Semiquantified Noncalcified Coronary Plaque in Systemic Lupus Erythematosus

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Abstract

Objective—A major cause of morbidity and mortality in systemic lupus erythematosus (SLE) is accelerated coronary atherosclerosis. New technology (computed tomographic angiography) can measure noncalcified coronary plaque (NCP), which is more prone to rupture. We report on a study of semiquantified NCP in SLE.

Methods—Patients with SLE (n = 147) with no history of cardiovascular disease underwent 64-slice coronary multidetector computed tomography (MDCT). The MDCT scans were evaluated quantitatively by a radiologist, using dedicated software.

Results—The group of 147 patients with SLE was 86% female, 70% white, 29% African American, and 3% other ethnicity. The mean age was 51 years. In our univariate analysis, the major traditional cardiovascular risk factors associated with noncalcified plaque were age (p = 0.007), obesity (p = 0.03; measured as body mass index), homocysteine (p = 0.05), and hypertension (p = 0.04). Anticardiolipin (p = 0.026; but not lupus anticoagulant) and anti-dsDNA (p = 0.03) were associated with higher noncalcified plaque. Prednisone and hydroxychloroquine therapy had no effect, but methotrexate (MTX) use was associated with higher noncalcified plaque (p = 0.0001). In the best multivariate model, age, current MTX use, and history of anti-dsDNA remained significant.

Conclusion—Our results suggest that serologic SLE (anti-dsDNA) and traditional cardiovascular risk factors contribute to semiquantified noncalcified plaque in SLE. The association with MTX is not understood, but should be replicated in larger studies and in multiple centers.

Key Indexing Terms

SYSTEMIC LUPUS ERYTHEMATOSUS; CARDIOVASCULAR DISEASE; RISK FACTORS; COMORBIDITY

Cardiovascular disease, specifically from accelerated premature atherosclerosis, is a major cause of morbidity and mortality in systemic lupus erythematosus (SLE)[1]. Patients with SLE are 2 to 9 times more likely than the general population to have myocardial infarctions[2,3,4].

The pathogenesis is multifactorial, including traditional cardiovascular risk factors, but also corticosteroids and inflammatory pathways[5,6,7,8].

Coronary calcium correlates well with the coronary atherosclerotic plaque burden. A report of the American College of Cardiology Foundation stated that helical computed tomography (CT) measurement of coronary artery calcium is recommended in patients with intermediate cardiovascular disease risk[9]. We have previously shown that age, body mass index (BMI), and diabetes mellitus are associated with coronary calcium in SLE[10]. Several other studies have shown more frequent and severe coronary artery calcification in SLE than in controls[11,12].

The risk of an acute cardiac event is affected by the presence, extent, location, characteristics, and metabolic activity of coronary atherosclerotic plaque[13,14,15]. Non-calcified plaque may be more metabolically active than highly calcified plaque and preliminary data suggest that the presence of noncalcified or only partially calcified plaques is associated with greater risk of unstable presentation[16]. Motoyama, *et al* reported that the appearance of low attenuation plaque on multidetector CT was an independent predictor of acute coronary syndrome events for a 2-year followup period[17]. Noncalcified plaque may be present in the absence of coronary artery calcification: in a Japanese study, the prevalence of noncalcified plaque was 11.1% in patients with no coronary artery calcium and 23.4% in patients with mild coronary artery calcium[18].

In our previous study of noncalcified plaque in SLE, we found that 54% of patients with SLE had noncalcified plaque[19]. The aim of our current study was to quantify the burden of noncalcified plaque in SLE and to determine the association of semiquantified noncalcified coronary plaque (NCP) with clinical and laboratory manifestations of SLE.

MATERIALS AND METHODS

The patients were part of the Hopkins Lupus Cohort, a prospective longitudinal study of lupus activity and outcomes. Patients were invited to join the Hopkins Lupus Cohort if they had a clinical diagnosis of lupus. Consecutive cohort members who met inclusion/exclusion criteria were invited to participate in our substudy. Exclusion criteria included a serum creatinine level 1.2 mg/dl, allergy to contrast material, pregnancy, or history of angina, myocardial infarction or stroke attributable to atherosclerotic disease. The study was approved by the Johns Hopkins University School of Medicine Institutional Review Board (NA_00002851). Written informed consent was obtained from each patient.

