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The Relationship Between Mental Health, Disease Severity and Genetic Risk for Depression in Early Rheumatoid Arthritis

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ABSTRACT

Objective

Reduced mental health is prevalent in rheumatoid arthritis (RA). Although longitudinal studies are limited, there is evidence that depression associates with worse disease outcomes. We evaluated reciprocal relationships between mental health, RA severity and genetic risks for depression over 2-years in a well-characterised cohort of RA patients.

Methods

We evaluated 520 early RA patients previously enrolled to two clinical trials. Mental health was measured using the SF-36 mental health (MH) domain and mental component summary scores (MCS). MCS/MH associations over two-years with disease activity (DAS28), disability (HAQ), pain visual analogue scale (VAS) scores, and a weighted genetic risk score (wGRS) for depression, were tested using linear mixed-effects and regression models.

Results

Poorer mental health associated with worse RA outcomes. Lower MCS scores (indicating worse mental health) were seen in patients with a greater genetic risk for depression (wGRS $\beta=-1.21; P=0.013$). Lower baseline MCS associated with lower 2-year improvements in DAS28 ($\beta=-0.02; P<0.001$), pain ($\beta=-0.33; P<0.001$), and HAQ ($\beta=-0.01; P=0.006$). Baseline MCS associated with changes in the swollen joint count ($\beta=-0.09; P<0.001$) and patient global assessment ($\beta=-0.28; P<0.001$), but not the tender joint count ($P=0.983$) and
erythrocyte sedimentation rate \( (P=0.973) \). Only baseline pain VAS \( (\beta=-0.07; \; P=0.002) \) associated with 2-year changes in MCS.

**Conclusions**

Reduced baseline mental health associated with lower improvements in disease activity, disability, and pain over two years, supporting current national guidelines recommending screening for depression in RA. Pain had a bidirectional relationship with mental health. Depression genetic risk had a significant association with mental health.

**Keywords**

Rheumatoid arthritis; mental health; disease activity; disability; pain; genetics.
LIST OF ABBREVIATIONS

CARDERA: Combination Anti-Rheumatic Drugs in Early RA; CBT: cognitive-behavioural therapy; DAS28: disease activity score on a 28-joint count; ESR: erythrocyte sedimentation rate; GWAS: genome-wide association study; HAQ: Health Assessment Questionnaire; HWE: Hardy-Weinberg equilibrium; LD: linkage disequilibrium; LOCF: last-observation carried forward; MAF: minor allele frequency; MCS: mental component summary score; MDD: major depressive disorder; MH: mental health; NICE: National Institute for Health and Care Excellence; PCS: physical component summary score; PGA: patient global assessment; $P_T$: $P$-value threshold; QC: quality control; RA: rheumatoid arthritis; RCT: randomised controlled trial; REC: Research Ethics Committee; SF-36: short form-36; SJC: swollen joint count; SNP: single nucleotide polymorphism; TJC: tender joint count; VAS: visual analogue scale; wGRS: weighted genetic risk score.
1. INTRODUCTION

Reduced mental health is prevalent in rheumatoid arthritis (RA), with major depression present in 16.8% of patients (1). The cause of this excess burden of mental health impairment is uncertain. Comorbid depression also appears to have a detrimental impact on the disease course of RA, being associated with increased healthcare utilisation and costs (2) and representing an independent risk factor for non-suicide related mortality (3). Determining the cause and effect of depression in RA is, therefore, a key research goal.

Research in this area has mainly involved cross-sectional studies in patients with long-standing RA. These identified associations between depression, and pain (4), disability (5) and arthritis disease activity (6). Their cross-sectional nature, however, made it impossible to infer causality. Whilst longitudinal studies are limited, there is some evidence for a bidirectional effect with pain in patients with musculoskeletal disorders, whereby depression influences pain and vice versa (7, 8). There is also some evidence that depression predicts the subsequent disease activity of RA, with an analysis of established RA patients finding a slower rate of decline in disease activity over time in patients with a history of depression (9). Depression also has a substantial genetic component (10), with several variants associated with depression identified in a genome-wide association study (11). This is consistent with previous twin studies of the heritability of Major Depressive Disorder (MDD), which found that the disorder has a heritability of 48-75%, depending on assumptions made on the prevalence of MDD in the general population (12). The role of these in determining mental health in RA has not previously been evaluated.

The aim of our study was to evaluate the relationship between mental health and disease activity, disability, pain, and genetic risk for depression over 2 years in a well-characterised
clinical trial cohort of patients with early RA. The direction of any associations was tested by examining the impact of baseline mental health on changes in disease activity, disability and pain, and vice versa.

