The change in dietary inflammatory index score is associated with control of long-term rheumatoid arthritis disease activity in a Japanese cohort: the TOMORROW study

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Research article

Keywords: Inflammation, Nutrition, Diet, Lifestyle, Rheumatoid arthritis

Posted Date: October 7th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-84976/v1

Version of Record: A version of this preprint was published at Arthritis Research & Therapy on April 8th, 2021. See the published version at https://doi.org/10.1186/s13075-021-02478-y.

Abstract

Background The dietary inflammatory index (DII®), a quantitative measure of the inflammatory potential of daily food and nutrient intake, and associations between a variety of health outcomes have been reported. However, to the best of our knowledge, there is no report which investigated the association between rheumatoid arthritis (RA) and DII. Therefore, we investigate the association between the DII and disease activity in patients with RA.

Methods We performed a cross-sectional and longitudinal analysis using 6 years of data (from 2011 to 2017) in TOMORROW, a 10-year prospective cohort study consisting of 208 RA patients and 205 gender- and age-matched non-RA controls recruited in 2010. Disease activity of RA patients was assessed annually using DAS28-ESR (disease activity score 28 joints and the erythrocyte sedimentation rate) as a composite measure based on arthritic symptoms in 28 joints plus global health assessment and ESR. Dietary data were collected in 2011 and 2017 using the brief-type self-administered diet history questionnaire (BDHQ). Energy-adjusted DII (E-DII™) score was calculated using 26 nutrients derived from the BDHQ. Data were analyzed with two-group comparisons, correlation analysis, and multivariable logistic regression analysis.

Results RA patients had significantly higher E-DII (pro-inflammatory) score compared to controls both in 2011 and 2017 ($p < 0.05$). E-DII score showed statistically significant negative correlation with age in RA patients, both in 2011 ($r = -0.20$) and 2017 ($r = -0.23$). Controls also showed a similar trend. In RA patients, E-DII score was not a factor associated with disease activity in a cross-sectional analysis. However, decline in E-DII (anti-inflammatory change) score was a factor that increased the odds of maintaining low disease activity (DAS28-ESR ≤ 3.2) or less for 6 years (OR: 4.33, 95%CI: 1.66-11.29, $p = 0.003$).

Conclusions E-DII score was high in RA patients and lowering E-DII score over time may be beneficial in controlling disease activity in patients with RA.

Trial registration UMIN Clinical Trials Registry, http://www.umin.ac.jp/ctr/, UMIN000003876. Registered 7 Aug 2010 - Retrospectively registered.

Background

Rheumatoid arthritis (RA) is an autoimmune disease that primarily results in destruction of joints and bones, and is caused by chronic inflammation. RA is triggered locally and systemically, and by the over-activation of immune cells and joint synovial cells. Reducing inflammation is one of the key strategies for treating RA [1]. RA is mainly treated by pharmacotherapy, which includes disease-modifying antirheumatic drugs (DMARDs), glucocorticoid, and biological or targeted synthetic DMARDs (b-, tsDMARDs) which are molecularly targeted drugs suppressing the immune mediators or JAK-STAT (Janus activated kinase-signal transducers and activators of transcription) pathway, a downstream signaling pathway in cytokine-bound cells. Suppression of various points of inflammation is important for controlling disease activity of RA [2].

The anti-inflammatory function of some nutrients has been reported in a variety of basic and clinical investigations and interventional studies, and many studies in patients with RA have been reported [3]. Classically, it has been reported that the intake of anti-inflammatory fatty acids such as n-3 fatty acids and γ-linolenic acid in RA patients has been shown to reduce inflammation and disease activity [4]. We reported that intake of monounsaturated fatty acids may be associated with suppression of disease activity in patients with RA [5]. In addition, there is a report that the intake of micro-nutrients such as curcumin (present in turmeric), which has anti-inflammatory effects, can reduce disease activity in RA patients [6]. Therefore, dietary therapy focusing on the function of nutrients in RA patients is attracting attention [7]. Dietary and nutritional therapies to suppress inflammation in RA patients include therapies that focus only on single nutrients, and dietary patterns reflecting differences in combinations of foods and nutrients [8]. In dietary-pattern interventions, it has been reported that a Mediterranean diet pattern that focuses on increasing consumption of plant foods and reducing intake of animal products has a beneficial effect on disease activity [9, 10]. Likewise, an anti-inflammatory dietary pattern that is rich in anti-inflammatory nutrients including n-3 fatty acids, antioxidant nutrients such as vitamins C and E, fiber and probiotics that can improve intestinal flora, also has a beneficial effect on disease activity [11].

Though there are several tools to evaluate dietary patterns, the dietary inflammatory index (DII®) focuses specifically on the effects of food and nutrients on inflammation [12]. The DII is a literature-derived index calculated from various food and nutrients that have been shown to have an effect on inflammation; and associations between the DII and a variety of outcomes have been reported, including risk of developing and dying of heart disease [13], colorectal cancer incidence [14], and overall cancer mortality [15]. However, to the best of our knowledge, there is no report which investigated the association between RA and DII. This study analyzed data within a prospective cohort study with the aim of comparing DII scores between RA patients and gender and age-matched controls, exploring factors affecting DII, and examining the association of DII with RA disease activity.

Methods

Study population

In this study, we used data from the TOMORROW (Total management of risk factors in rheumatoid arthritis patients to lower morbidity and mortality) study, a 10-year prospective cohort study consisting of 208 RA patients and 205 gender- and age-matched non-RA controls that began in 2010 at Osaka City University Hospital in Osaka, Japan [5]. The study concept and details of the design, including recruitment methods of the control subjects, were as reported in previous reports [5, 16, 17]. Briefly, in the TOMORROW study, approximately 50% of RA patients using bDMARDs were recruited to investigate the effect of bDMARDs on a variety of outcomes, and disease activity was assessed in annual surveys. In this study, we used six years of data from 2011 to 2017 because we administered nutrition surveys in two of these years (i.e., 2011 and 2017). After excluding subjects who had died, who wished to withdraw consent, or for whom relocation made it difficult to continue the study, there were 202 subjects with RA and 202 controls in 2011, and 179 RA patients and 187 controls in 2017.

