.001\); odds ratio 20.25, 95% CI 4.31–95.22; \(\phi = 0.40\)). A minority (18%) of the total sample of 154 answered that hypertension is a symptom of RA on the PKQ; this was slightly more common among those who had CVD (24%), but not a significant difference (see Table 1).

Demographic and clinical differences in RA patients by the presence/absence of co-morbid CVD
As shown in Table 1, compared with those without CVD, the 44 participants with co-morbid CVD were significantly older (\(P < 0.001\); difference in means 12.35, 95% CI 7.41–17.29; \(\tau = 0.31\)). The group with co-morbid CVD contained a lower proportion of women (61%) than those without CVD (78%; \(P < 0.05\); odds ratio 2.26, 95% CI 1.06–4.81; \(\phi = -0.17\)). Participants in the group with co-morbid CVD were less likely to be in employment (10%) than those without CVD (35%; \(P < 0.001\); odds ratio 5.49, 95% CI 1.83–16.50; \(\phi = -0.27\)). However, participants with co-morbid CVD were equally likely to be of manual SES (35%) as participants without CVD (35%). Participants with co-morbid CVD were also equally likely to be married or living as such (70%) compared with participants without CVD (81%). Similarly, participants with co-morbid CVD were equally likely to be RF positive (64%) as participants without CVD (61%). Co-morbid CVD was not more common in the early, intermediate or established RA duration groups (see Table 1). Furthermore, participants with co-morbid CVD were equally likely to have another physical co-morbidity (75%) as participants without CVD (70%).

Details of RA activity are also shown in Table 1. Participants with co-morbid CVD did not differ from those without CVD in ESR, CRP, pain, fatigue or functional disability.

Differences in psychological morbidity in RA patients by the presence/absence of co-morbid CVD
Compared with those without CVD, the 44 participants with co-morbid CVD had significantly higher depression (\(P < 0.05\); difference in means 1.62, 95% CI 0.34–2.89; \(\tau = 0.16\); see Table 1). Over a quarter of those with co-morbid CVD (26%) were probably depressed (HADS depression \(> 10\)), significantly more than the 11% of others (\(P < 0.05\); odds ratio 2.78, 95% CI 1.12–6.93, \(\phi = 0.19\); see Table 1). Participants with co-morbid CVD did not differ from those without CVD in anxiety (difference in means 0.31, 95% CI \(-1.10–1.72\); \(\tau = 0.00\); see Table 1) or frequency of surpassing the probable anxiety cut-off (HADS anxiety \(> 10\)) (odds ratio 1.00, 95% CI 0.45–2.21; \(\phi = 0.00\); see Table 1).

Differences in psychosocial factors in RA patients by the presence/absence of co-morbid CVD
Compared with those without CVD, the 44 participants with co-morbid CVD had significantly lower optimism (\(P < 0.01\); difference in means 1.72, 95% CI 0.49–2.94; \(\tau = -0.21\); see Table 1), there were no differences in pessimism, self-efficacy for pain or other symptoms (fatigue and mood), acceptance of illness or social support.

Controlled analyses of predictors of depression in RA patients
In the ANCOVA controlling for age, sex, employment status and optimism, the difference in depression by presence/absence of co-morbid CVD became non-significant (\(F(1, 139) = 0.98, P = 0.32\);
Depression as covariates. A significant difference existed in depression by employment status and having low optimism also represented. These relationships are summarized in Fig. 1, with the initial rheumatoid arthritis by presence/absence of co-morbid cardiovascular disease: *P < 0.05; **P < 0.01; ***P < 0.001.

Depression did not relate to age [F(1, 139) = 3.61, P = 0.06; r_p = −0.16] or sex [F(1, 139) = 0.04, P = 0.85; r_p = −0.02] as covariates. A significant difference existed in depression by employment status [F(1, 139) = 13.28, P < 0.001; r_p = −0.30] and (continuous) optimism [F(1, 139) = 33.46, P < 0.001; r_p = −0.44]. These relationships are summarized in Fig. 1, with the initial associations of presence of co-morbid CVD with being out of employment and having low optimism also represented.