2. METHODS

2.1 Participants

We studied patients in the Combination Anti-Rheumatic Drugs in Early RA (CARDERA) genetics cohort. It has been described in detail previously (13). In brief, it comprises European ancestry RA patients enrolled to two multicentre randomised controlled trials (RCTs), CARDERA-1 and CARDERA-2 (14, 15). Both recruited patients with early RA (<2 years duration) and active disease defined as three of ≥3 swollen joints, ≥6 tender joints, ≥45-min morning stiffness, or erythrocyte sedimentation rate (ESR) ≥28 mm/h. CARDERA-1 recruited patients between 2000-2002; CARDERA-2 recruited patients between 2003-2010. CARDERA-1 randomised patients to receive either (1) methotrexate; (2) methotrexate and ciclosporin; (3) methotrexate and prednisolone; (4) methotrexate, ciclosporin and prednisolone. CARDERA-2 randomised patients to receive either (1) methotrexate or (2) methotrexate and anakinra. As the original aim of the CARDERA studies was to investigate the performance of combination therapy with reference to monotherapy, a placebo group was not assigned. Rheumatoid Factor (RF), a biomarker providing clinical information on the antibody composition of patient serum, was assayed as described previously (16). Follow-up was 2 years. The current analysis is restricted to the 520 patients with baseline mental health data available.
2.2 Disease Outcomes

The following disease outcomes were captured. Firstly, disease activity (how active a patient’s arthritis is) was recorded using the disease activity score with 28-joint counts (DAS28). This composite score combines information on the number of swollen and tender joints (assessed by a clinician from 28 joint counts), the patient global assessment of disease activity (PGA, which involves a patient rating their overall disease activity on a 100mm visual analogue scale) and the erythrocyte sedimentation rate (ESR) in a mathematical formula to give an assessment of RA activity ranging from 0 to 10. Lower scores indicate less active disease, with scores >5.1, <3.2 and <2.6 indicating high disease activity, low disease activity, and remission, respectively. Secondly, disability was recorded using the health assessment questionnaire (HAQ), a patient-completed questionnaire giving a score of function ranging from 0 to 3. HAQ scores of <1, 1-2, and >2 indicate mild, moderate, and severe disability, respectively. Thirdly, pain was recorded using a 100mm patient completed pain visual analogue scale (VAS), a method for quantifying the severity of self-reported pain (17). Fourthly, health-related quality of life (HRQoL) was recorded using the short form-36 (SF-36), which is described in detail below. In CARDERA-1 the aforementioned outcomes were captured every 6-months. In CARDERA-2 they were captured at 0, 6, 12 and 24 months.

2.3 Mental Health

The SF-36 is a generic measure of health status, capturing HRQoL across 8 domains (four physical and four mental) (18). These domains are scored 0-100, with higher scores indicating better HRQoL. They can be normalised, z-transformed and combined into mental and physical component summary scores (MCS and PCS, respectively) providing summary
measures of overall mental and physical health, relative to a population mean score of 50 (SD 10) (19).

We used the mental health (MH) domain score and MCS as measures of mental health in our analysis. Both have been used to screen for depression, with an MCS cut-off of 42 having a sensitivity and specificity of 74% and 81%, respectively for detecting depressive disorder (20). They also associate with depression severity, both cross-sectionally and over time (21).

2.4 Genotyping
CARDERA patients were genotyped on the Illumina ImmunoChip array (described in detail previously (13)). Single nucleotide polymorphism (SNP) markers were removed that had >5% missingness, were duplicates, were not in Hardy-Weinberg equilibrium (HWE; \( P < 0.00001 \)), and had a minor allele frequency (MAF) <0.01. From 196,524 pre-QC markers, 138,873 were available in the final dataset. Imputation was subsequently performed using IMPUTE2 (22) and the 1,000 Genomes Phase 1 integrated variant version 3 (March 2012) reference panel (variants filtered with a European MAF <0.01). Post-imputation SNPs were removed with low INFO scores (<0.7), MAF<0.05, HWE \( P < 0.000001 \) and genotyping rate < 0.1, resulting in 429,193 available markers.

2.5 Genetic Risk for Depression
The Psychiatric Genomics Consortium MDD GWAS mega-analysis failed to find a locus of genome-wide significance, likely reflecting limited power caused by the genetic architecture of MDD (small effect sizes of individual genetic variants) and the high prevalence of MDD, which increases the difficulty in recruiting large samples of screened, low risk controls (23). We therefore tested a weighted genetic risk score (wGRS), combining loci of nominal
association with MDD for an association with mental health in CARDERA. This approach is commonly used in studies of polygenic disorders, whose genetic architecture comprises thousands of very small effect common alleles (24, 25). We used a \( P \)-value threshold (\( P_T \)) for SNPs to include in the wGRS of 0.05 (representing nominal association with MDD). A continuous wGRS based on MDD GWAS results has been shown to predict depression in independent cohorts, with a \( P_T \) of 0.05 demonstrated to generate a wGRS that most strongly predicts MDD risk (26). After linkage disequilibrium (LD) pruning, 3,010 SNPs were included in the wGRS. The wGRS was generated for each individual in CARDERA by calculating the number of nominally associated risk alleles they carried, weighted by the log odds ratio (OR) from the MDD mega-analysis, summed across SNPs.

