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Rheumatoid arthritis

Hand-dominant joint involvement pattern associates with favourable, and polyarthritis with unfavourable, treatment response to both csDMARDs and bDMARDs in early rheumatoid arthritis: a combined analysis of NORD-STAR and BeSt trials

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ABSTRACT

Objectives: To investigate the association between joint involvement pattern (JIP) subgroups and treatment responses to conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) and biological disease-modifying antirheumatic drugs (bDMARDs), and to compare the impact of JIP subgroups with other clinical parameters in treatment-naïve patients with early rheumatoid arthritis (RA).

Methods: An individual patient data meta-analysis was conducted using 2 randomised controlled trials, NOrdic Rheumatic Diseases Strategy Trials And Registries (NORD-STAR) and Behandel-Strategieën (BeSt), including 1250 treatment-naïve patients with early RA. JIP subgroup assignment was based on 4 previously identified subgroups defined by baseline clinical characteristics, primarily joint involvement in the 66/68 joint scheme. Treatment outcomes were measured using the longitudinal Clinical Disease Activity Index (CDAI) and other disease activity indices through week 48. Associations of the JIP subgroups and other clinical predictors were evaluated using a mixed-model analysis.

Results: Patients with a hand-dominant JIP (JIP-Hand) showed significantly better CDAI scores after treatment (Beta for CDAI = −1.4 [95% CI, −2.3 to −0.55]; p = .0016), whereas those with a polyarthritis pattern (JIP-Poly) exhibited worse outcomes (Beta = 0.95 [95% CI, 0.064-1.8]; p = .035). Female sex was also associated with worse CDAI scores (Beta = 1.2 [95% CI, 0.40-2.0]; p = .0031), whereas anticitrullinated protein antibodies did not show a significant association (Beta = 0.19 [95% CI, −0.69 to 1.1]; p = .67). When compared across groups, csDMARDs and combined bDMARDs were similarly effective in the respective JIP subgroups (interaction $p > .10$).

Conclusions: In early RA, csDMARD and bDMARD treatments resulted in the greatest improvement in disease activity in JIP-Hand and the least improvement in JIP-Poly.

KEY MESSAGES

WHAT IS ALREADY KNOWN ON THIS TOPIC

- Anticitrullinated protein antibodies (ACPAs) and rheumatoid factor (RF) are weak predictors of short-term treatment response in early rheumatoid arthritis (RA).
- Baseline joint involvement pattern (JIP) subgroups have been proposed as clinical subgroups for early RA.

WHAT THIS STUDY ADDS

- Hand-dominant JIP (JIP-Hand) was associated with greater improvement in the Clinical Disease Activity Index (CDAI) and remission, whereas polyarthritis (JIP-Poly) was associated with poorer outcomes.
- Sex showed a stronger effect on CDAI scores than ACPAs or RF.
- No heterogeneity in the treatment effect by JIP subgroup was observed between the conventional synthetic disease-modifying antirheumatic drug (csDMARD) and biological disease-modifying antirheumatic drug (bDMARD) arms.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- JIP subgrouping may provide a simple stratification associated with prognosis in early RA, pending further validation.
- Prospective studies are needed to validate JIP subgrouping and assess whether it can inform treatment decisions and remission targets.

INTRODUCTION

Rheumatoid arthritis (RA) is a heterogeneous disease, both in clinical phenotype and in response to treatment. The presence of anticitrullinated protein antibodies (ACPAs) or rheumatoid factor (RF) autoantibodies, as well as higher baseline disease activity, is established to be associated with worse radiographic outcomes [1,2]. Most standard clinical and laboratory parameters are considered insufficiently sensitive when used alone to predict treatment response [3]. The presence of ACPAs is associated with more severe radiographic joint damage after several years; however, it is only associated with a very small increase in disease activity after treatment [4–6]. Additionally, because ACPAs, RF, and higher disease activity are all components of the 2010 classification criteria for RA [7], the majority of patients with early RA possess at least 1 of these classical poor prognostic factors, which complicates patient stratification [8]. There is a strong need to identify novel predictors of treatment response in RA.

We recently reported the existence of 4 joint involvement pattern (JIP) subgroups in treatment-naïve early RA using deep learning and clustering of baseline clinical characteristics [9]. These patterns were characterised by arthritis of the feet (JIP-Foot), oligoarticular disease (JIP-Oligo), arthritis of the hands (JIP-Hand), and polyarthritis (JIP-Poly). Rigorous validation confirmed the robustness and replicability of these JIPs across both historical trial data and an independent hospital cohort. Furthermore, we observed a clear difference in treatment outcomes: patients with JIP-Hand demonstrated higher retention rates during initial methotrexate (MTX) treatment and higher remission rates than other subgroups, even after adjusting for baseline disease activity and other established prognostic markers. These results prompted us to explore whether the JIP subgroups are associated with differential treatment effects across other cohorts and to identify potentially optimal therapies.

In this study, we conducted an individual patient data (IPD) meta-analysis of 2 randomised controlled trials: the NOrdic Rheumatic Diseases Strategy Trials And Registries (NORD-STAR) and Behandel-Strategieën (BeSt; meaning ‘treatment strategies’) trials [10,11]. Both studies focused on treatment-naïve patients with early RA and compared the effects of conventional synthetic disease-modifying antirheumatic drug (csDMARD) and biological disease-modifying antirheumatic drug (bDMARD) treatments. Our

aim was to determine whether these JIP subgroups are predictive of disease activity across different treatment types and to compare their effects with those of other clinical parameters.

METHODS

NORD-STAR trial

In the NORD-STAR trial [10,12], 812 patients with disease-modifying antirheumatic drug (DMARD)-naive early RA (according to the 2010 American College of Rheumatology [ACR]/European Alliance of Associations for Rheumatology [EULAR] classification criteria; symptom duration <2 years) were enrolled in Sweden, Denmark, Norway, Finland, the Netherlands, and Iceland.