This study was conducted after written informed consent was obtained from all study subjects in accordance with the Declaration of Helsinki, and the research protocol was approved by the Ethics Committee of the Osaka City University Hospital (Approval number; 1660). This study was registered as clinical observation one in University Hospital Medical Information Network; UMIN000003876.

Subject's basic characteristics

Anthropometric measurements were collected as previously reported [5]. Smoking and drinking history was based on 2010 data; i.e., at the time of enrollment, and medication for RA was surveyed annually.

Food And Nutrients Intake Status

Daily dietary and nutrient intake status were assessed in 2011 and 2017 using the brief-type self-administered diet history questionnaire (BDHQ), a validated instrument which queries the intake of 60 foods from which about 100 nutrients are estimable [18, 19]. As previously reported, in 202 RA patients and controls in 2011, one subject whose intake was less than 600 kcal/day (deemed to be a gross underestimate) was excluded from each group [5]. Therefore, data from 201 patients and 201 control subjects were finally included in each analysis in 2011. In 2017, 177 RA patients and 183 controls were included in the final analysis; i.e. after excluding data from two patients and four controls whose intakes were underestimated in either 2011 or 2017.

Clinical Assessment

Disease activity was assessed using the DAS28-ESR (Disease activity scores in 28 joints using erythrocyte sedimentation rates), which is a composite score derived from four components to evaluate the disease activity of RA [20]. The four components are; 1) the number of swollen joints out of the 28 joints assessed, 2) the number of tender joints out of the 28, 3) ESR as a marker of systemic inflammation and 4) global assessment of health indicated by a visual analogue scale. Disease activity was classified according to the European League against Rheumatic Diseases (EULAR) disease activity classification, with DAS28-ESR 3.2 or less as low disease activity (LDA) [21]. Thirty-five patients with a DAS28-ESR of 3.2 or less on all assessments across study years during the 6-year period from 2011 to 2017 were assigned to be in LDA group. Activity of daily living (ADL) was assessed using the modified health assessment questionnaire disability index (mHAQ-DI) [22]. The degree of change in disease activity between 2011 and 2017 was assessed based on the EULAR response [23], and patients who showed moderate and good responses were assigned to responder. Specifically, a DAS of 5.1 or lower in 2011 and improved more than 0.6 in 2017 was evaluated as a responder, and a DAS of greater 5.1 in 2011 and improved more than 1.2 in 2017 was evaluated as a responder.

Calculation of DII

DII score was calculated based on the BDHQ data. The DII may be calculated from the intake of up to 45 food parameters (i.e. foods and nutrients) [12]. However, only 26 items (alcohol, thiamine, riboflavin, vitamin B6, vitamin B12, beta carotene, carbohydrate, cholesterol, energy, fat, fiber, folic acid, iron,

magnesium, monounsaturated fatty acids, niacin, n-3 polyunsaturated fatty acids; PUFA (polyunsaturated fatty acid), n-6 PUFA, protein, total PUFA, saturated fatty acids, vitamin A, vitamin C, vitamin D, vitamin E, zinc) were available from the BDHQ and were used for calculating the DII. A higher, more positive, DII score indicates a more pro-inflammatory diet, while a lower DII score indicates a more anti-inflammatory diet [12]. Because total energy intake affects overall nutrient intake, energy-adjusted DII (E-DII™) scores were calculated using the density approach, and these were used in this study analyses. This required employing a world comparative database also adjusted for energy intake [25]. All analyses reported here are based on the E-DII. The change value in E-DII from 2011 to 2017 was presented as ΔE-DII calculated as follows: ΔE-DII = E-DII in 2017 – E-DII in 2011.

Statistical analysis

The Statistical Package for Social Sciences (SPSS) software version 25.0 (IBM Corp, Armonk, NY, USA) was used for all statistical analyses. The normality of the data was assessed with the Shapiro-Wilk test. Data comparison between the two groups was performed by Mann–Whitney U test or Wilcoxon signed-rank test. The statistical differences in the categorical data were tested by Chi-square test or Fisher's exact test. The effect size was calculated as r for numeric data and Cramer's V for categorical data. Spearman's rank-order correlation coefficient was calculated. The covariates used in multivariable logistic regression analysis were examined using the forced-entry method. In an analysis of all cases examining the association between being RA and having an E-DII score negative, the presence of RA, gender, and age (cut off value was overall median age; years < 61 or years ≥ 61) were selected as entry items. In the cross-sectional analysis of the association between disease activity and E-DII score in RA patients, we included gender, age, body mass index (BMI) by group (BMI < 18.5 kg/m^2, 18.5 kg/m^2 ≤ BMI < 25 kg/m^2, 25 kg/m^2 ≤ BMI), smoking (with or without smoking within 1 year), anti-cyclic citrullinated peptide (CCP) antibody (positive or negative), and E-DII score (positive or negative - no subject had a score of zero). Drinking history was not included in the analysis because alcohol consumption was included in computing the E-DII score. The use of bDMARDs in each year was included because, of the medications for RA, bDMARDs are the ones that are most likely to affect disease activity, based on the algorithms for medication in RA patients [2].

In the longitudinal analysis, we tried to identify the factors to keep LDA or less during 6 years. Because 35 patients were able to maintain their disease severity at LDA or less during the 6-year interval, we included gender, age, bDMARDs use, and ΔE-DII score. P values less than 0.05 (2-tailed) were considered statistically significant.

Results

Comparison of E-DII score in RA patients and controls

Compared to controls, RA patients had significantly higher E-DII score both in 2011 and 2017 (Fig. 1A). E-DII score was lower in both RA patients ($p = 0.09$) and controls ($p < 0.05$) in 2017 compared to 2011. In

multivariable logistic regression analysis, having RA was a factor that appeared to be associated with higher odds of having a positive (pro-inflammatory) E-DII score (OR: 1.57; 95%CI: 0.97–2.65, $p = 0.07$) with marginal significance in 2017 (Fig. 1B), although it didn't even approach marginal significance in 2011 ($p = 0.19$). Age was a factor significantly associated with a lower odds ratio of having a positive E-DII score both in 2011 and 2017. Being male was significantly associated with a higher odds ratio of having a positive E-DII score both in 2011 and 2017.