2.6 Statistical Analysis

2.6.1 Associations with Mental Health

Two different modelling approaches were used to evaluate the relationship between mental health, RA severity measures and genetic risk for depression. The first approach established whether mental health was associated with either RA severity measures or the wGRS for depressive disorder over time. This used a linear mixed-effects model, which incorporated either MCS or MH measured at each time-point as the response variable, regressed on the corresponding predictors (wGRS, DAS28 and its components, HAQ, or pain VAS) from each time-point. Effect size estimates (\( \beta \)-values) for predictor variables provided information on the average differences in the MCS or MH score over the 2-year time period, relative to the average predictor variable score. We have included a level-1 random effect of individual, fitting random intercepts for each individual. These models have a level-2 random effect for time-point, modelling deviation from the overall effect of time-point on outcome within each
individual, as random slopes. We specify this correlation structure using the lme4 package in R (27). The following variables were tested for their associations with MCS: age, gender, disease duration, and rheumatoid factor (RF) status. Of these, only gender improved the model fit - as determined using a stepwise selection approach, with the optimal model determined using the Akaike information criterion - and so only this variable was included as a covariate (Tables A.1 and A.2, Supplemental Digital Content 1, http://links.lww.com/PSYMED/A380). The wGRS was standardised to a z-score, in order to provide interpretable β-values. Examination of residuals from a model containing time, gender and treatment only confirmed a good model fit (Supplementary Figure A.1, Supplemental Digital Content 1, http://links.lww.com/PSYMED/A380), and variance inflation factors calculated for each predictor ensured multi-collinearity between RA outcomes and DAS28 components was not an issue (Table A.3, Supplemental Digital Content 1, http://links.lww.com/PSYMED/A380).

The second approach evaluated the direction of associations between mental health and RA severity, by testing if mental health at study baseline associated with 2-year changes in RA outcomes over time, or vice versa. This used linear regression models to look at the association between a) baseline MCS or MH and 2-year changes in RA severity measures, and b) baseline RA severity measures and 2-year changes in mental health scores. These models included the baseline response variable score, treatment and gender as covariates. Examination of model residuals confirmed good model fits (Figure A.1, Supplemental Digital Content 1, http://links.lww.com/PSYMED/A380).
2.6.2 Missing Data Imputation

In the original CARDERA-1 trial, missing data at each time-point had previously been imputed using last-observation carried forward (LOCF) analysis for study end-points (DAS28, HAQ and SF-36). LOCF is a commonly used procedure to address missing data in clinical trials with repeated measures over multiple time points. For each individual, missing values at a time point are replaced by the last observed value of that variable (14, 28). In the original CARDERA-2 trial missing data were not imputed (29). For consistency in the current analysis we imputed missing, previously non-imputed CARDERA-1 data (SJC, TJC, ESR, PGA, pain VAS) and missing CARDERA-2 data using LOCF. The largest amount of missing data was seen for pain VAS (11% of observations missing across all time-points). We repeated our analysis with non-imputed data only; this excluded a significant impact of the LOCF assumption (Table A.4, Supplemental Digital Content 1, http://links.lww.com/PSYMED/A380).

2.6.3 Statistical Software

Analyses were performed in the statistical environment R (R Foundation for Statistical Computing, Vienna, Austria), PRSice (version 1.2) (30), IMPUTE2 (22) and PLINK (version 1.9) (31).

2.7 Ethics, Consent and Permissions

CARDERA-1 (South Thames Multi Centre Research Ethics Committee (REC) reference: MREC (1) 99/04) and CARDERA-2 (South East REC reference: MREC 02/1/089) were ethically approved. Approval was obtained to genotype archived DNA (NRES Committee East of England – Essex REC reference: 11/EE/0544). All patients provided consent.
3. RESULTS

3.1 Patient Baseline Characteristics

Most patients were female (69%; Table 1) and possessed Rheumatoid Factor (RF) in their serum (67%). Baseline disease activity was high (mean DAS28 5.88), disability moderate (mean HAQ 1.56) and disease duration short (mean duration 3.3 months). Baseline mental health was reduced relative to the general population (mean MCS score 40.6, which is 9.4 units lower than the general population mean).

3.2 Disease Severity Associations with Mental Health

In a gender and treatment adjusted linear mixed-effects model, DAS28 ($P<0.001$), HAQ ($P<0.001$) and pain VAS ($P<0.001$) significantly associated with MCS (Table 2). On average over two years MCS scores were 2.22, 6.07 and 0.14 units lower per unit increase in DAS28, HAQ and pain VAS scores, respectively. This indicates that the higher a patient’s disease activity, disability and pain levels, the worse their mental health. In multivariate models all three disease severity measures retained a highly significant association with MCS (Table 2): HAQ ($\beta=-3.88; P<0.001$), DAS28 ($\beta=-0.91; P<0.001$), pain VAS ($\beta=-0.05; P<0.001$). Similar associations were seen with the MH domain.