Participants were randomly assigned in a 1:1:1:1 ratio to 4 treatment arms. All arms included MTX. In arm 1, called 'active conventional treatment,' participants received either (1) orally administered prednisolone (Sweden, Norway, Netherlands, and Iceland) or (1) sulfasalazine, hydroxychloroquine, and intra-articular glucocorticoid injections in swollen joints (Denmark and Finland). In arm 2, participants received certolizumab pegol. In arm 3, participants received abatacept, while those in arm 4 received tocilizumab. Intra-articular glucocorticoid injections were administered in all treatment arms as needed (or whenever a swollen joint was present in arm 1B), with restrictions during weeks 20 to 24 and 44 to 48 to minimise impact on efficacy outcomes at 24 and 48 weeks. Seventeen Finnish patients who were randomised to tocilizumab but received active conventional treatment due to the unavailability of tocilizumab were included in the active conventional treatment arm. In treatment part I, patients were followed for up to 80 weeks, with visits every 2 weeks for the first 8 weeks, every 4 weeks for the next 16 weeks, every 8 weeks until week 56, and thereafter every 12 weeks, with specified adjustments based on clinical condition. From week 48, patients who had sustained Clinical Disease Activity Index (CDAI) remission for 24 consecutive weeks were eligible to enter treatment part 2 (second randomisation to early or late dose reduction), with eligibility reassessment at each visit through week 80.

BeSt trial

In the BeSt trial [11,13], 508 patients with DMARD-naive early RA (according to the 1987 ACR classification criteria; symptom duration ≤2 years) were enrolled in the Netherlands. They were randomised into 4 treatment strategy arms: (1) sequential monotherapy starting with MTX, (2) step-up combination therapy starting with MTX, (3) initial combination therapy with MTX, sulfasalazine, and prednisone, or (4) initial combination therapy with infliximab and MTX.

Disease activity was evaluated every 3 months, and patients were treated with a target of low disease activity (Disease Activity Score [DAS]44 ≤ 2.4). If the DAS44 was >2.4, treatment was intensified. If sustained low disease activity (DAS44 ≤ 2.4 for ≥6 months) was achieved, treatment was tapered to monotherapy at a maintenance dose and discontinued when sustained remission (DAS44 ≤ 1.6 for ≥6 months) was achieved.

Outcome measures

The primary outcome of this study was the CDAI score through week 48 after treatment. This is because the NORD-STAR dataset contains clinical data for 48 weeks but not for 52 weeks. We chose CDAI as the primary outcome because it does not include an acute-phase reactant component, such as erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), which were inhibited by tocilizumab in the NORD-STAR arm 4. The secondary outcomes were DAS28-CRP, the Health Assessment Questionnaire (HAQ), CDAI remission, and CDAI50 (≥50% improvement from baseline in CDAI) over the same period. In the BeSt dataset, for which DAS44 data were available, DAS44 was also included, and the results were compared with those based on CDAI (and DAS28-CRP). We also compared MTX monotherapy retention at week 24 in the BeSt trial. We utilised baseline data, as well as data from weeks 4, 8, 12, 16, 24, and 48 for the NORD-STAR analysis, and data from weeks 12, 24, 36, and 48 for the BeSt analysis.

JIP subgroup assignment to the NORD-STAR dataset

We performed JIP subgrouping as described in our previous study [9], which was based on 1387 early RA patients from the Leiden University Medical Center (LUMC). The JIP subgroups were based on baseline clinical variables, including age, sex (as a binary variable), serologic status (RF and ACPAs), location of joint involvement (swollen and tender joints in the 66/68 joint scheme), and ESR. The robustness of the 4 JIP subgroups was established in the original Leiden cohort, where extensive bootstrapping analyses demonstrated high stability of subgroup assignment across resampled datasets [9]. We made some modifications to the input datasets: (1) we excluded blood profiles (haemoglobin, haematocrit, leukocyte, and thrombocyte levels) because these datasets were not available; (2) we also ignored the hip and acromioclavicular joints due to missing data from 1 or more centres; (3) we substituted CRP for ESR in cluster assignment for the Danish and Icelandic cohorts (n = 196) based on our finding of high concordance between CRP- and ESR-based cluster classifications in the BeSt trial (Supplementary Fig S1).

To add NORD-STAR samples to the previously learned embeddings of the original Leiden dataset, we utilised POODLE (https://github.com/levrex/Poodle) which enables the one-by-one projection of new samples into existing embeddings. Patients were assigned to JIP subgroups based on their similarity to each JIP cluster's average profile (derived from the original LUMC data) (Supplementary Fig S2) [9].

JIP subgroup assignment to the BeSt dataset

We used age, sex, serological status (RF and ACPAs), location of joint involvement (swollen and tender joints in the 66/68 joint scheme), ESR, and blood profiles (haemoglobin, haematocrit, leukocyte, and thrombocyte levels) at baseline as input data for the JIP subgroups [9]. Due to missing input variables, we excluded 62 of 508 patients and assigned 446 (88%) patients with RA with complete data to the JIP subgroups.

Statistical analysis

The outcomes were assessed separately for the studies and then combined in a one-stage IPD meta-analysis.

In the initial analysis of overall treatment, the primary outcome (CDAI score) was analysed using a mixed-effects linear regression model with the lmer function from the R lme4 package (version 1.1-35.1), with JIP subgroup assignment as the independent variable. The model was adjusted for baseline CDAI scores, time after treatment, and the random effect of individual patients. In the IPD meta-analysis, the model was additionally adjusted for the random effects of treatment arms and strategies:

$$CDAI \sim JIP\_i + baseline\_CDAI + time + (1|individual\_id) + (1|treatment) \quad (1)$$

where *CDAI* represents CDAI scores after treatment (excluding baseline CDAI scores); *JIP_i* represents the assignment of JIP_i in contrast to the other 3 JIP subgroups combined; *baseline_CDAI* represents CDAI scores at baseline before treatment; *time* represents the number of weeks after initial treatment; *individual_id* represents the sample IDs assigned to each individual; and *treatment* represents 1 of the treatment arms of the NORD-STAR study and the treatment strategies of the BeSt dataset.