The Association Between E-DII Scores And Age

Because E-DII score were lower in 2017 compared to 2011 in both RA patients and controls, and because being older was significantly associated with lower E-DII score, we examined the association between E-DII score and age in RA patients and controls in 2011 and 2017, respectively. E-DII score in 2011 and 2017 showed a significant negative correlation with age in both RA patients and controls (Fig. 2).

Comparison of clinical parameters between the low and high E-DII score groups in RA patients

The basic characteristics of RA patients and controls according to E-DII in 2011, are shown in Tables 1 and 2, respectively. Because RA patients are characterized by high E-DII scores, we divided RA patients into two groups, E-DII score positive (pro-inflammatory) and negative (anti-inflammatory), and compared RA-related laboratory data (Table 1). The results showed that the percentage of women, RA duration, and DAS28-ESR were significantly higher, and BMI, number of patients who have a drinking habit, were significantly lower in the E-DII score negative group than in the positive group. Age was higher in E-DII score negative group than in the E-DII positive group. In controls, similar results were obtained with respect to gender and drinking habits (Table 2).

Table 1 Subject characteristics in two groups according to E-DII score in 2011 in RA patients

	E-DII score negative (n = 126)	E-DII score positive (n = 75)	p value	effect size
Women	116 (92)	54 (72)	<0.001	0.27
Age (years)	62.0 (16.0)	59.0 (24.0)	0.06	0.13
Height (cm)	154.1 (10.6)	157.3 (13.3)	0.05	0.14
Weight (kg)	52.2 (13.2)	56.0 (15.5)	0.002	0.21
BMI (kg / m^2)	21.8 (5.1)	23.0 (5.4)	0.02	0.16
Smoking	30 (24)	28 (37)	0.05	0.14
Drinking habits	45 (36)	43 (57)	0.003	0.21
RF (IU / ml)	48 (107)	41 (83)	0.44	0.06
RF positive	95 (75)	55 (73)	0.74	0.02
Anti-CCP (U / ml)	61.8 (87.2)	81.2 (90.4)	0.55	0.04
Anti-CCP positive	102 (81)	67 (89)	0.16	0.11
RA duration (years)	12.2 (16.9)	8.1 (12.1)	0.03	0.15
csDMARDs user	115 (91)	69 (92)	1.00	0.01
bDMARDs user	71 (56)	45 (60)	0.66	0.04
GC user	29 (23)	25 (33)	0.14	0.11
ESR (mm / hr)	24 (26)	15 (19)	0.002	0.22
MMP-3 (ng / ml)	60.8 (62.9)	76.2 (95.8)	0.07	0.13
hs-CRP (mg / l)	0.12 (0.36)	0.10 (0.45)	0.94	0.01
mHAQ-DI	0.25 (0.88)	0.38 (1.00)	0.49	0.05
DAS28-ESR	3.6 (2.1)	3.2 (1.8)	0.02	0.17

In Age, Height, Weight, BMI, RF, CCP, RA duration, ESR, MMP-3, hs-CRP, mHAQ-DI, DAS28-ESR, data are showed as median (inter quarter range) and other categorical data are shown as patient number (%). There was no patient with an E-DII score of zero.

bDMARDs biological disease-modifying antirheumatic drugs, *BMI* body mass index, *CCP* anti-cyclic citrullinated peptide antibody, *csDMARDs* conventional synthetic disease-modifying antirheumatic drugs, *DAS28-ESR* disease activity scores in 28 joints using erythrocyte sedimentation rates, *E-DII* energy adjusted dietary inflammatory index, *GC* glucocorticoid, *hs-CRP* high sensitivity C-reactive protein, *mHAQ-DI* modified health assessment questionnaire disability index, *MMP* matrix metalloproteinase, *RA* rheumatoid arthritis, *RF* rheumatoid factor

Table 2 Subject characteristics in two groups according to E-DII in 2011 in Control

	E-DII score negative (n = 138)	E-DII score positive (n = 63)	*p* value	effect size
Women	124 (90)	45 (71)	0.002	0.23
Age (years)	61.0 (17.0)	57.0 (17.0)	0.001	0.24
Height (cm)	154.9 (9.0)	161.3 (11.5)	<0.001	0.31
Weight (kg)	53.5 (11.5)	58.7 (14.3)	0.004	0.20
BMI (kg / m^2)	22.2 (4.1)	22.7 (4.5)	0.30	0.07
Smoking	16 (11)	13 (21)	0.13	0.12
Drinking habits	62 (45)	43 (68)	0.002	0.22
RF (IU / ml)	3 (0)	3 (3)	0.20	0.09
RF positive	14 (10)	8 (13)	0.63	0.04
Anti-CCP (U / ml)	0.6 (0.1)	0.6 (0.3)	0.049	0.14
Anti-CCP positive	4 (3)	1 (2)	1.00	0.04
ESR (mm / hr)	9 (9)	7 (8)	0.03	0.15
MMP-3 (ng / ml)	42.0 (23.1)	45.4 (29.8)	0.51	0.05
hs-CRP (mg / l)	0.03 (0.04)	0.03 (0.06)	0.51	0.05

In Age, Height, Weight, BMI, RF, CCP, ESR, MMP-3, hs-CRP, data are showed as median (inter quarter range) and other categorical data are shown as subject number (%). There was no subject with an E-DII score of zero.
BMI body mass index, *CCP* cyclic citrullinated peptide antibody, *E-DII* energy adjusted dietary inflammatory index, *hs-CRP* high sensitivity C-reactive protein, *MMP* matrix metalloproteinase, *RF* rheumatoid factor