3.3 MDD Genetic Risk Score Associations with Mental Health

A significant association was seen between the wGRS for depression and MCS ($P=0.013$) and MH ($P=0.041$) (Table 2). The association with MCS ($P=0.033$) but not MH ($P=0.080$) was retained in multivariate models including DAS28, HAQ and pain VAS as covariates. Higher wGRS scores, which indicate a greater genetic risk for depression, associated with worse mental health (lower MCS and MH scores) (MCS $\beta=-1.21$; MH $\beta=-1.37$). Repeating
the analysis with a linear mixed-effects model that incorporated a wGRS*time interaction term provided some evidence that genetic risk for depression also predicted the rate at which mental health improved across time-points, with a significant association seen between the wGRS*time term and MH (\(P=0.039; \beta=-0.83\)) but not MCS (\(P=0.330; \beta=-0.30\)).

3.4 DAS28 Component Associations with Mental Health

In a gender and treatment adjusted linear mixed-effects model all four DAS28 components – SJC, TJC, ESR and patient global assessment (PGA) – associated with MCS and MH scores when tested individually (Table 2). Higher scores in each DAS28 component associated with lower MCS and MH scores; this indicates that more active disease is linked with poorer mental health. On average over two years MCS scores were 0.32, 0.07, 0.13 and 0.27 units lower per unit increase in SJC, ESR, PGA, and TJC scores, respectively. In multivariate models including all 4 DAS28 components the TJC failed to retain a significant association with MCS (\(P=0.461\)) and MH (\(P=0.519\)).

3.5 Direction of Association between RA Outcomes and Mental Health

3.5.1 Association between Baseline Disease Severity and Changes in Mental Health

The only baseline RA severity measure that had a significant association with two-year changes in both MCS and MH scores was pain VAS (Table 3). Higher baseline pain VAS scores (indicating greater levels of pain) associated with lesser increases in MCS and MH scores (indicating lower improvements in mental health). The increase in MCS was 0.07 units less per 1mm increase in baseline pain VAS. A significant association between the baseline TJC and 2-year changes in MH domain scores was also seen (\(P=0.023\)), although this variable did not significantly associate with 2-year changes in MCS scores (\(P=0.122\)).
3.5.2 Association between Baseline Mental Health and Changes in RA Outcomes

Baseline MCS and MH domain scores had significant inverse associations with two-year changes in DAS28 (MCS and MH \( P < 0.001 \)), pain VAS (MCS and MH \( P < 0.001 \)) and HAQ (MCS \( P = 0.006 \); MH \( P = 0.008 \)) (Table 3). Lower baseline MCS and MH scores (indicating poorer mental health) associated with lesser improvements in DAS28, pain VAS, and HAQ scores. The effect sizes were, however, modest: per 10 unit increase in baseline MCS, the two-year reductions in DAS28, HAQ and pain VAS were 0.20, 0.10 and 3.30 units greater, respectively (Table 3).

Dividing patients into octiles based on their baseline MCS and plotting the mean disease severity measure in each octile demonstrated the effect of baseline MCS on RA outcomes (Figure 1). Trends towards a) worse disease outcomes at each time point and b) lower improvements in disease outcomes over 2-years across increasing baseline MCS octiles were seen (Figure 1). Over two years, mean DAS28, HAQ and pain VAS scores changed by -1.14, -0.23 and -8.11 units, respectively in the lowest MCS octile (group 1) and -1.94, -0.49 and -18.49 units, respectively in the highest MCS octile (group 8).

Examining individual DAS28 components revealed that baseline MCS and MH scores had significant inverse associations with two-year changes in the SJC (MCS and MH \( P < 0.001 \)) and PGA (MCS and MH \( P < 0.001 \)) but not the TJC (MCS \( P = 0.983 \); MH \( P = 0.226 \)) and ESR (MCS \( P = 0.973 \); MH \( P = 0.355 \)) (Table 3). This differential impact on DAS28 components is shown in Figure 2. Over two years, mean SJC, PGA, TJC and ESR levels changed by -0.17, -13.91, -8.02 and -11.98 units, respectively in the lowest MCS octile (group 1) and -4.69, -20.46, -5.97 and -11.03, respectively in the highest baseline MCS octile (group 8).
4. DISCUSSION

Our study evaluated the relationship between mental health and disease activity, disability, pain, and genetic risk for depression over 2 years in a well-characterised clinical trial cohort of patients with early RA. It has three key findings. The first, and most clinically important, is that low mental health associated with poorer disease outcomes. In a repeated measures analysis, lower MCS and MH scores had significant associations with more active disease, increased disability and greater pain over two years; as MCS and MH scores increased over time DAS28, HAQ and pain levels fell. Lower baseline MCS and MH scores (indicating worse mental health) associated with a reduced improvement in disease activity and disability, suggesting that depression predicts the degree to which RA improves over time. The relationship between pain and mental health appeared bidirectional, with baseline pain associating with lower improvement in MCS and MH domain scores and vice versa; this is in keeping with existing studies of musculoskeletal disorders (7, 8).