In all mixed-model analyses, we calculated *p* values using likelihood-ratio tests comparing the fit of the full model with a reduced model omitting the target variable, and we used one-way analysis of variance (ANOVA) for comparisons (R version 4.3.1, anova function; R Foundation for Statistical Computing).

$$\text{Full model: } CDAI \sim JIP\_i + baseline\_CDAI + time + (1|individual\_id) + (1|treatment) \quad (2)$$

$$\text{Reduced model: } CDAI \sim baseline\_CDAI + time + (1|individual\_id) + (1|treatment) \quad (3)$$

To evaluate the overall model fit, we calculated conditional R^2 values for the full models using the partR2 package (version 0.9.2) [14]. Conditional R^2 values represent the variance explained by fixed and random effects together relative to the total variance in the response.

To evaluate the impact of baseline CDAI adjustment, in addition to the random effect for patients, we also tested the association without including the baseline_CDAI term as a covariate:

$$CDAI \sim JIP\_i + time + (1|individual\_id) + (1|treatment) \quad (4)$$

Secondary outcomes, CDAI remission and CDAI50, were assessed using a logistic mixed-effects regression model with the glmer function from the lme4 package, incorporating baseline CDAI and the same covariates. DAS28-CRP, HAQ, and DAS44 were analysed using mixed-effects linear regression models with the same covariates, except that baseline DAS28-CRP, HAQ, or DAS44 scores were used instead of baseline CDAI scores.

To determine the extent to which clinical variables are predictive, CDAI scores were analysed using an IPD meta-analysis with a mixed-effects linear regression model, with age, sex, RF, ACPAs, and symptom duration as independent variables:

$$CDAI \sim clinical\_predictor + baseline\_CDAI + time + (1|individual\_id) + (1|treatment) \quad (5)$$

where *clinical_predictor* represents either *age, sex, RF, ACPA*, or *symptom duration*, and the other covariates are defined as in the previous model; *age* represents age at baseline, *sex* represents the categorical value of female, *RF* represents RF positivity status at baseline, *ACPA* represents ACPA positivity status at baseline, symptom *duration* represents disease symptom duration at baseline, and the other variables retain their previous definitions.

Moreover, in a direct comparison between JIP subgroup assignment and clinical predictors, the association between CDAI scores and JIP subgroup assignment was analysed using an IPD meta-analysis with a mixed-effects linear regression model, including additional clinical covariates.

$$CDAI \sim JIP\_i + baseline\_CDAI + time + (1|individual\_id) + (1|treatment) + age + sex + \text{RF} + ACPA + Duration \quad (6)$$

In secondary analysis, we investigated the effect of concomitant bDMARD use with MTX vs the sole use of csDMARDs. To this end, we categorised treatment arms and strategies involving the initial concomitant use of bDMARDs with MTX as 'bDMARD treatment,' including NORD-STAR arm 2 (certolizumab pegol), arm 3 (abatacept), arm 4 (tocilizumab), and the BeSt strategy 4 (initial combination therapy with infliximab). All other treatment arms or strategies were classified as 'csDMARD treatment.' The primary outcome, CDAI scores, was analysed using a mixed-effects linear regression model, in which an interaction term between JIP subgroup and biological treatment served as an independent variable to examine whether the impact of JIP subgroups varied across bDMARD treatments.

$$CDAI \sim JIP\_i : bio\_treatment + JIP\_i + bio\_treatment + CDAI\_baseline + time + (1|sample\_id) + (1|study) \quad (7)$$

where *bio_treatment* represents the categorical distinction between bDMARD and csDMARD treatments; *study* represents the categorical difference between the NORD-STAR and BeSt datasets; and the other variables retain their previous definitions.

In the predefined statistical analysis plan, we determined that if a significant interaction (*p* value <.10) between JIP subgroup assignment and bDMARD treatment was observed, we would stratify the model and conduct separate analyses for each treatment group.

In the analysis of MTX monotherapy retention in the BeSt dataset, we examined the association between MTX monotherapy retention and the JIP subgroups using the following logistic regression model:

$$MTX\_mono \sim JIP\_i + CDAI\_baseline \quad (8)$$

where *MTX_mono* is a binary variable indicating whether patients in the sequential monotherapy or step-up combination therapy strategies remained on MTX monotherapy (either the initial MTX 15 mg/wk regimen or the subsequent MTX 20-25 mg/wk regimen) at week 24.

For the NORD-STAR visits, CDAI data were complete; DAS28-CRP data were missing in 9.0% of cases, and HAQ in 11%. For the BeSt visits, CDAI data were missing in 5.4% of cases, DAS28-CRP in 30%, and HAQ in 0.1%. No methods were used to address missing data, as mixed models are inherently designed to manage missing data in the dependent variable.

Patient and public involvement statement

Patients or the public were not involved in this study.

RESULTS

Four JIP subgroups of patients with early RA

Utilising the original 'embedding' of patients with early RA into 4 JIP subgroups, we successfully projected patients with early RA from the NORD-STAR (804 out of 812 patients with

RA, 99%) and BeSt (446 out of 508, 88%) trials into the same 4 JIP subgroups (Methods, Fig 1, and Supplementary Fig S2). These JIP subgroups were determined using only baseline clinical characteristics, primarily joint involvement in the 66/68 joint scheme. In both the NORD-STAR and BeSt datasets, JIP-Foot consisted of younger patients, predominantly involving the small joints of the feet (Table, Fig 1, and Supplementary Tables S1 and S2). JIP-Oligo included patients with a limited number of affected joints. JIP-Hand comprised older patients with a hand-dominant pattern. JIP-Poly represented patients with the highest disease activity, characterised by widespread polyarthritis, including both hand and foot small joints and/or multiple large joints. Patients whose polyarthritis was limited to the small joints of the hands were classified as JIP-Hand. These patterns were quite consistent with those reported in our previous study [9], demonstrating the reproducibility of the 4 JIP subgroups across cohorts.