Association Between DII And Disease Activity In RA Patients

The DAS28-ESR was higher in the E-DII score negative group than the positive group. Because factors such as gender and age also may affect disease activity, we examined the association between E-DII score and DAS28-ESR in detail. We classified RA patients as DAS28-ESR 3.2 or less or higher than 3.2, and the association between positive and negative of E-DII score adjusted by basic patient characteristics (gender, age, BMI, bDMARDs use, smoking, and anti-CCP antibody positivity) was examined by multivariable logistic regression analysis. A cross-sectional analysis conducted using 2011 and 2017 data showed no significant association between DAS28-ESR and E-DII score (data not shown). We also examined longitudinally the association of E-DII score and RA patients who had been able to maintain LDA or less for 6 years from 2011 to 2017, and adjusted for gender, age and bDMARDs use. Negative E-DII score in 2011 was associated with lower odds of maintaining LDA or less ($p = 0.06$) (Fig. 3A). When

dividing E-DII score in 2011 into quartiles, the lowest quartile was a significant factor for lower odds of maintaining LDA or less (p = 0.049) (Fig. 3B). The analysis focused on the change in E-DII score, from 2011 to 2017 (ΔE-DII). Negative ΔE-DII score (lower E-DII score in 2017 compared to 2011) was a significant factor (OR: 4.33, 95%CI: 1.66–11.29, p = 0.003) associated with LDA for 6 years (Fig. 4A). When ΔE-DII score was divided into quartiles, each of the items above was a potentially relevant factor when the lowest quartile was used as a reference (2nd ; p = 0.055, 3rd ; p = 0.005, highest quartile; p = 0.059) (Fig. 4B).

The degree of disease activity improvement from 2011 to 2017 was assessed according to the EULAR response, and the association of E-DII score in the 54 subjects with changes according to the EULAR response was examined using multivariable logistic regression analysis. There were no significant items, and the positive E-DII score in 2011 (OR: 1.47; 95% CI: 0.72–2.99, p = 0.29), and negative ΔE-DII score (OR: 0.95; 95% CI: 0.47–1.91, p = 0.88) also showed no significance.

Discussion

In the present study, we used the E-DII, which quantifies the inflammatory potential of diet based on reported intake and controlling for energy density of the diet. We investigated E-DII characteristics and their association with disease activity in RA patients, including comparison with non-RA controls. The results suggested that E-DII was higher (pro-inflammatory) in RA patients than in controls, and that the daily nutrient composition based on reported dietary intake and were more likely to trigger inflammation in RA patients. The results were the same at two separate time points, in 2011 and 2017. We also found that the odds of having a high E-DII score (pro-inflammatory) appeared to be higher in RA patients than in controls in 2017 (with marginal significance). These results might indicate that diet-associated inflammation may be related to the pathogenesis of RA. The association between E-DII and the onset of RA needs to be investigated in large prospective cohort studies of non-RA subjects to determine whether E-DII had any effect on the development of newly incident RA. A large prospective cohort study has examined the association between Empirical Dietary Inflammatory Pattern (EDIP) calculated from 18 foods and beverages and the development of RA. The results suggest that EDIP may be associated with the development of RA; albeit limited to subsets of both age and gender [26]. However, EDIP is based on reduced rank regression of food items commonly consumed in the US and hence cannot be generalized to all populations. Similar prospective studies using the E-DII will be needed in the future.

Our data showed that E-DII score was negatively correlated with age in both 2011 and 2017, and diets of older adults were more anti-inflammatory dietary. Older age also was a factor associated with lower the odds of a high E-DII score. In addition, E-DII was lower in 2017 compared to 2011, not only in RA but also in controls. These results suggest that aging may influence DII scores in the presence or absence of RA. The inverse relationship between age and DII score has been seen in other [27, 28], but not all populations [29–32]. A survey of Japanese residents aged 55 years and older reported that the proportion of people who subjectively perceive their health to be poor increases as they get older, and the proportion of people

who try to eat a well-balanced diet is higher [33]. This may have been one of the factors that influenced the association between age and E-DII.

In our analysis, being male was a factor significantly associated with a higher odds ratio of having a positive E-DII score both in 2011 and 2017. In the above-mentioned research in Japan, men were nearly 5–20% less likely than women to take care of their diet for their health [33]; this also depends on age, and this may be a factor that explains our result.

Because of the higher E-DII score in RA patients compared to controls, we examined the association of E-DII with parameters such as disease activity in RA by comparing the E-DII score positive group and the negative group. The E-DII score negative group had a higher DAS28-ESR; however, because they tended to have a higher proportion of women, a higher age, and lower percentage who had smoking habits and BMI than in the E-DII score positive group, we used multivariable logistic regression analysis to examine the association between disease activity and E-DII to adjust these basic characteristics. There was no significant association between DAS28-ESR and E-DII score in multivariable analyses that adjusted for these factors and for medication for RA in cross-sectional analysis. However, in the longitudinal analysis, positive E-DII score at the start of observation and lower E-DII score at 6 years compared to the start of observation were associated with maintaining LDA for 6 years. Although it is seemingly contradictory that a positive E-DII score at the start of the observation may lead to a long-term reduction in disease activity, this may suggest that there is room to lower E-DII for patients with a positive E-DII score and who are being managed relatively well with less than LDA at the time of the study, and that interventions to lower E-DII score may subsequently maintain LDA in the long term. On the other hand, changes in disease activity at the start of observation and 6 years later according to the degree of EULAR response and E-DII showed no significant association. This result might indicate the impact of E-DII on controlling disease activity may be less important and may contribute to maintaining disease activity in patients whose base disease activity is relatively well maintained. However, there are currently few reports of control of long-term disease activity and changes in diet and nutrient intake in patients with RA. So, the results of this study could be used in future intervention studies. In fact, a randomized controlled trial (RCT) has been reported that verified that switching dietary content to a pattern that is expected to have anti-inflammatory effects suppressed disease activity after 10 weeks [11]. Thus, more long-term disease intervention studies are warranted.