The second finding was that swollen, but not tender joint counts had a significant association with reduced mental health. In a multivariate model incorporating all four DAS28 components, the Tender Joint Component of the DAS28 (TJC) failed to retain a significant association with MCS and MH scores. In established RA patients attending routine clinics the opposite relationship appears true, with an analysis of the CORRONA registry reporting that a lifetime depression history associated with slower improvements in the TJC but not the SJC (9). One explanation for the lack of association between MCS/MH scores and the TJC in CARDERA is that the short disease duration of patients means the pain pathway sensitisation characterising fibromyalgic RA – which could be particularly influenced by mental health – is yet to occur. An explanation for the association observed between MCS/MH scores and the
SJC is that overlapping pro-inflammatory cytokines, which are present in high levels in early active RA, play important roles in mediating both reduced mental health and RA activity. Whilst this hypothesis is supported by evidence that administering IL-1β and TNF-α induces depressive behaviour in mice (32) and that these cytokines are elevated in the serum of depressed patients (33, 34), it fails to explain why baseline mental health scores did not predict changes in ESR levels. There is an extensive body of literature investigating the pathophysiology of inflammation-related depression (35), with one proposed mechanism being the activation of the enzyme Indoleamine 2,3-dioxygenase (IDO) by inflammatory cytokines, which catabolises tryptophan leading to a downstream depletion in serotonin (36) – indeed inflammation-related depression appears to dependant on the activation of IDO (37). In light of this, anti-inflammatory medication has been proposed as a treatment for inflammation-related depression, however its efficacy is still contested (38) – therefore further research is required in other early active RA cohorts to confirm the generalisability of our results.

Our third finding was that genetic risk for MDD was a significant predictor of mental health. We tested a wGRS combining 3,010 SNPs of nominal association with MDD in the publically available Psychiatric Genomics Consortium GWAS for its association with mental health in CARDERA. Whilst a significant association with lower MCS and MH scores was observed, the comparatively large standard error of the wGRS variable makes any conclusions on its relative importance challenging. The significant interaction term for wGRS*time predicting MH, indicating slower improvements in mental health amongst individuals with high MDD genetic risk, is consistent with previous work indicating that depression genetic risk increases an individual’s sensitivity to adverse environmental effects (39, 40). Taken together, these findings support the notion that depression is a complex
disorder with a modest, albeit important, genetic contribution comprising thousands of alleles of a small effect size.

Our study replicates existing research that depression and pain have a bidirectional relationship. In CARDERA, baseline MCS and MH scores predicted two-year changes in pain VAS and vice versa. This finding has been documented in psoriatic arthritis, with Husted et al identifying a small bidirectional relationship between MCS and pain in 394 patients followed up for a mean of 7.5 years (7). It has also been reported in patients with persistent back, hip or knee pain (8), back pain (41, 42) and pain from a variety of disorders (43). The complex nature of pain makes it difficult to discern mechanisms by which this pain-depression bidirectional relationship could occur. Possible mechanisms include: (1) low mood could affect pain through promoting maladaptive coping strategies, especially catastrophizing (perceiving a situation to be worse than it is) (44); (2) pain could affect mental health through reducing daily activities (45) and reducing social activities (46); (3) imbalances in shared neurotransmitters (serotonin and norepinephrine) in affective and nociceptive pathways could contribute to both mood and pain (45). Further research is required to better characterise the mechanisms underlying this complex relationship.

Supporting our finding that mental health predicts disease outcomes across time-points, other studies have reported a detrimental impact of reduced mental health on patients’ responsiveness to anti-inflammatory medication - specifically anti-TNF - as defined by DAS28 change (47, 48). This effect is highly relevant to stratified medicine in RA. Although in CARDERA, the impact of baseline MCS on improvements in disease outcomes over two-years was modest, if considered alongside other poor prognostic markers, such as ACPA
status (49), HLA variants (50), smoking and gender (51), it could provide clinically-useful prognostic information, guiding decisions on treatment intensity and facilitating a stratified approach to managing early RA patients.

Our study has several strengths. These include its large size, recruitment from multiple centres spanning two clinical trials, the measurement of multiple disease outcomes in a highly standardised manner, and the short disease duration of RA (mean 3.3 months) leaving it well placed to examine the effects of mental health in very early disease. It also has several weaknesses. As a secondary post-hoc analysis of existing RCTs, it did not test a pre-specified hypothesis according to a pre-determined analysis plan. It evaluated a clinical trial cohort of severe RA patients, limiting its generalisability to patients seen in routine clinical practice. Additionally, we only evaluated European ancestry individuals; the relevance of our findings to other ethnic populations is uncertain.