The median baseline symptom duration was similar between NORD-STAR and BeSt (157 vs 165 days), whereas JIP-Foot showed the longest median symptom duration. Symptom duration is unlikely to fully explain the subgroup differences, as it did not follow a clear gradient across groups (eg, JIP-Poly did not have the longest symptom duration).

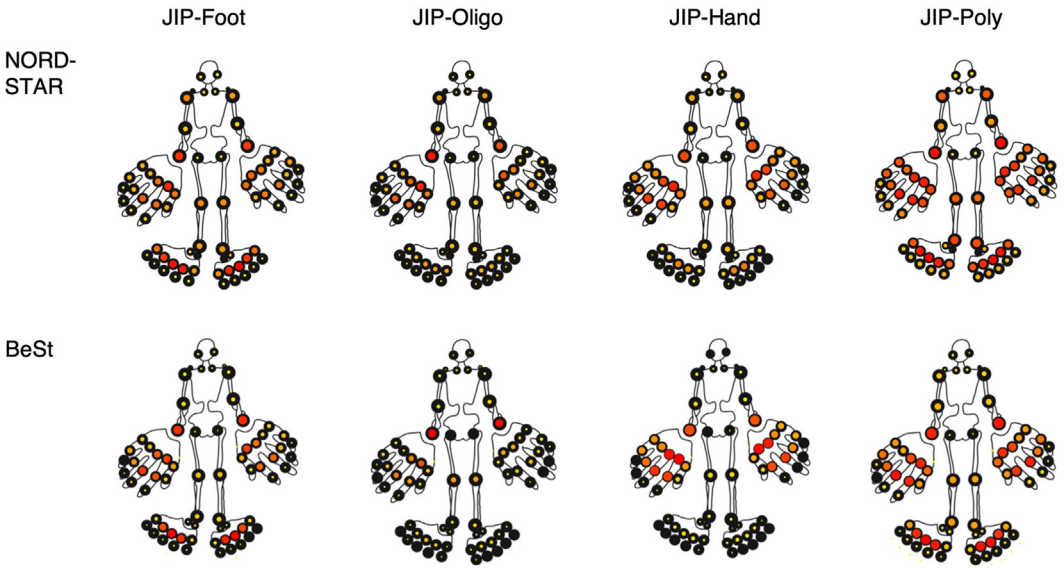

Figure 1. Joint involvement pattern (JIP) subgroups in the NOrdic Rheumatic Diseases Strategy Trials And Registries (NORD-STAR) and Behandel-Strategieën (BeSt) trials. The mannequin plots show joint involvement across the 4 JIP subgroups in the NORD-STAR and BeSt datasets. The mannequins are presented as heatmaps, displaying the prevalence of joint involvement (tender or swollen) with colour coding (red = 100%, yellow = 0%). The size of each joint also reflects the prevalence of joint involvement. In NORD-STAR (N = 804), the proportions of the JIP subgroups were: arthritis of the feet (JIP-Foot): 30.3% (n = 244); oligoarticular disease (JIP-Oligo): 27.2% (n = 219); arthritis of the hands (JIP-Hand): 18.2% (n = 146); and polyarthritis (JIP-Poly): 24.3% (n = 195). In BeSt (N = 446), the proportions of the JIP subgroups were: JIP-Foot: 13.5% (n = 60); JIP-Oligo: 15.0% (n = 67); JIP-Hand: 28.9% (n = 129); and JIP-Poly: 42.6% (n = 190).

Table
Baseline characteristics of the combined analysis cohort

JIP subgroup	JIP-foot	JIP-oligo	JIP-hand	JIP-poly
N	304	286	275	385
Age, y	50 (41-61)	55 (47-64)	60 (51-69)	55 (43-65)
Sex, female	218 (72)	200 (70)	174 (63)	264 (69)
Symptom duration, d	175 (103-256)	166 (101-333)	151 (88-248)	153 (92-308)
RF, positive	230 (76)	215 (75)	192 (70)	257 (67)
ACPA, positive	251 (83)	241 (84)	186 (68)	253 (66)
ESR, mm/hr	23 (11.8-36)	29 (16-44.2)	35 (22-54)	36 (18-58)
CRP, mg/L	9 (3-20.8)	10 (4-26.5)	17 (6-35)	18 (7-50.2)
SJC	9 (6-14)	7 (4-10)	12 (8-15)	17 (12-24)
TJC	15 (10-20)	9 (5-14)	15 (10-21)	28 (17-35)
CDAI	25 (18-32)	22 (16-28)	31 (26-38)	38 (30-46)
DAS28-CRP	4.9 (4.1-5.5)	4.6 (3.9-5.3)	5.4 (4.8-6.1)	6 (5.2-6.6)
HAQ	1 (0.8-1.4)	1 (0.5-1.4)	1.1 (0.6-1.5)	1.4 (0.9-1.9)

Demographics for the individual NOrdic Rheumatic Diseases Strategy Trials And Registries (NORD-STAR) and Behandel-Strategieën (BeSt) trials are provided in Supplementary Tables S1 and S2. Data are presented as median (IQR) or as n (%).
ACPA, anticitrullinated protein antibody; CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; DAS28, Disease Activity Score 28; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; JIP, joint involvement pattern; JIP-Foot, arthritis of the feet; JIP-Hand, arthritis of the hands; JIP-Oligo, oligoarticular disease; JIP-Poly, polyarthritis; RF, rheumatoid factor; SJC, swollen joint count in the 66/68 joint scheme; TJC, tender joint count in the 66/68 joint scheme.

JIP-Hand predicted better outcomes

We hypothesised that JIP subgroups, defined solely by baseline clinical characteristics, would predict the primary outcome (CDAI scores) after treatment. In both the NORD-STAR and BeSt datasets, all JIP subgroup patients responded well to treatment (Fig 2A, B).