Although it has been reported that a vegetarian diet; i.e., excluding animal products improves disease activity in RA patients, there are issues that need to be resolved, such as unintended weight loss due to reduced energy intake and difficulty in adhering to the diet [34]. Although the number of dropouts due to difficulties in adherence to the diet is not described in the crossover RCT dietary intervention described above, it is not necessary to completely restrict animal products; thus the anti-inflammatory diet may not appear drastically different from ones normal daily diet [11] and may be relatively easy to continue. In the diet of patients with RA, it is important to note that there are few side effects and high compliance with the diet in the subjects, therefore providing an ideal situation in which to validate long-term effects, and dietary interventions focusing on anti-inflammatory effects.

Despite its strengths as a prospective cohort, the limitations of this study need to be considered. First, this study was conducted at one institution and the number of subjects was relatively small. Only a small number of patients had been under control for 6 years with LDA or less (n = 35, 19.8%). Therefore, a prospective multicenter, cohort study with a large number of patients is desirable in order to increase statistical power. Second, there were nearly four times as many women as men in this study. Although epidemiologic evidence indicates that women have a higher prevalence of RA, research studies that focus on men also are needed. Third, the E-DII score is calculated from self-reported intake. So, there are limitations in both the nature of self-report and the nutrient database on which the values are calculated. Fourth, this study suggests that E-DII may affect the maintenance of disease activity, studies also are needed to examine the relationship between the intake of each nutrient or food alone, which is necessary for the calculation of E-DII, and disease activity in RA patients.

Conclusions

E-DII score was high in RA patients and lowering E-DII score over time may be beneficial in controlling disease activity.

List Of Abbreviations

ADL: activity of daily living; BDHQ: brief-type self-administered diet history questionnaire; bDMARDs: biological disease-modifying antirheumatic drugs; BMI: body mass index ; CCP: cyclic citrullinated peptide ; CI: confidence interval; csDMARDs: conventional synthetic disease-modifying antirheumatic drugs; DAS28-ESR: disease activity scores in 28 joints using erythrocyte sedimentation rates; E-DII: energy adjusted dietary inflammatory index; EULAR: European League against Rheumatic Diseases; GC: glucocorticoid,; hs-CRP: high sensitivity C-reactive protein; JAK-STAT: Janus activated kinase-signal transducers and activators of transcription; LDA: low disease activity; mHAQ-DI: modified health assessment questionnaire disability index; MMP: matrix metalloproteinase; OR: odds ratio; PUFA: polyunsaturated fatty acid; RA: rheumatoid arthritis; RF: rheumatoid factor; TOMORROW: total management of risk factors in rheumatoid arthritis patients to lower morbidity and mortality; tsDMARDs: targeted synthetic disease-modifying antirheumatic drugs

Declarations

Ethics approval and consent to participate

This study was conducted after written informed consent was obtained from all study subjects in accordance with the Declaration of Helsinki, and the research protocol was approved by Ethics Committee of the Osaka City University Hospital (Approval number; 1660)

Consent for publication

Consent for publication, using data from the TOMORROW study, has been obtained from all study subjects

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

YS, MT, KM, and DH declare that they have no competing interests.

YM: Grant/research support from: Yamada Research Grant

NS is an employee of Connecting Health Innovations LLC (CHI).

TO: Grant/research support from: AbbVie, Eisai, Mitsubishi Tanabe Pharma Corporation and Nipponkayaku, Speakers bureau: AbbVie, Asahikasei, Astellas Pharma Inc, Ayumi Pharmaceutical, Bristol-Myers Squibb, Chugai Pharmaceutical, Daiich Sankyo, Eisai, Janssen, Lilly, Mitsubishi Tanabe Pharma Corporation, Novartis Pharma, Ono Pharmaceutical, Pfizer, Sanofi, Takeda Pharmaceutical, Teijin Pharma and UCB

KI: Grant/research support from: Janssen Pharmaceutical K.K., Astellas Pharma Inc., Sanofi K.K., Abbvie GK, Takeda Pharmaceutical Co. Ltd., QOL RD Co. Ltd., Mitsubishi Tanabe Pharma, Ono Pharmaceutical Co. Ltd., Eisai Co., Ltd., Speakers bureau: Daiichi Sankyo Co. Ltd., Mitsubishi Tanabe Pharma, Janssen Pharmaceutical K.K., Astellas Pharma Inc., Takeda Pharmaceutical Co. Ltd., Ono Pharmaceutical Co. Ltd., Abbvie GK, Pfizer Inc., Eisai Co., Ltd., Chugai Pharmaceutical Co., Ltd.

JRH owns controlling interest in Connecting Health Innovations LLC (CHI), a company that has licensed the right to his invention of the dietary inflammatory index (DII®) from the University of South Carolina in order to develop computer and smart phone applications for patient counseling and dietary intervention in clinical settings.

TK: Grant/research support from: AbbVie, Astellas Pharma Inc, Bristol-Myers Squibb, Chugai Pharmaceutical, Eisai, Janssen, Lilly, Mitsubishi Tanabe Pharma Corporation, MSD, Ono Pharmaceutical, Pfizer, Roche, Takeda Pharmaceutical, Teijin Pharma, and UCB, Speakers bureau: AbbVie, Astellas Pharma Inc, Bristol-Myers Squibb, Chugai Pharmaceutical, Eisai, Janssen, Lilly, Mitsubishi Tanabe Pharma Corporation, MSD, Ono Pharmaceutical, Pfizer, Roche, Takeda Pharmaceutical, Teijin Pharma, and UCB.

Funding

This study has not received specific funding from any source.

Authors' contributions

YM statistically analyzed data and made the Tables and Figures. YM, NS, DH, JRH, TK were a major contributor in writing the manuscript and interpretation of data. NS, JRH calculated E-DII score. YS, MT, TO, KM, KI, TK contributed to the conception and design of the study, and acquisition of data. All authors read and approved the final manuscript.

Acknowledgements

We would like to thank the Center for Drug & Food Clinical Evaluation, Osaka City University Hospital, Atsuko Kamiyama, and Tomoko Nakatsuka for management of the study and data collection and cleaning, and for their support in conducting this study. We would also like to thank all study participants.