Current National Institute for Health and Care Excellence (NICE) guidelines for RA management recognise the importance of assessing for co-morbid depression, recommending this as part of an annual review process (52). Our findings strongly support this recommendation in early RA. One unresolved issue is the impact of treating depression on the disease course of RA. Whilst we did not evaluate the impact of mental health therapies on RA outcomes, there is some evidence that psychological interventions (such as cognitive-behavioural therapy (CBT), disclosure therapy and biofeedback), are useful adjunctive management tools in RA patients. Two systematic literature reviews have evaluated the evidence base for this. Astin et al reported significant pooled effect sizes for psychological interventions at reducing post-interventional pain, disability, and psychological status across
25 trials (53). Similarly, Dissanayake et al found evidence for the efficacy of disclosure therapy and CBT with maintenance therapy across 4 and 5 studies, respectively (54). The evidence base is, however, limited with both reviews noting that available trials had methodological limitations. Further research is required to better define the impact of specific psychological interventions at improving disease outcomes in large, well-conducted clinical trials of RA patients.

5. CONCLUSIONS

In this cohort of 520 early, active RA patients reduced mental health (captured using the SF-36) associated with worse disease outcomes. Lower MCS and MH scores (indicating poorer mental health) significantly associated with more active disease, increased disability and greater pain over two years. Worse baseline mental health associated with lesser improvements in RA outcome measures, suggesting that depression predicts the rate at which RA improves over time. A bidirectional relationship was observed between mental health and pain, replicating existing work in musculoskeletal disorders. Depression genetic risk had a significant, albeit modest impact on mental health. Our findings support current NICE RA management guidelines recommending the annual screening of RA patients for co-morbid depression. Further research is needed to establish the impact of specific mental health management strategies on improving RA outcomes.
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Figure 1. Mean DAS28, HAQ and Pain VAS Stratified by Baseline MCS Octile

MCS divided into octiles (8 quantiles); mean scores with standard error bars for octiles 1, 4, 5 and 8 plotted at each time point; to facilitate visual interpretation octiles 2, 3, 6 and 7 are not plotted, although the same trends are observed (See Figure A.2, Supplemental Digital Content 1, http://links.lww.com/PSYMED/A380). Color figure available online only at www.psychosomaticmedicine.org.

Figure 2. Mean DAS28 Components Stratified by Baseline MCS Octile

MCS divided into octiles (8 quantiles); mean scores with standard error bars for octiles 1, 4, 5 and 8 plotted at each time point; to facilitate visual interpretation octiles 2, 3, 6 and 7 are not plotted, although the same trends are observed (Figure A.3, Supplemental Digital Content 1, http://links.lww.com/PSYMED/A380). Color figure available online only at www.psychosomaticmedicine.org.
Figure 1

Baseline MCS Quantile 1 4 5 8
Figure 2

SJC

PGA

TJC

ESR

Baseline MCS Quantile 1 4 5 8
Table 1. CARDERA Genetics Cohort Baseline Characteristics

| Characteristic       | Summary Statistic |
|----------------------|-------------------|
| **Demographic**      |                   |
| Number (%) Female    | 358 (69%)         |
| Mean Age in Years (SD)| 54.7 (12.6)        |
| **RA Specific**      |                   |
| Mean RA Duration in Months (SD) | 3.3 (4.9) |
| Number (%) RF-Positive | 350 (67%)       |
| Mean DAS28 (SD)      | 5.88 (1.29)       |
| Mean HAQ (SD)        | 1.56 (0.70)       |
| **Mental Health**    |                   |
| Mean MCS (SD)        | 40.6 (14.1)       |
| Mean MH (SD)         | 61.0 (18.0)       |
| **Treatment**        |                   |
| Number (%) Receiving MTX | 159 (31%)      |
| Number (%) Receiving MTX and CIC | 108 (21%) |
| Number (%) Receiving MTX and Pred | 102 (20%) |
| Number (%) Receiving Triple Therapy | 107 (21%) |
| Number (%) Receiving MTX and anakinra | 44 (8%) |