The adjusted IPD meta-analysis examining the association between JIP subgroups and the progression of CDAI scores after treatment yielded R^2 values of 0.66 to 0.67, indicating a good fit of the models (Supplementary Table S3). The result showed that JIP-Hand patients exhibited significantly better CDAI scores after treatment (Beta = −1.4 [95% CI, −2.3 to −0.55]; p = .0016; Fig 2C), indicating that JIP-Hand patients showed a 1.4-point improvement in CDAI after treatment compared with the other 3 JIP subgroups, averaged across all time points. In contrast, JIP-Poly was associated with worse CDAI scores after treatment (Beta = 0.95 [95% CI, 0.064-1.8]; P = .035). The estimated effect of JIP-Hand on CDAI was similar in both trials (Fig 2D), but numerically larger in BeSt (Beta = −1.7; p = .070) than in NORD-STAR (Beta = −1.2; p = .019). This likely reflects the less intensive initial treatment in BeSt, which was conducted more than 2 decades ago, and may make differences between JIP subgroups more apparent than in the more aggressively treated NORD-STAR cohort.

In these analyses, we added baseline CDAI scores to the model to adjust for baseline differences, as they significantly affect the progression of CDAI scores after treatment. Without this adjustment, JIP-Poly exhibited the highest baseline CDAI and Beta values, while JIP-Oligo showed the opposite (Supplementary Table S4). Although individual joint involvement was included in the JIP subgroup assignment, we did not find strong correlations among the 4 JIP subgroups and baseline CDAI scores (Pearson's r = −0.35 to 0.44), indicating that multicollinearity is not a concern in this adjustment. To ensure that our findings were not driven by the choice of baseline disease activity covariate, we reran the models with baseline DAS28-CRP adjustment and obtained consistent results (Supplementary Fig S3).

In line with the primary outcome, JIP-Hand assignment was associated with better DAS28-CRP after treatment (Beta = −0.18 [95% CI, −0.30 to −0.062]; p = .0028; Supplementary Fig S4 and Supplementary Table S5), a higher likelihood of achieving CDAI remission (odds ratio [OR], 1.7 [95% CI, 1.2-2.4]; p = .0054; Supplementary Fig S5 and Supplementary Table S6), and a higher likelihood of achieving CDAI50 (OR, 1.6 [95% CI, 1.1-2.2]; p = .0074; Supplementary Fig S6 and Supplementary Table S7). The CDAI-based analysis correlated very well with the DAS44-based analysis in the BeSt dataset, which included both hand and foot joint counts (Pearson's r = 0.95; p = .053; Supplementary Fig S7). These results confirmed the robust association between JIP-Hand and improved disease activity outcomes after treatment. However, we found no association with HAQ (Beta = −0.0051 [95% CI, −0.058 to 0.048]; p = .86; Supplementary Fig S8 and Supplementary Table S8), possibly reflecting the complex nature of assessing functional ability.

Published CDAI minimal clinically important differences (MCID) are defined according to baseline disease activity (high,

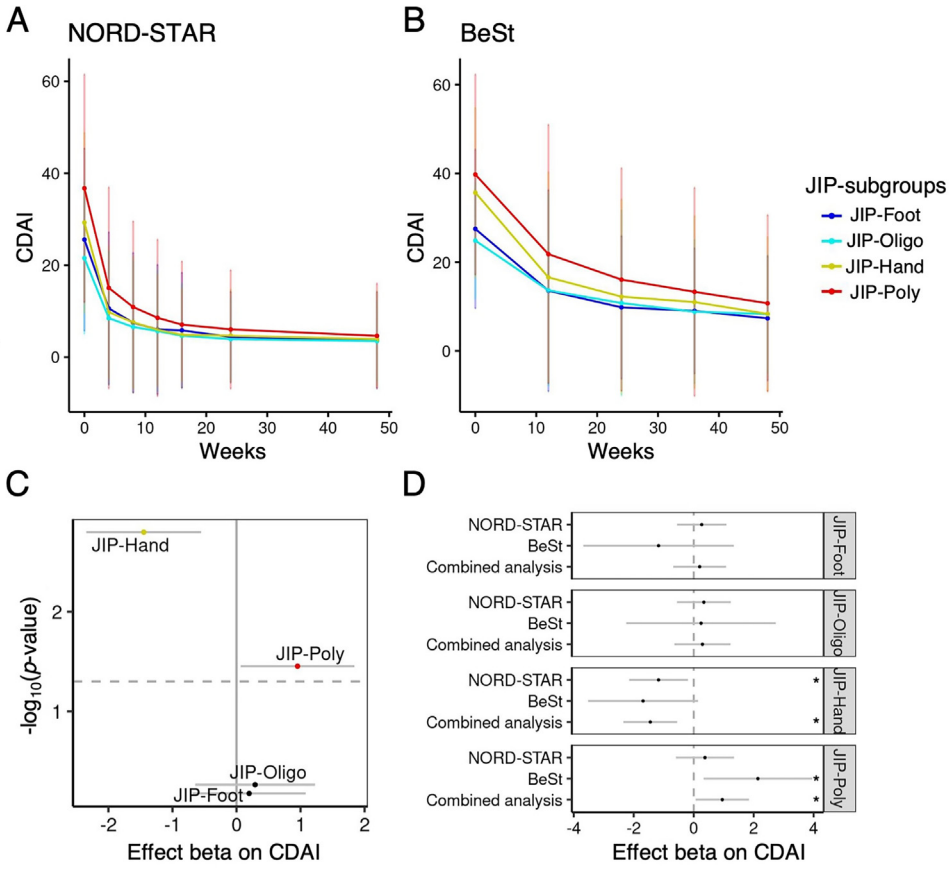

Figure 2. JIP-Hand is associated with lower Clinical Disease Activity Index (CDAI) scores after treatment. A and B, Line plots showing chronological CDAI changes in the (A) NOrdic Rheumatic Diseases Strategy Trials And Registries (NORD-STAR) and (B) Behandel-Strategieën (BeSt) datasets, stratified by the 4 JIP subgroups. C, Estimated effect of Beta on CDAI scores in the linear mixed-model analysis. The y-axis represents the log10 of the p values. The horizontal dashed line indicates a significance threshold of p values <.05. JIP subgroups with p values <.05 are coloured. D, Estimated Beta effect on CDAI scores in the individual NORD-STAR and BeSt datasets and in the meta-analysis. *p values <.05. A-D, Error bars indicate 95% CIs. JIP-Foot, arthritis of the feet; JIP-Oligo, oligoarticular disease; JIP-Poly, polyarthritis.