Discussion

We found that RA patients with co-morbid CVD had higher depression and were more likely to surpass cut-offs indicating probable clinical depression than RA patients without CVD. The differences represented a small but statistically significant effect in terms of τ or φ values and the difference in means used in power calculations, and hence may be of limited clinical significance. Being out of employment and of low optimism mediated the difference in depression by co-morbid CVD, both being more prevalent among RA patients with co-morbid CVD in the present cross-sectional study and representing more moderately sized effects. Moreover, being out of employment and of low optimism replaced presence/absence of co-morbid CVD as the variables that were significantly related to depression in multivariate analyses (Fig. 1), thus satisfying all conditions of a mediational relationship [36], albeit cross-sectionally. Causal inference cannot be drawn because it is equally possible that depression contributes to being unable to work or to low optimism. However, these findings confirm previously reported associations of depression with low optimism in RA patients [37] as well as providing novel evidence that depression may relate to the worse cardiovascular outcomes of RA. In addition, it suggests that, as in the general population [6], depression may relate to the worse cardiovascular outcomes of patients with RA. The exact mechanisms for this require further investigation. A larger sample size could have allowed investigation of the presence/absence of co-morbid CVD and being out of employment, thus highlighting useful flags for depression in RA patients. No difference existed on anxiety, which suggests that the association may be unique to depression, perhaps through some affect-specific process such as self-discrepancy [38].

Nearly a quarter of all RA patients thought hypertension was a symptom of RA: this misperception was redressed during debriefing. Moreover, only a quarter of patients with RA and CVD recorded the latter as a co-morbidity when listing their other illnesses. This may be because many cases of CVD are silent [5], and that is why symptoms of CVD were not measured in the present study (e.g. using an assessment of angina such as that by Rose [39]). Checklists of co-morbidities (e.g. [40]) may be more accurate than symptom measures or the limited open question used in this study by acting as a prompt. Irrespective of this, rheumatologists need to raise awareness of both the association and distinction between RA and CVD, given the negative impact such lack of knowledge may have on symptom reporting, health behaviours, adherence to medications [41] and ultimately outcome.

The HADS was employed to measure depression and anxiety in the present study. Clinical interview would have been the ideal way to confirm the presence of clinical depression or anxiety but previous research suggests that the HADS performs comparatively well [24] and levels of depression and anxiety were very similar to previous studies using the HADS in RA [2]. Lack of optimism is not an explicit symptom of depression [42] but is implicated in cognitive theory of depression [43] and hence included in many questionnaire measures [44], including the HADS (item 12 on looking forward with enjoyment to things). Our findings may therefore be a partial artefact of this measurement overlap, but the correlation of this item with optimism scores was not inflated. This does not detract from the clinical application of a lack of optimism in RA patients being a warning for depression, especially among patients with co-morbid CVD. LOT scores have not been translated to clinically significant differences for RA or any illness. The mean difference of 2 between the RA patients with versus without CVD on the optimism subscale indicates a change of answer from ‘agree’ to ‘disagree’ on one of the four items (e.g. I always look on the bright side of things), which we conjecture may reflect a notable difference in thinking.

Our measures included several psychosocial factors, but the assessment was not exhaustive. Furthermore, interactive effects can also occur for predictors of depression in RA patients [45] but were not tested in the present study. Other limitations include the self-report nature of measures (other than biological measures of RA activity and diagnoses of RA, CVD and other physical conditions, drawn from hospital records), the high prevalence of other physical co-morbidities (because it is difficult to thoroughly differentiate the effects of these varied conditions), the relatively small sample size (and hence moderately low power) and the potential lack of generalizability beyond the White British population. Despite these limitations, the finding that depression was higher among RA patients with co-morbid CVD (and related to their lower optimism and higher frequency of being out of work) adds to the growing understanding of depression associated with RA. In addition, it suggests that, as in the general population [6], depression may relate to the worse cardiovascular outcomes of patients with RA. The exact mechanisms for this require further investigation. A larger sample size could have allowed investigation of other psychosocial factors and potentially important medical factors, such as the effects that medications for RA and CVD may have on mood, especially depression. A stricter definition of CVD, excluding the preponderance of hypertension cases, may also be beneficial in future studies. A longitudinal design would also help define causality in further research and should ideally be used to investigate predictors of the onset of CVD in RA.

The psychological well-being of RA patients should be considered alongside the physical impact. RA patients with co-morbid CVD appear to be an important group to target for screening for depression and appropriate intervention. Preventing depression from persisting or worsening in these patients may improve both the quality and duration of their lives.

**Key message**

- Rheumatoid arthritis patients with co-morbid cardiovascular disease have higher depression and lower optimism and are less likely to be in employment than those without cardiovascular disease.
Acknowledgements

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