Cohort size used in analysis = 520 patients; SD = standard deviation; MTX = methotrexate; CIC = ciclosporin; pred = prednisolone; triple therapy = MTX, CIC and pred; RF = rheumatoid factor; DAS28 = disease activity score on a 28-joint count; HAQ = health assessment questionnaire; MCS = SF-36 mental component summary score; MH = SF-36 mental health domain. A DAS28 of 5.88 indicates highly active disease. A HAQ of 1.56 indicates moderate disability. An MCS of 40.6 is 9.4 units lower than that observed in the normal population (which has a mean score of 50.0 units).
Table 2. Longitudinal Associations between Mental Health, RA Outcomes and Depression Genetic Risk Score

| Mental Component Summary | Gender and Treatment Adjusted Model | Multivariate Model* | Gender and Treatment Adjusted Model | Multivariate Model* |
|--------------------------|-------------------------------------|---------------------|-------------------------------------|---------------------|
| Mental Health (MH) Domain | B (SE) | P-value | B (SE) | P-value | B (SE) | P-value | B (SE) | P-value |
| RA Outcomes              |        |         |        |         |        |         |        |         |
| DAS28                    | -2.22  | <0.001  | -0.91  | <0.001  | -2.97  | <0.001  | -1.37  | <0.001  |
|                         | (0.16) |          | (0.21) |          | (0.21) |          | (0.27) |          |
| HAQ                     | -6.07  | <0.001  | -3.88  | <0.001  | -8.41  | <0.001  | -5.75  | <0.001  |
|                         | (0.40) |          | (0.48) |          | (0.53) |          | (0.63) |          |
| Pain VAS                | -0.14  | <0.001  | -0.05  | <0.001  | -0.17  | <0.001  | -0.05  |          |
|                         | (0.01) |          | (0.01) |          | (0.01) |          | (0.02) | 0.007   |
| Genetic Risk            |        |         |        |         |        |         |        |         |
| MDD wGRS                | -1.21  | 0.013   | -0.92  | 0.033   | -1.37  | 0.041   | -1.05  | 0.080   |
|                         | (0.48) |          | (0.43) |          | (0.67) |          | (0.60) |          |
| DAS28 Components        |        |         |        |         |        |         |        |         |
| SJC                     | -0.32  | <0.001  | -0.12  | 0.003   | -0.47  | <0.001  | -0.25  | <0.001  |
|                         | (0.04) |          | (0.04) |          | (0.05) |          | (0.05) |          |
| ESR                     | -0.07  | <0.001  | -0.04  | 0.003   | -0.11  | 0.001   | -0.06  | <0.001  |
|                         | (0.01) |          | (0.01) |          | (0.02) |          | (0.02) |          |
| PGA                     | -0.13  | <0.001  | -0.11  | <0.001  | -0.16  | <0.001  | -0.11  | <0.001  |
|                         | (0.01) |          | (0.01) |          | (0.01) |          | (0.01) |          |
| TJC                     | -0.27  | <0.001  | -0.03  | 0.461   | -0.34  | <0.001  | -0.03  |          |
|                         | (0.04) |          | (0.04) |          | (0.05) |          | (0.05) | 0.519   |
DAS28 = disease activity score on a 28-joint count; HAQ = health assessment questionnaire; pain VAS = pain visual analogue scale score; MDD wGRS = weighted genetic risk score for major depressive disorder; SJC = swollen joint count; ESR = erythrocyte sedimentation rate; PGA = patient global assessment of disease activity; TJC = tender joint count. All linear mixed-effects models include gender, treatment and time as explanatory variables; * = multivariate model for RA outcomes and genetic risk also includes DAS28, HAQ, pain VAS and MDD wGRS as explanatory variables; multivariate model for DAS28 components also includes SJC, ESR, PGA and TJC as explanatory variables.
Table 3. Direction of Associations between Mental Health and RA Outcomes

| Mental Component Summary Score (MCS) | Mental Health (MH) Domain Score  |
|-------------------------------------|----------------------------------|
| Model 1: Baseline MCS Predicting Two-Year Changes in RA Outcomes | Model 2: Baseline RA Outcomes Predicting Two-Year Change in MCS |
| Model 2: Baseline RA Outcomes Predicting Two-Year Change in MCS | Model 2: Baseline RA Outcomes Predicting Two-Year Change in MH |
| B (SE) | P-value | B (SE) | P-value | B (SE) | P-value | B (SE) | P-value |
|-------|---------|-------|---------|-------|---------|-------|---------|
| DAS28 | -0.02 (0.01) | <0.001 | -0.31 (0.45) | 0.492 | -0.01 (0.00) | <0.001 | -0.83 (0.61) | 0.170 |
| SJC   | -0.09 (0.02) | <0.001 | 0.04 (0.09) | 0.625 | -0.07 (0.02) | <0.001 | 0.06 (0.12) | 0.577 |
| ESR   | 0.00 (0.07) | 0.973 | 0.03 (0.02) | 0.203 | -0.05 (0.06) | 0.355 | 0.01 (0.03) | 0.590 |
| PGA   | -0.28 (0.08) | <0.001 | -0.03 (0.02) | 0.144 | -0.27 (0.06) | <0.001 | -0.05 (0.03) | 0.061 |
| TJC   | 0.00 (0.02) | 0.983 | -0.12 (0.07) | 0.122 | -0.02 (0.02) | 0.226 | -0.23 (0.10) | 0.023 |
| HAQ   | -0.01 (0.00) | 0.996 | 0.50 (0.85) | 0.554 | 0.00 (0.00) | 0.008 | 0.19 (1.13) | 0.865 |
| Pain  | -0.33 (0.08) | <0.001 | -0.07 (0.02) | 0.002 | -0.31 (0.06) | <0.001 | -0.08 (0.03) | 0.005 |
| VAS   | | | | | | | | |
DAS28 = disease activity score on a 28-joint count; HAQ = health assessment questionnaire; pain VAS = pain visual analogue scale score; SJC = swollen joint count; ESR = erythrocyte sedimentation rate; PGA = patient global assessment of disease activity; TJC = tender joint count. All linear regression models include gender, treatment and baseline measure of response variable tested as covariates.
THE RELATIONSHIP BETWEEN MENTAL HEALTH, DISEASE SEVERITY AND GENETIC RISK FOR DEPRESSION IN EARLY RHEUMATOID ARTHRITIS