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Figures

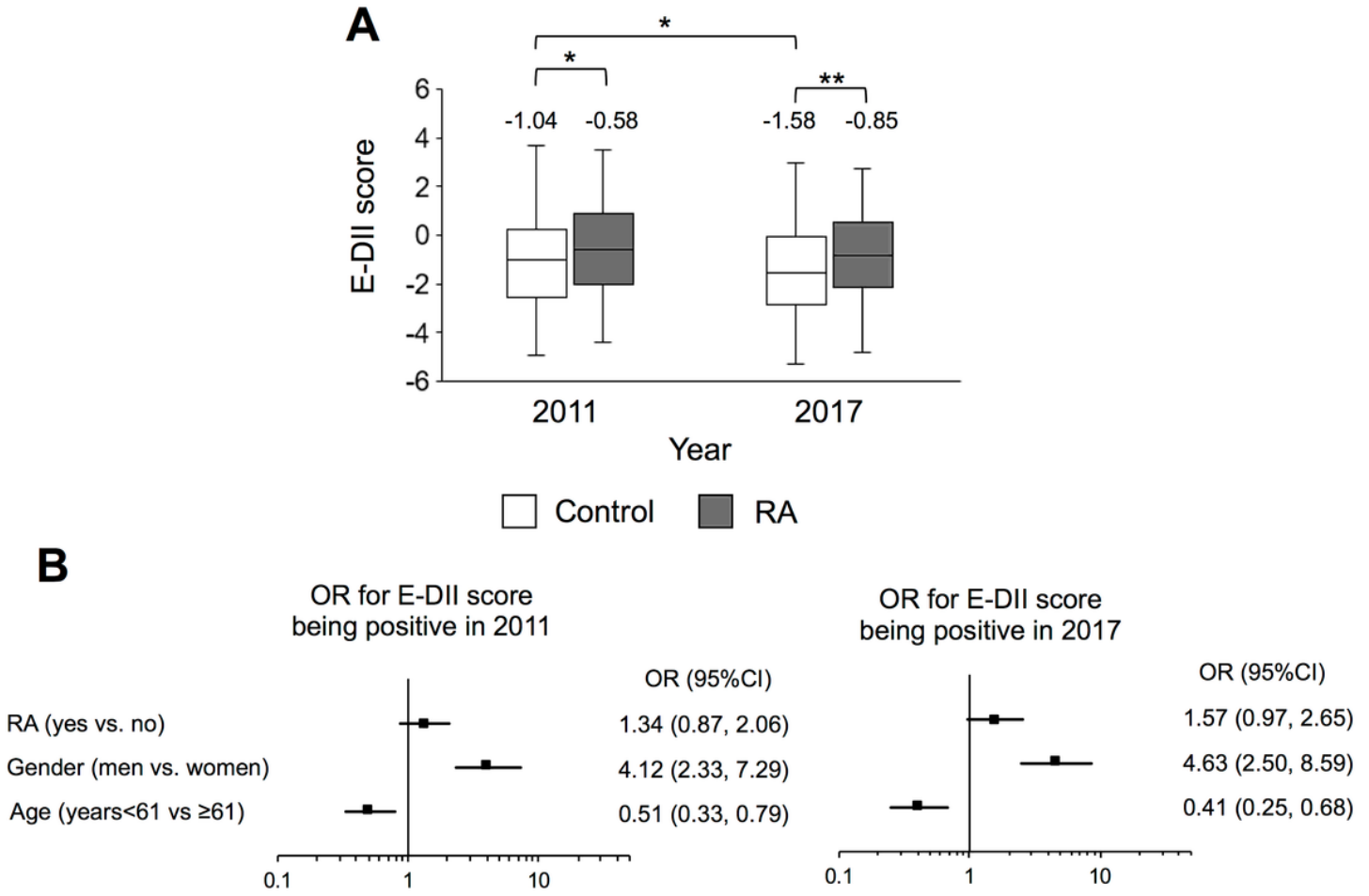

Figure 1

Figure 1

E-DII in control and RA patients and the effect of RA on E-DII score A: Comparison of E-DII between controls (white) and RA patients (grayscale) in 2011 and 2017. The data are presented as boxplots. **; p <0.01. *; p <0.05. Effect size for each statistic; Control vs RA: in 2011 = 0.13, in 2017 = 0.16. 2011 vs 2017: Control = 0.16, RA = 0.12. The figures shown above the boxplots are the median values. B: Forest plot of the odds ratio for E-DII score being positive calculated by multivariable logistic regression analysis The forced-entry method was used for the three covariates shown in the figure. Left panel: data in 2011, right panel: data in 2017. The results show the odds for E-DII score positive. The odds for RA was shown as odds for RA (i.e., Control as referent), the odds for gender was shown as odds for men (i.e., women as referent), and the odds for age was shown as odds for years ≥ 61 (i.e., years < 61 as referent). CI confidence interval, E-DII energy adjusted dietary inflammatory index, OR odds ratio, RA rheumatoid arthritis

