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Modifiable Lifestyle Factors Associated With Response to Treatment in Early Rheumatoid Arthritis

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Objective. We aimed to evaluate the associations between response to algorithm-directed treat-to-target conventional synthetic disease-modifying antirheumatic drug therapy and potentially modifiable lifestyle factors, including dietary fish oil supplementation, body mass index (BMI), and smoking history in a rheumatoid arthritis (RA) inception cohort.

Methods. Patients with RA with a duration of less than 12 months were reviewed every 3 to 6 weeks to adjust therapy according to disease response. All patients received advice to take fish oil supplements, and omega-3 status was measured as plasma levels of eicosapentaenoic acid (EPA). Lifestyle factors and other variables potentially prognostic for 28-joint Disease Activity Score (DAS28) remission and DAS28 low disease activity (LDA) at the 12-month visit were included in multivariable logistic regression models.

Results. Of 300 participants, 57.7% reached DAS28 LDA, and 43.7% were in DAS28 remission at 1 year. Increase in plasma EPA was associated with an increase in the odds of being in LDA (adjusted odds ratio [OR] = 1.27; $P < 0.0001$) and remission (adjusted OR = 1.21; $P < 0.001$). There was some evidence that the effect of BMI on LDA might be modified by smoking history. An increase in BMI was associated with a decrease in the odds of being in LDA in current and former smokers but had no impact on LDA in patients who had never smoked. There were no meaningful associations between BMI or smoking history and remission.

Conclusion. Omega-3 status, BMI, and smoking history are potential predictors of outcome in early RA. The possibility of an effect modification by smoking on the predictive value of BMI merits further investigation.

INTRODUCTION

There is evidence that potentially modifiable lifestyle factors, such as dietary omega-3 fats (1-3), smoking status (4-6), and body mass index (BMI) (7-9), have a role in rheumatoid arthritis (RA) outcomes.

A double-blind randomized controlled trial (RCT) demonstrated a beneficial effect of dietary fish oil supplements on American College of Rheumatology (ACR)–defined remission in early RA (1). In that study, plasma levels of eicosapentaenoic acid (EPA), the main omega-3 fatty acid in fish oil, were directly associated with ACR-defined remission (2). Another cross-sectional analysis of baseline data from a cohort study showed that increased fish consumption was associated with lower 28-joint Disease Activity Score (DAS28) scores and C-reactive protein (CRP) levels (3).

Meta-analyses of case-control and cohort studies reported that smoking is a risk factor for the development of RA. Smokers have a higher risk for developing rheumatoid factor (RF)–positive and anti–citrullinated protein antibody (ACPA)–positive disease (6,10), and there is a dose response for risk with pack-years of smoking (5). Although current guidelines recommend that patients with RA be advised to cease smoking (11), the evidence of a role for smoking in the progression or activity of RA remains equivocal (12-15).

A meta-analysis showed reduced attainment of minimal disease activity (MDA) in patients with obesity and RA compared with normal-weight patients with RA, but there was no adjustment for

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SIGNIFICANCE & INNOVATIONS

- Fish and fish oil intake, body mass index (BMI), and smoking are potentially modifiable factors associated with response to drug treatment in early rheumatoid arthritis (RA).
- Plasma omega-3 levels were strongly and favorably associated with the response to treatment in early RA.
- There was some indication of effect modification by smoking history on the relationship between BMI and disease outcomes.
- The results on the BMI/smoking interaction are novel and are a prompt for analysis with other data sets.

smoking (8). In two UK early RA cohorts, adjustment for potential confounders, including smoking status, slightly strengthened the relationship between obesity and less frequent low disease activity (LDA) (16). In a Canadian early RA cohort, adjustment for potential confounders, including smoking status, had little to no effect on the relationship between reduced sustained remission in patients with RA who have obesity and overweight (9). In RCTs involving golimumab, obesity but not overweight status decreased the rate of remission using the DAS28, but again there was no adjustment for smoking history (17). When measured continuously, BMI was not associated with DAS28 remission at 6 months after rituximab treatment, although no correction was made for smoking history (18). Overall, few studies have examined BMI as a continuous variable.