CDAI > 22: MCID = 12; moderate, CDAI = 10-22: MCID = 6; low, CDAI < 10: MCID = 1) [15]. In our cohorts, on average, 77% of NORD-STAR and 53% of BeSt participants achieved CDAI low disease activity or remission during follow-up (Supplementary Fig S9). In this context, the JIP-Hand subgroup showed a modest but consistent advantage, corresponding to an additional improvement of approximately 1.4 CDAI points over the follow-up period, supporting the potential clinical relevance of the observed effect.

Female sex is a predictor of outcome

To evaluate the effect size of JIP-Hand as a predictor of favourable outcomes, we compared the effect sizes of the associations between the 5 candidate clinical predictors (age, sex, RF, ACPAs, and symptom duration) and CDAI scores after treatment. We used the same models as those in the JIP subgroup analysis to ensure comparability and adjusted for baseline CDAI differences and other covariates (Methods). Among these predictors, female sex had the strongest effect (Beta = 1.2 [95% CI, 0.40-2.0]; p =.0031; Fig 3A and Supplementary Table S9), indicating that CDAI scores for female patients were 1.2 points higher than those for male patients across all time points. We observed consistent sex effects on CDAI scores in both the NORD-STAR and BeSt datasets (Fig 3B, C). Although ACPAs are an established predictor of poor radiographic prognosis, we did not observe a significant impact on CDAI scores after treatment (Beta = 0.19 [95% CI, −0.69 to 1.1]; p =.67; Fig 3D, E).

To further confirm the association between JIP-Hand assignment and CDAI scores after treatment, we adjusted the linear mixed-model analysis to include additional covariates for the 5 clinical features mentioned above (Methods). We found no strong correlation between JIP-Hand assignment and these clinical features (Pearson's r = −0.16 to 0.050). Even after adjusting for the effects of these additional covariates, JIP-Hand assignment remained independently associated with better CDAI scores after treatment (Beta = −1.3 [95% CI, −2.2 to −0.43]; p = .0039; Fig 3F and Supplementary Table S10). Similarly, JIP-Poly was independently associated with lower CDAI scores (Beta = 0.95 [95% CI, 0.066-1.8]; p = .034).

No significant heterogeneity between JIP subgroups and biological treatment response

Next, we tested whether JIP subgroups have variable effects on CDAI scores across different treatments. Due to the small sample sizes resulting from combining JIP subgroups with the 4 treatment arms or strategies in both the NORD-STAR and BeSt studies (Supplementary Tables S1 and S2), we did not test the separate treatment arms or strategies within each study. Instead, we focused on the differences between csDMARD and bDMARD treatments. In both studies, patients with early RA were randomised to receive either csDMARD or bDMARD (with MTX) treatment, allowing us to assess whether patients in specific JIP