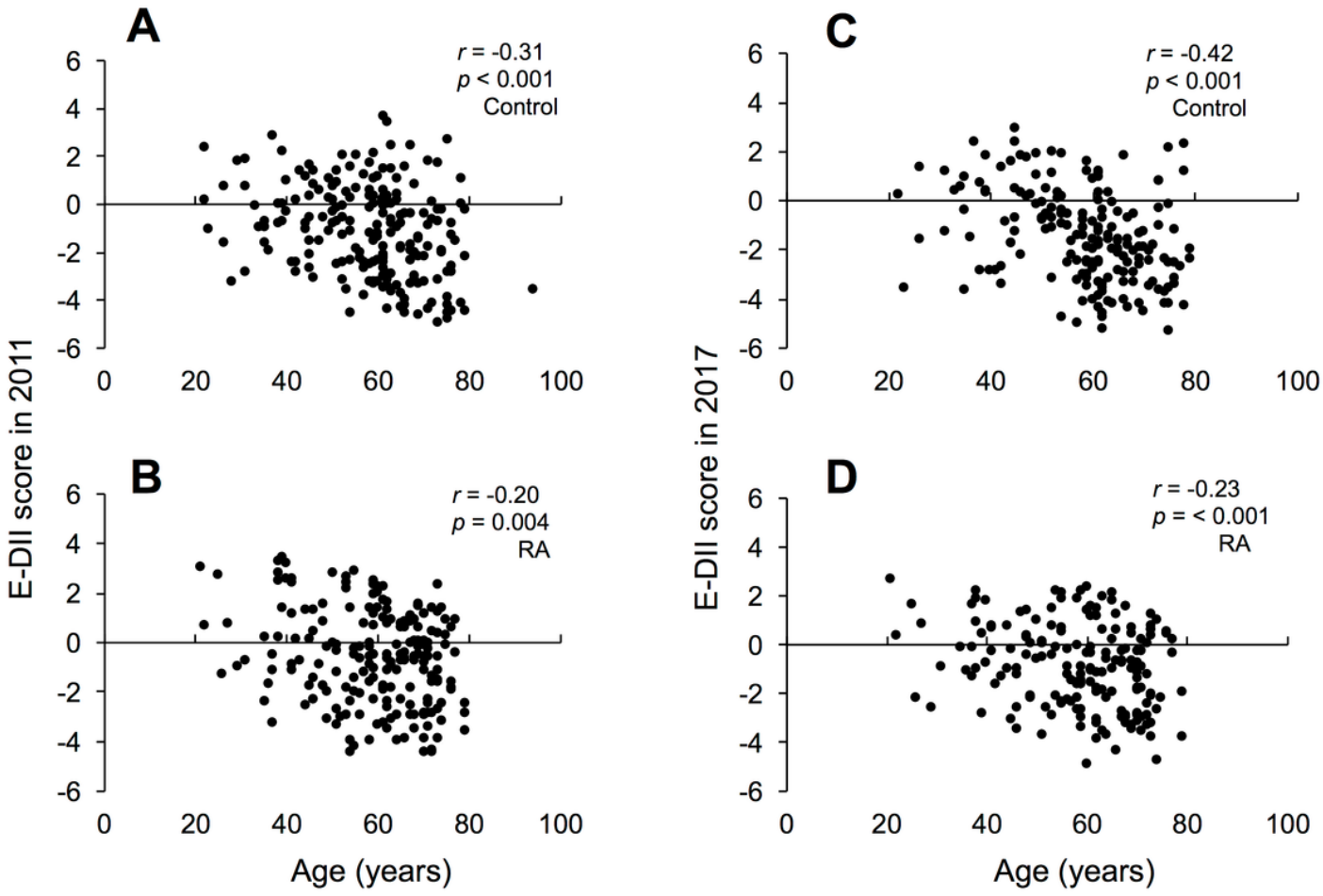

Figure 2

Figure 2

Scatter plots of E-DII and age in both control and RA patient groups A: E-DII and age (years) in controls in 2011 B: E-DII and age (years) in RA patients in 2011 C: E-DII and age (years) in controls in 2017 D: E-DII and age (years) in RA patients in 2017 The correlation coefficient was calculated as Spearman's rank-order correlation coefficient. E-DII energy adjusted dietary inflammatory index, RA rheumatoid arthritis