SUPPLEMENTARY MATERIAL APPENDICES

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Table A.1. Selection of Modelling Covariates in Linear Mixed-Effects Model

| Variable        | Elimination Number | P-Value |
|-----------------|--------------------|---------|
| RF-Positive     | 1                  | 0.780   |
| Disease Duration| 2                  | 0.354   |
| Age             | 3                  | 0.286   |
| Treatment       | kept               | 0.027   |
| Gender          | kept               | 0.001   |
| Time            | kept               | <0.001  |

A stepwise AIC was used to select modelling covariates that significantly predicted MCS scores over time within a linear mixed-effects model. After three iterations, only treatment, gender and time were significant predictors of MCS and were included as modelling covariates (treatment and gender as fixed-effects, and a random effect of time).
Supplementary Table A.2. Associations between Modelling Covariates and MCS in Linear Mixed-Effects Model

| Variable       | Coefficient | SE  | P-Value |
|----------------|-------------|-----|---------|
| **Treatment**  |             |     |         |
| Methotrexate Monotherapy | Reference | Reference | Reference |
| Ciclosporin-Methotrexate     | -2.50       | 1.37 | 0.069   |
| Prednisolone-Methotrexate    | -0.32       | 1.40 | 0.818   |
| Methotrexate-Prednisolone-Ciclosporin | 2.27       | 1.37 | 0.099   |
| Methotrexate-Anakinra        | 1.52        | 1.89 | 0.421   |
| **Gender**     | 3.35        | 1.04 | 0.001   |
| **Time**       | 1.71        | 0.31 | <0.001  |

Model includes MCS as response variable and treatment, gender and time as explanatory variables.
Table A.3. Variance Inflation Factors (VIF) for Predictors in Multivariate Linear Mixed-Effects Models

A: VIF for RA severity metrics

| Variables | VIF |
|-----------|-----|
| HAQ       | 1.55|
| DAS28     | 2.01|
| Pain      | 1.76|
| wGRS      | 1.02|

Model includes MCS as response variable and treatment, gender, time, HAQ, DAS28, Pain VAS, and wGRS as explanatory variables.

B: VIF for DAS components

| Variables | VIF |
|-----------|-----|
| ESR       | 1.12|
| TJC       | 1.51|
| SJC       | 1.41|
| PGA       | 1.51|

Model includes MCS as response variable and treatment, gender, time, ESR, TJC, SJC, and PGA as explanatory variables.
To ensure LOCF imputation had not biased our results we repeated the analysis using non-imputed data. The results are highly similar, confirming the LOCF assumption was met. A linear mixed-effects models is used in this analysis, including MCS as the response variable and time, treatment, gender and each RA outcome as an explanatory variable in seven separate models (one per RA outcome).
Figure A.1. Residual Plots from Linear Mixed-Effects and Linear Regression Models

A, C, E, G and I are histograms of residuals from each model; B, D, F, H and J are plots of the fitted values against the residuals from each model; A and B = linear mixed-effects model including MCS as the response variable and gender, treatment and time as explanatory variables; C and D = linear regression model including 2-year change in DAS28 as the response variable and baseline MCS, baseline DAS28, gender and treatment as explanatory variables; E and F = linear regression model including 2-year change in HAQ as the response variable and baseline MCS, baseline HAQ, gender and treatment as explanatory variables; G and H = linear regression model including 2-year change in pain VAS as the response variable and baseline MCS, baseline pain VAS, gender and treatment as explanatory variables; I and J = linear regression model including 2-year change in MCS as response variable and baseline MCS, gender and treatment as explanatory variables.
Figure A.2. Mean DAS28, HAQ and Pain VAS Stratified by Baseline MCS Octile

MCS divided into octiles (8 quantiles); mean scores with standard error bars for octiles are plotted at each time point.
Figure A.3. Mean DAS28 Components Stratified by Baseline MCS Octile

MCS divided into octiles (8 quantiles); mean scores with standard error bars for octiles are plotted at each time point.