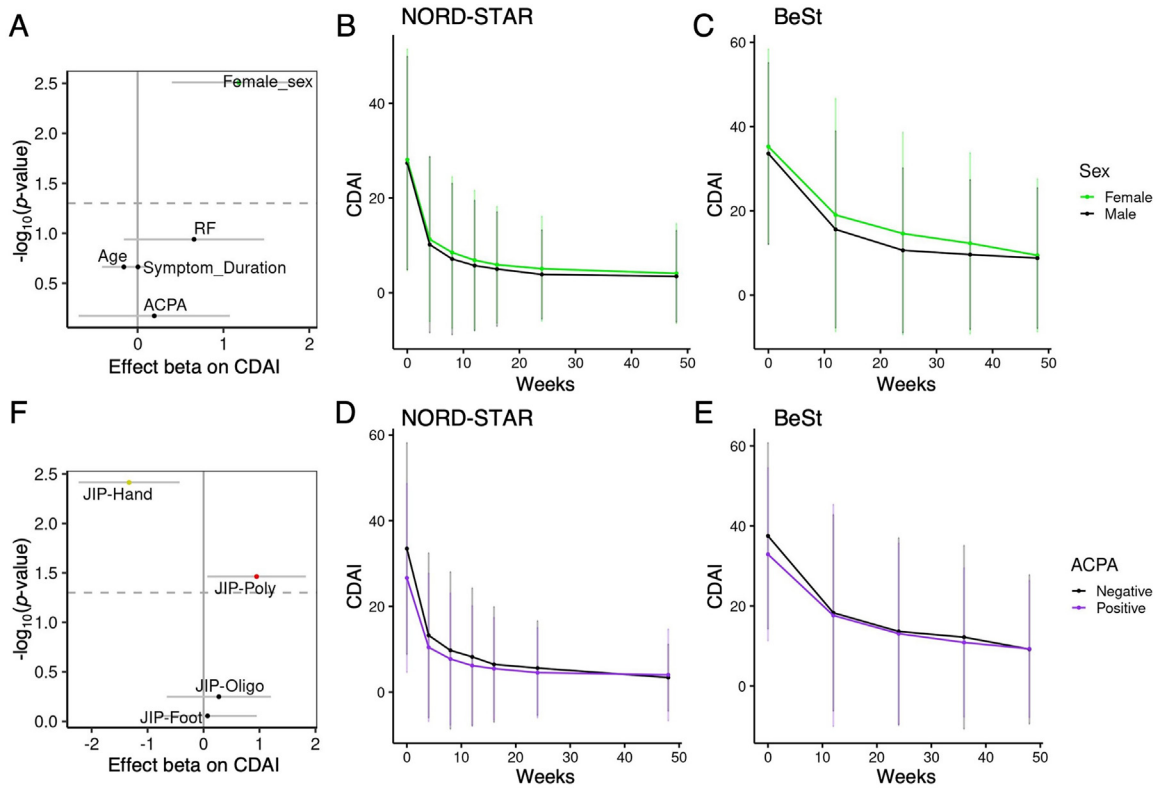

Figure 3. Sex and arthritis of the hands (JIP-Hand) are predictive of the Clinical Disease Activity Index (CDAI). A and F, Estimated effect of Beta on CDAI scores in the linear mixed-model analysis. In (A), candidate clinical predictors were independently tested for association with CDAI progression after treatment, and in (F), joint involvement pattern (JIP) subgroups were tested for association with CDAI progression after additional adjustment for the clinical covariates shown in (A) (Methods). The age effect was estimated at 10 years, and the symptom duration was 30 days. The y-axis represents the log10 of the p values. The horizontal dashed line indicates a significance threshold of p values <.05. Explanatory clinical variables with p values <.05 are coloured. B-E, Line plots showing chronological CDAI changes in the NOrdic Rheumatic Diseases Strategy Trials And Registries (NORD-STAR) and Behandel-Strategieën (BeSt) datasets stratified by (B-C) sex or (D-E) anticitrullinated protein antibody (ACPA) positivity. A-F, Error bars indicate 95% CIs. JIP-Foot, arthritis of the feet; JIP-Oligo, oligoarticular disease; JIP-Poly, polyarthritis; RF, rheumatoid factor.

subgroups benefited more from early addition of biological treatment than from conventional treatment. We categorised treatment arms and strategies involving the initial concomitant use of bDMARDs with MTX as 'bDMARD treatment,' which included NORD-STAR arm 2 (certolizumab pegol), arm 3 (abatacept), arm 4 (tocilizumab), and the BeSt strategy 4 (initial combination therapy with infliximab). All other treatment arms or strategies were classified as 'csDMARD treatment.'

To evaluate whether the impact of JIP subgroups varied with csDMARD or bDMARD treatment, we analysed the interaction term between JIP subgroup assignment and bDMARD treatment in an IPD meta-analysis (Methods). The interaction term results showed no significant association with CDAI scores after treatment (JIP-Foot p =.48; JIP-Oligo p = .29; JIP-Hand p = .58; JIP-Poly p = .94). We also found no significant association with DAS28-CRP, CDAI remission, or HAQ (Supplementary Table S11). Similarly, no significant heterogeneity was observed in the separate analyses of the NORD-STAR and BeSt trials, except for the association between CDAI remission and bDMARD-treated JIP-Hand patients in the BeSt study (p = .029; Supplementary Fig S10 and Supplementary Tables S12 and S13). Therefore, csDMARDs and bDMARDs were similarly effective or ineffective in the JIP subgroups.

JIP-Hand and response to MTX monotherapy in the BeSt dataset

Finally, taking advantage of the treatment-switching design of the BeSt trial (based on achieving low disease activity on the DAS44), we compared MTX monotherapy retention across the JIP subgroups. Two of the 4 BeSt treatment strategies started with MTX monotherapy; patients who responded well continued on MTX monotherapy, whereas treatment failure led to combination therapy or a switch to other treatments. We observed a trend towards higher MTX monotherapy retention at week 24 in the JIP-Hand subgroup (OR, 1.5 [95% CI, 0.95-2.4]; p = .08; Supplementary Fig S11), consistent with our previous findings [9] and further supporting a link between JIP-Hand and a better response to MTX therapy.

DISCUSSION

In this study, we performed an IPD meta-analysis of 2 randomised controlled trials involving treatment-naïve patients with early RA to determine whether JIP subgroups of RA are predictive of disease activity following treatment. We found that patients with a hand-dominant pattern of RA, classified as JIP-Hand, were associated with better treatment responses, whereas patients in JIP-Poly experienced worse responses, even after adjusting for baseline disease activity measures and other clinical predictors. This observation was consistent across patients treated with either csDMARDs or bDMARDs in combination with MTX. However, the average between-subgroup differences were modest and should be interpreted cautiously.

These results align with our previous study using 3 independent datasets [9], in which JIP-Hand was associated with better MTX retention and higher remission rates, whereas the opposite was observed for JIP-Poly. The reproducible 4 JIP subgroup patterns of early RA and their differential responses to treatment support the notion that these JIP subgroups reflect pathophysiologically distinct subpopulations of early RA. Although the effect size of JIP-Hand was relatively small, with a 1.4-point improvement in CDAI scores, it represents a clinically significant additional improvement in CDAI scores after treatment, exceeding the minimal clinically important improvement cutoff for low disease activity patients of 1 [15]. It significantly increased the likelihood of achieving CDAI remission or CDAI50, with ORs of 1.7 and 1.6, respectively. Furthermore, the effect size of JIP-Hand was comparable with or numerically larger than that of any of the clinical predictors we tested. Because the JIP subgroups we propose can be identified using only routine baseline clinical evaluations, they may serve as useful clinical predictors of treatment response in early RA.

We expected that JIP-Hand would be associated with worse functional disability; however, the HAQ did not differ clearly between JIP subgroups. One explanation is that HAQ captures global functional limitation and is strongly influenced by pain, fatigue, and psychological factors (eg, depressive symptoms), which may dilute the impact of joint location [16,17]. In addition, early intensive treatment may rapidly improve function across subgroups, and potential differences may be more detectable only in patients with persistent symptoms or structural damage, which was not the focus of this study.

In our analysis, we did not observe a significant impact of ACPAs or RF autoantibodies on the treatment-induced decrease in disease activity. Although ACPAs have been established as a clinical biomarker for identifying a subpopulation of seropositive patients with RA at increased risk of long-term radiographic joint damage, their presence has not been shown to be predictive of disease activity over a period of 1 to 2 years [4,5,18,19]. Meanwhile, we observed larger effects of sex differences on disease activity, with female patients having CDAI scores 1.2 points higher than those of male patients. In line with this finding, female patients have been reported to exhibit worse disease activity measures in large RA cohorts [20−22]. A recent post hoc analysis of the NORD-STAR trial reported a higher CDAI remission rate in men [23]. Our study was consistent with previous reports in showing that female sex is associated with higher disease activity in early RA, although the effect size was modest.