There is evidence from both RCT data and long-term observational data for improved clinical and patient-reported outcomes associated with treat-to-target (T2T) strategies in the management of RA (19). With the exception of the fish oil supplementation RCT (1), to our knowledge, none of the other studies that involved fish intake, smoking, and body weight were done in the context of modern T2T approaches applied uniformly in the study cohort. Also, there have been no data on these three potentially modifiable lifestyle factors collected simultaneously from a single cohort that allow for the examination of interactions between them. The possibility of effect modification between these modifiable factors would be important to understand for purposes of tailoring patient advice. We examined the effect of these lifestyle factors on the response to treatment in an early RA cohort that used protocolized T2T conventional synthetic disease-modifying antirheumatic drug (csDMARD) therapy (20).

PATIENTS AND METHODS

Participants. Consecutive patients with recent onset polyarthritis who were attending the Early Arthritis Clinic at the Royal Adelaide Hospital were assessed. Those with disease-modifying antirheumatic drug (DMARD)–naïve RA (according to the 1987 revised ACR criteria) with polyarthritis of less than 12 months' duration for whom the decision had been made to commence

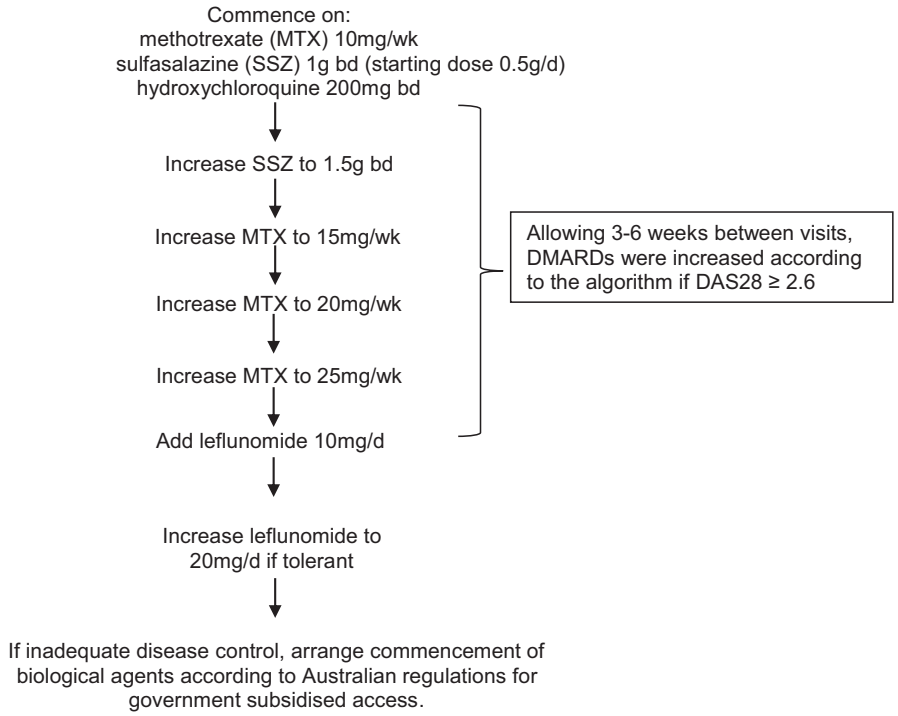

Figure 1. Treatment of recent onset rheumatoid arthritis in the Royal Adelaide Hospital Early Arthritis Clinic. DAS28, 28-joint Disease Activity Score; DMARD, disease-modifying antirheumatic drug; MTX, methotrexate; SSA, sulfasalazine.

triple therapy with the csDMARDs sulfasalazine (SSZ), hydroxychloroquine, and methotrexate (MTX) and who provided consent were included in this cohort. Within this cohort of 300 patients, which accrued over 17 years of clinic activity, were 139 patients who had participated in an RCT of fish oil supplementation that was embedded in the usual clinic practice (1). Recruitment was balanced throughout this period, with 15.8 ± 4.4 (mean ± SD) participants enrolled per year, and the same clinicians were involved in the assessment of patients over this period.