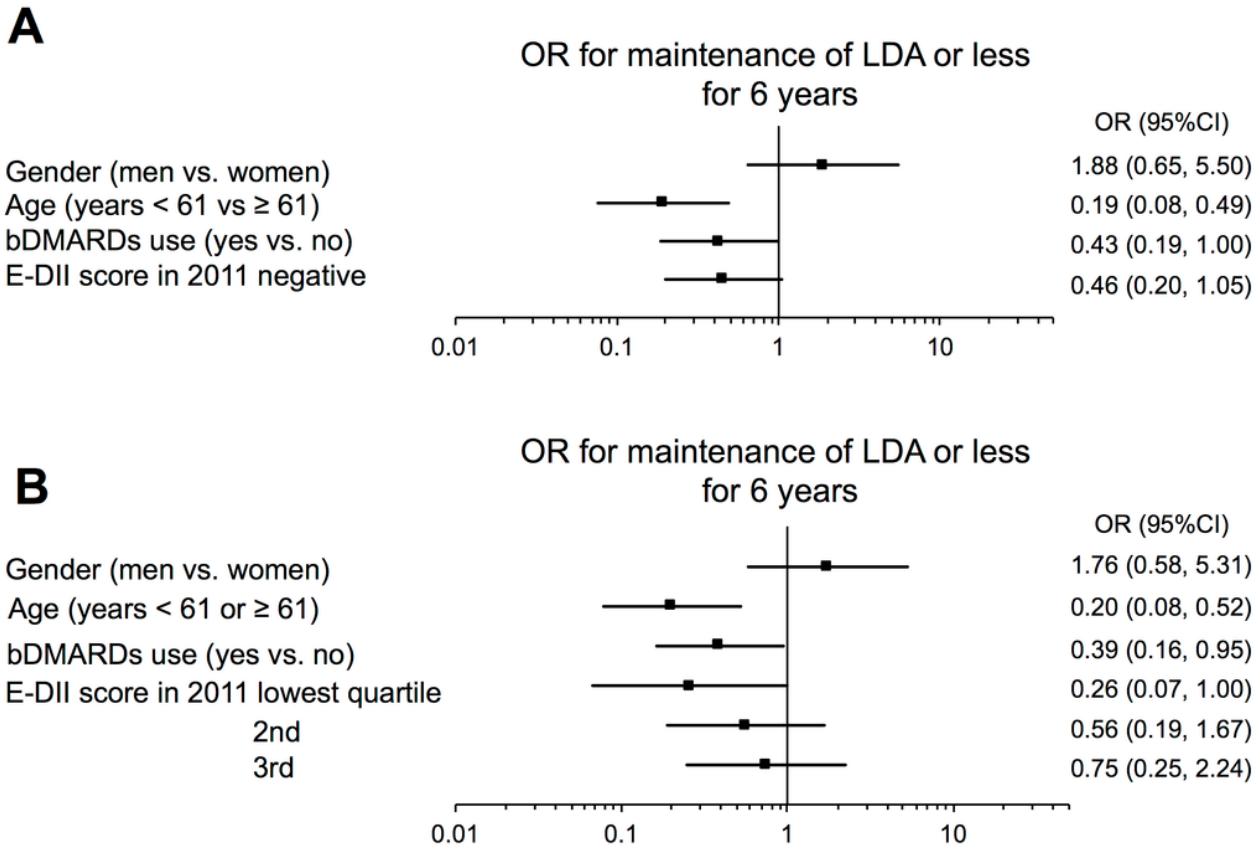

Figure 3

Figure 3

The effect of E-DII in 2011 on maintenance of LDA or less over 6-year period. Data were analyzed with multivariable logistic regression analysis, and results were shown as forest plot of the odds ratio for maintenance low disease activity (LDA; DAS28-ESR≦3.2) or less for a 6-year period from 2011 to 2017. The forced-entry method was used for the four covariates shown in the figure. The odds for gender was shown as odds for men (i.e., women as referent), and the odds for age was shown as odds for years ≥ 61 (i.e., years < 61 as referent). A: E-DII score was divided into positive and negative, B: E-DII score was divided into quartiles (with highest E-DII as referent). bDMARDs biological disease-modifying antirheumatic drugs, CI confidence interval, DAS28-ESR disease activity score with 28 joint using erythrocyte sedimentation rate, E-DII energy-adjusted dietary inflammatory index, OR odds ratio

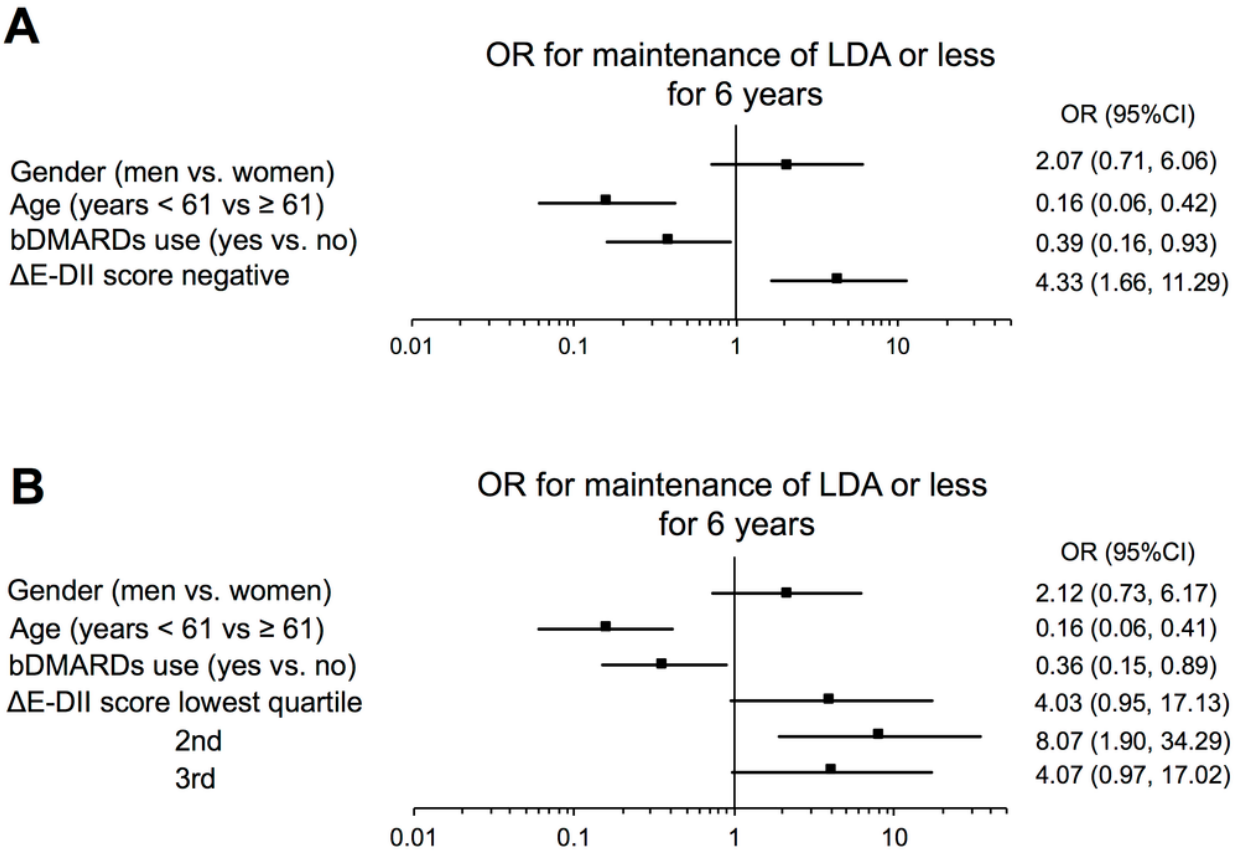

Figure 4

Figure 4

The effect of changes in E-DII on maintenance of LDA or less over 6-year period. Data were analyzed with multivariable logistic regression analysis, and results were shown as forest plot of the odds ratio for maintenance low disease activity (LDA; DAS28-ESR≦3.2) or less for a 6-year period from 2011 to 2017. ΔE-DII indicates the change of the score from 2011 to 2017. The forced-entry method was used for the four covariates shown in the figure. The odds for gender was shown as odds for men (i.e., women as referent), and the odds for age was shown as odds for years ≥ 61 (i.e., years < 61 as referent). A: ΔE-DII score was divided by change value positive or negative, B: ΔE-DII was divided into quartile (with highest E-DII as referent). bDMARDs biological disease-modifying antirheumatic drugs, CI confidence interval, DAS28-ESR disease activity score with 28 joint using erythrocyte sedimentation rate, E-DII energy adjusted dietary inflammatory index, OR odds ratio