To demonstrate an independent association with CDAI scores, we included JIP subgroup assignments, along with covariates such as sex and autoantibody status, in our models. Because these clinical predictors were included in the input dataset for JIP subgroup assignment, we carefully assessed their independence. This analysis was feasible because JIP subgroup assignments were derived from deep learning applied to over 300 clinical features, resulting in negligible or weak linear relationships between the JIP subgroups and these features. The analysis indicated that the prognostic effect of JIP-Hand on treatment response is largely independent of traditional clinical predictors such as sex and autoantibody status.

The IPD meta-analysis revealed no significant interaction between JIP subgroups and biological treatment on disease activity, indicating no heterogeneity in biological treatment effects across the JIP subgroups. Generally, using interaction term analysis to compare treatment effects across subgroups is preferable to separate stratified analyses [24]. Although interaction tests tend to be more robust, they may still lack sufficient power, potentially leading to incorrect conclusions about subgroup effects. We assessed only the overall biological treatment effect, without focusing on specific bDMARDs, due to the small sample sizes in each JIP subgroup and treatment combination. Consequently, we may have overlooked JIP subgroup-specific interactions with particular treatments, highlighting the need for further research with larger cohorts.

In addition to analyses across all treatment strategies, we examined a more tangible clinical endpoint in the BeSt trial: retention on MTX monotherapy in the arms that initiated MTX. In this treat-to-target setting, good responders can remain on

MTX, whereas insufficient responders are escalated to combination or alternative therapy. We observed a trend towards higher MTX monotherapy retention at week 24 in the JIP-Hand subgroup (OR, 1.5), consistent with our previous study [9] and supporting the notion that patients with JIP-Hand are, on average, more likely to respond adequately to standard-dose MTX. This links the JIP subgroups to a familiar clinical decision point and further illustrates their potential clinical relevance. These findings do not, in themselves, warrant a different standard treatment pathway from baseline or after MTX failure. Rather, JIP subgroup information should be interpreted as an adjunct to established poor prognostic factors and may help refine risk stratification and the intensity of monitoring. This framework provides a practical basis for stratified analyses in future cohorts and trials to test whether certain therapeutic strategies can be optimised for patient groups that appear less well served by current approaches.

The underlying mechanism for the better outcomes observed in JIP-Hand and the worse outcomes in JIP-Poly remains unclear. One potential explanation for the better prognosis observed in JIP-Hand could be that most current RA disease activity indices, including CDAI and DAS28-CRP, tend to overlook foot involvement, leading to seemingly better outcomes in patients with JIP-Hand. However, this does not account for the worse outcomes in JIP-Poly, which involves both hand and foot joints, nor for the intermediate response observed in JIP-Foot patients. To address this possibility, we also analysed DAS44 trajectories in the BeSt trial, which included both hand and foot joints. We observed a similar pattern of more favourable improvement in JIP-Hand and less favourable outcomes in JIP-Poly, suggesting that these differences are not solely driven by the underestimation of foot disease activity in 28-joint indices. We acknowledge that foot examination is often less reliable than hand examination in routine practice, which may introduce additional measurement noise (even with DAS44) and thus attenuate between-subgroup differences. The presence of painful distal interphalangeal joints (DIPs) due to hand osteoarthritis did not have a large effect on JIP-Hand assignment, as only 37/416 (8.9%) patients had osteophytes in DIPs in the BeSt trial [25]. One hypothesis is that distinct RA synovial pathotypes [26−28], which are associated with varying treatment responses, may be linked to differences in the anatomical distribution of affected joints. Further investigations are needed to clarify the biological basis of these JIP subgroups.

There are several limitations of our study. First, due to the post hoc nature of our analysis, treatment was not randomised across arms or strategies within the JIP subgroups, which could introduce potential biases. However, we observed that treatment arms or strategies were almost evenly randomised within each JIP subgroup, suggesting minimal impact of this bias. Our primary aim was to assess whether the JIP subgroups have prognostic value across different csDMARD/bDMARD strategies, so we analysed all treatment arms together and adjusted for treatment strategy in the models. Second, assignment of the JIP subgroups requires baseline clinical information, thereby limiting the scheme's clinical applicability. In addition, our analyses were limited to ACPA positivity; baseline ACPA titres were not analysed. Furthermore, because JIP subgroups exist on a continuum rather than in clearly separate modules, patients with clinical manifestations at the border of multiple categories are necessarily assigned to a single JIP subgroup, potentially obscuring nuanced presentations. Third, although our analysis is based on a statistically robust IPD meta-analysis and a mixed-effects model approach, complete clinical data were not available for every patient at baseline or at each visit, which may affect the accuracy of our findings. Moreover, because JIP subgroups are defined from JIPs and CDAI scores include joint counts, we cannot fully exclude residual confounding, despite adjustment for baseline disease activity. Fourth, although the use of trial data may, in general, limit the generalizability of the findings to broader, real-world populations, both the BeSt and NORD-STAR studies recruited consecutive patients with active arthritis, making it unlikely that selection bias occurred.

In conclusion, our IPD meta-analysis of 2 randomised controlled trials highlights the potential utility of JIP subgroups in predicting disease activity in patients with early RA, although all subgroups showed a clinically good response. Our findings encourage future studies to test whether baseline JIP subgrouping adds prognostic value beyond established predictors and whether it can inform risk stratification and monitoring, before considering any role in guiding treatment intensity.

Competing interests

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Patient consent for publication

Not required.

Ethics approval

The NORD-STAR and BeSt trials were approved by the relevant national and institutional ethics committees. All participants gave written informed consent.

Provenance and peer review

Not commissioned, externally peer reviewed.

Data availability statement

Data are available upon reasonable request. Individual patient data from the NORD-STAR and BeSt trials can be requested from the respective trial investigators, in accordance with institutional and national regulations.

Supplementary materials

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