Treatment. Treatment in this clinic is protocol driven and has been described elsewhere (20). Both the RCT participants and the observational cohort patients were treated according to the same protocol, which had a T2T intent with the target being a DAS28–erythrocyte sedimentation rate (ESR) of less than 2.6 (remission). Triple csDMARD therapy was initiated and escalated according to an algorithm that is responsive to disease activity (Figure 1). It is also standard practice for all patients in this clinic to receive a recommendation to take 10 to 15 ml of fish oil per day, and this will provide at least 3 g of combined EPA and docosahexaenoic acid (DHA) per day, which is considered an anti-inflammatory dose (21,22). The extent to which this advice is followed is a matter of patient preference. Those in the RCT were randomized to receive either 5.5 or 0.4 g combined EPA and DHA per day in a blinded and masked fashion (1).

Study outcomes. Patients were assessed every 3 to 6 weeks until the target DAS28 level was reached, after which reviews occurred every 3 months. RA outcomes included the routine assessment of DAS28 scores employing ESR, in which remission is defined as a DAS28 score of less than or equal to 2.6 and a DAS28 LDA score of less than or equal to 3.2 (23). Blood was taken at each clinic visit for plasma EPA, which was measured as a percentage of total fatty acids as described previously (24).

Statistical methods. DAS28 remission at 12 months (score of less than or equal to 2.6) included DAS28 LDA (score of less than or equal to 3.2). Prognostic variables for DAS28 remission and DAS28 LDA at 12 months were identified using multivariable logistic regression models. Prognostic variables evaluated in the models included sex, baseline BMI, baseline age, baseline smoking status (current, former, or never), baseline RF, anti–citrullinated protein antibody status, shared epitope, and mean plasma EPA level over 1 year. Associations between variables were described using odds ratios (ORs) and 95% confidence intervals (CIs). All analyses were performed using Stata software version 15 (StataCorp).

RESULTS

Participants had recent onset RA with a median duration of 16.0 weeks, and the baseline DAS28 score was 5.4 ± 1.3 (mean ± SD) (high disease activity) (Table 1). Of 300 participants, 179 (57.6%) were in DAS28 LDA and 136 (43.7%) were in DAS28 remission at 1 year. Patient group (RCT or clinic) was examined but excluded from the multivariable logistic model because it was not related to either DAS28 remission or LDA at 1 year.

Table 1. Demographics and baseline clinical characteristics

Patient Characteristics	Results
Age at onset, mean ± SD, y	55.5 ± 14.9
Female sex, n (%)	211/300 (70.3)
Duration of polyarthritis, median (IQR), wk	16.0 (11.1-24.6)
RF +ve, n (%)	181/299 (60.5)
ACPA +ve, n (%)	156/289 (54.0)
Shared epitope +ve, n (%)	191/197 (64.3)
BMI, median (IQR)	27.3 (24.3-31.1)
Smoking history, n (%)	
Current smoker	51 (17.0)
Former smoker	99 (33.0)
Never smoked	143 (47.7)
Unknown	7 (2.3)
DAS28-ESR, mean ± SD	5.4 ± 1.3

Abbreviation: ACPA, anticitrullinated protein antibody; BMI, body mass index; DAS28, 28-joint Disease Activity Score; ESR, erythrocyte sedimentation rate; IQR, interquartile range; RF, rheumatoid factor; +ve, positive.

The variability in uptake of advice to take fish oil supplements led to a wide range of plasma EPA levels among clinic patients who did not take part in the RCT. The variability in plasma EPA levels in the RCT participants overlapped with that of the other clinic patients, and the data from the two groups were pooled in the analyses (Figure 2). A higher mean plasma EPA level (measured as a percentage of total fatty acids) was associated with an increase

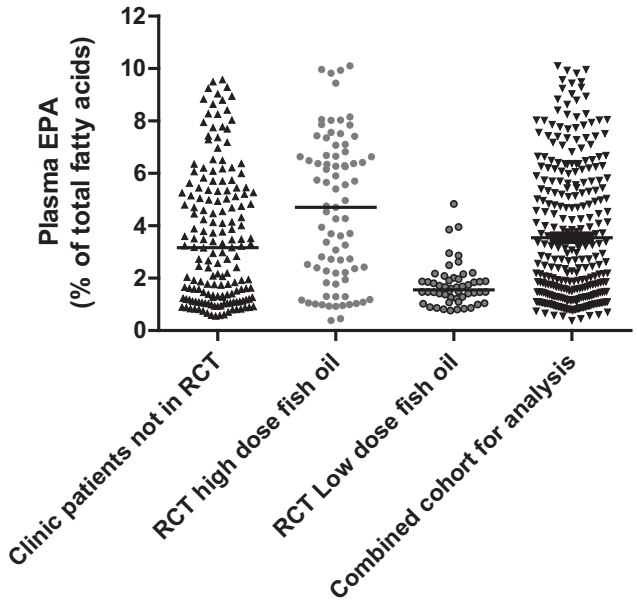

Figure 2. Mean plasma eicosapentaenoic acid (EPA) (percentage of total fatty acid) for clinic patients who did not participate in the randomized controlled trial (RCT) and for those who did take part in the RCT, which had low-dose and high-dose fish oil arms. Horizontal bars represent medians.

Table 2. Adjusted odds ratios of DAS28 low disease activity at 1 y after commencing treatment[a]

Variable	Odds Ratio	Lower 95% CI	Upper 95% CI	*P*
Plasma EPA	1.268	1.116	1.440	**0.003**
Smoking	...	...	...	0.106[b]
BMI	...	...	...	0.936[b]
Interaction of BMI x smoking history	...	...	...	0.066[c]
BMI (current smoker)	0.803	0.670	0.962	**0.017**
BMI former smoker	0.913	0.842	0.991	**0.029**
BMI never smoked	1.004	0.919	1.097	0.936
Shared epitope status				
Positive	1.215	0.637	2.319	0.555
Anti-CCP status at baseline				
Positive	1.378	0.642	2.957	0.410
RF status at baseline				
Positive	1.188	0.586	2.406	0.633
Female sex	0.583	0.290	1.170	0.129
Age at baseline, y	0.986	0.965	1.007	0.198
Cohort				
RCT	0.601	0.335	1.077	0.087
Non-RCT	1	...	...	...

Abbreviation: anti-CCP, anti–citrullinated protein antibody; BMI, body mass index; CI, confidence interval, EPA, eicosapentaenoic acid; RCT, randomized controlled trial; RF, rheumatoid factor.
[a]Odds ratios are adjusted for all other variables shown in the model.
[b]Main-effect *P* value should be ignored when an interaction term is present.
[c]Global *P* value.
Bold indicates significant value $P < 0.05$.

in the odds of being in DAS28 LDA at 1 year (adjusted OR = 1.27; 95% CI 1.12-1.45; $P < 0.0001$) and DAS28 remission at 1 year (adjusted OR = 1.21; 95% CI 1.08-1.36; $P < 0.001$) (Table 2). All two-way interactions involving BMI, sex, and EPA were examined one at a time in separate multivariable logistic regression models. There was no evidence of an interaction between plasma EPA and any of the other variables.

There was evidence for an interaction between smoking status and BMI on DAS28 LDA. An increase in BMI was associated with a decrease in the odds of being in DAS28 LDA in current and former smokers, but BMI had no impact on LDA in patients who had never smoked (Table 2) (Figure 3).

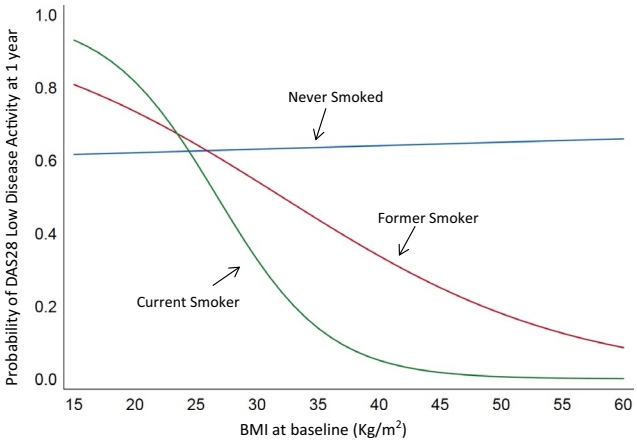

Figure 3. Predicted probability of 28-joint Disease Activity Score (DAS28) low disease activity at 1 year by body mass index (BMI) and smoking status.

Smoking history was not associated with DAS28 remission. There was a modest association of BMI with DAS remission (OR = 0.94; 95% CI 0.89-0.99; $P = 0.034$).

Neither shared epitope or RF ACPA positivity appeared to be associated with either DAS28 remission or LDA.

DISCUSSION

These results, which combine data from our early RA cohort treated according to our standard T2T practice and an RCT nested within this standard practice, demonstrate a strong positive association between plasma levels of EPA and odds of achieving DAS28 LDA and DAS28 remission. They provide evidence for the efficacy of fish oil supplementation as an adjunct to T2T therapy in the management of patients with early RA. They are consistent with a recent review and meta-analysis of fish oil supplementation in RA that concluded that fish oil has an important role in the management of RA when used in conjunction with other pharmacotherapy (25).

Importantly, there is biological plausibility for these observations. EPA exerts anti-inflammatory effects by competitively inhibiting the production of pro-inflammatory prostaglandins and leukotrienes and by its conversion to E-resolvins, which suppress inflammation (26,27). Resolvins derived from both EPA and DHA, the two main omega-3 fatty acids in fish oil, can suppress inflammatory cytokine production, including tumor necrosis factor α (TNF-α) (28), and have been shown to suppress inflammation in animal models (29).

Related to the effect of omega-3 fatty acids on disease activity are reports that increased omega-3 fatty acid intake is asso-

ciated with decreased risk for onset of RA. This was seen in a cohort of US women aged less than or equal to 55 years but not more than 55 years (30) and in a Swedish cohort of women in whom the risk was adjusted for age (31). In a sample selected for ACPA positivity from a public RA screening in Colorado, red blood cell omega-3 fatty acid content was inversely associated with the incidence of inflammatory arthritis (32).

Smoking is a risk factor for the development of RA, especially seropositive disease (5-6,10). Even though current guidelines for RA treatment recommend cessation of smoking, the effect of smoking status on disease outcome is less clear than that on RA incidence. Analysis of a North American registry comprising recent onset and established RA (Corrona) indicated that disease activity at baseline was worse in smokers relative to nonsmokers but that there was no difference in the change in the Clinical Disease Activity Index for those who ceased smoking vs. those who continued smoking (12). In an early RA Spanish clinic, there was no difference between smokers and nonsmokers in the clinical disease response to treatment (33). In an early RA French cohort, smoking had no effect on clinical disease response to treatment, and radiographic disease progression was less in current smokers compared with nonsmokers (15). However, current smoking at baseline predicted a poor European League Against Rheumatism response to treatment at 12 months in a Swedish early arthritis cohort (34). Although there have been some specific smoking cessation studies in RA, they were concerned with the success/failure of smoking cessation and did not measure clinical outcomes (35,36).

In the absence of adjustment for smoking history, BMI was not found to be associated with DAS28 remission at 6 months after rituximab treatment (18). There have been few studies with BMI as a continuous variable, with most studies of body weight using categories for analysis. Secondary analysis of data from two RCTs involving golimumab intervention indicated that obesity, but not overweight status, decreased the rate of DAS28 remission at 24 weeks, but there was no correction for smoking history (17). A meta-analysis also showed that relative to normal weight, attainment of MDA was lower for patients with RA and obesity but not for patients who had overweight. Again, no adjustment was made for smoking (8). Data from two early RA inception cohorts (the Early Rheumatoid Arthritis Study [ERAS] and Early Rheumatoid Arthritis Network [ERAN]) show that obesity was associated with decreased DAS28 LDA compared with normal/overweight in groups at 2 years but not at 5 years and that adjusting for potential confounders, including smoking status, increased the magnitude of the association (16). Unlike our current study, treatment was not standardized, and SSZ was the main starting DMARD in the late 1980s (ERAS), with a gradual switch to MTX as the starting DMARD after 2002 (ERAN), and there was little use of combination therapy (37). In a Canadian early RA cohort, patients with obesity and overweight had decreased sustained remission compared with normal body weight groups; adjustment for potential confounders, including smoking, had little effect on the hazard ratios (9).

Overall, the published literature has discrepant reports for the effect of smoking on disease response to treatment. The interaction between smoking and BMI on response to treatment in early RA in the present study suggests that future studies of smoking and RA outcomes should be adjusted for BMI and assessed for effect modification by BMI. Also, those studies that primarily examine the effect of BMI on RA outcomes should be adjusted for smoking history. It is difficult to explain an interaction between smoking and BMI for RA outcomes by considering mechanistic interactions, especially because the mechanism for the poorer outcomes in individuals with obesity and increased incidence in smokers are speculative.

Excess adipose tissue can produce inflammatory adipokines as well as TNF-α and interleukin 6, and circulating levels of these cytokines are elevated in obesity (38). In support of excess adipose tissue being causal, weight loss, especially that after bariatric surgery, reduced the plasma ESR and CRP level and improved RA disease activity (39,40).

The risk of smoking relates mainly to RA incidence rather than disease severity, and it does not appear to be a general or broad toxicity agent. The shared epitope genotype increases the smoking-related risk for RA in patients who are ACPA positive, strongly suggesting that smoking is a trigger for an adaptive immune response (10). A proposed two-step model for smoking/shared epitope/ACPA linkage leading to inflammatory arthropathy involves the interaction of ACPA and locally generated citrullinated peptides within the joint space, with the formation of immune complexes (41). Because ACPA status precedes clinical RA by several years and does not change during the disease (41,42), it is unlikely that cessation of smoking in this group would decrease disease activity, and this has been observed (12). Thus, the possibility of a mechanistic interaction between smoking and body weight cannot be proposed given current knowledge. An alternative explanation would be that smoking and BMI are proxies for another factor, such as socioeconomic status or medication adherence, for example, that influences outcomes in RA.

The strengths of the present study include the reporting of objective and validated outcome measures. Patients enrolled in the cohort were well characterized regarding nonmodifiable and modifiable factors, including a biomarker of fish and fish oil intake, and received contemporary, protocolized T2T therapy. The limitations of this study are that it is an observational study, and causal relationships are precluded. A prospective intervention study would be needed to assess whether weight loss in smokers would improve clinical outcomes. A further limitation is that relevant potential confounders are not captured. As stated above, smoking and BMI may be proxies for socioeconomic status, physical activity, and medication adherence, for example, and these were not measured.

Omega-3 status in patients with early RA receiving T2T is positively associated with increased odds of achieving DAS28 LDA at 1 year. The effect modification by smoking status on the association of BMI with treatment outcomes in early RA is novel and requires exploration with other data sets. If it is supported by further studies, it could inform lifestyle counseling for patients with RA. At this time, it is clear that modifiable factors are associated with RA outcomes, and the impact of potentially modifiable factors should be taken into account in the routine care of patients with RA.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Proudman had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Brown, James, Cleland, Proudman.
Acquisition of data. Brown, Lee, Hill, Wechalekar, Stavrou, Cleland, Proudman.
Analysis and interpretation of data. Metcalf, Bednarz, Spargo, James, Proudman.

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