As part of the Hopkins Lupus Cohort Study, all patients had been seen quarterly since cohort entry for assessment of disease activity [by the Physician's Global Assessment, on a 0–3 visual analog scale, and the Safety of Estrogens in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI)][20]. The patients also had regular laboratory tests (complete blood count, erythrocyte sedimentation rate, serum creatinine, cholesterol, urinalysis, urine protein/creatinine ratio, C3, C4, and anti-dsDNA), and cardiovascular risk factors were assessed.

Image acquisition and evaluation

Computed tomographic angiography (CTA) was performed to determine the prevalence and amount of noncalcified plaque. Multidetector CT (MDCT) scans were evaluated semiquantitatively by a blinded radiologist, using dedicated software (Circulation, Siemens Medical Solutions)[21,22]. The Agatston scoring system was used to quantify coronary artery calcification[23]. The standard coronary CT protocol was used with administration of intravenous Visipaque 320 at an injection rate of 5 cc/s for 100 cc and an immediate 50 cc

saline chaser bolus at the same injection site[24]. The presence or absence of calcification in each coronary artery was assessed (right coronary, circumflex, left main, and left anterior descending). Overall semiquantitative plaque score was the sum of plaque severity multiplied by plaque composition, divided by the number of vessels examined. Severity was calculated as 0 = absent, 1 = mild, 2 = moderate, and 3 = severe for each coronary artery segment, according to the American Heart Association classification[25,26]. Plaque composition was calculated as 0 = 0%, 1 = 1%–25%, 2 = 26%–50%, 3 = 51%–75%, and 4 = 76%–100% in the noncalcified portion of coronary plaque for each coronary artery segment (Figure 1). Mild stenosis was defined as < 25%, moderate 25%–49%, and severe 50%. Coronary artery side branches were not included in the analysis for practical reasons, because the main branches have the bulk of disease. Similarly, noninterpretable coronary segments were excluded from our analysis. A segment was determined nonevaluable when either poor contrast-to-noise ratio or motion deemed detection of plaque impossible in the segment.

We tried to minimize partial volume by using thin-sliced pulse image processing, and we used specific construction kernels that decrease or minimize blooming of calcium. There might still be some residual effect. Kilovolt peak (kVp) was adapted per the patient's BMI. For patients with a BMI > 30: 120 kVp; < 30: 100 kVp; and < 20: 80 kVp.

Good to moderate interobserver agreement has been found in studies to detect noncalcified plaque[27,28]. To assess the degree of interobserver variability, we had a second physician read the scans for 9 patients (71 vessels). The correlation coefficient between the overall score between the 2 observers based on the 9 patients was 0.93. The kappa statistic for the assessment of noncalcified plaque (present or absent) in the 71 vessels was 0.42, which is considered moderate agreement.

Statistical analysis

All results for continuous variables were expressed as means, unless specified otherwise. Continuous variables were analyzed with a 2-sided t-test or ANOVA. Categorical variables were compared by Fisher's exact test. To the joint association between predictors and the quantity of noncalcified plaque, we fit multiple linear regression models. Statistical analysis was performed using SAS (v 9.2, SAS Institute).

RESULTS

One hundred forty-seven patients were enrolled. The mean age was 51 years (range 26–78 yrs). The group of patients was 86% female, 70% white, 27% African American, and 3% other ethnicity. The patients met these cumulative American College of Rheumatology revised classification criteria for SLE[29,30]: malar rash (56%), discoid rash (20%), photosensitivity (57%), oral ulcers (56%), arthritis (78%), serositis (49%), renal disorder (41%), neurologic disorder (7%), immunologic disorder (93%), and antinuclear antibody positivity (97%).

There was positive correlation between the Agatston score for coronary artery calcium and our semiquantified noncalcified plaque score (r = 0.29). This was mainly induced because almost all of those with a positive Agatston score had a positive noncalcified coronary plaque (NCP) score (45/47, 96%), while of those with an Agatston score of 0, only half (52/99, 53%) had a positive NCP score.

Table 1 shows semiquantified NCP and its association with demographic variables, traditional cardiovascular risk factors, serologic variables, and treatment. Semiquantified noncalcified plaque was strongly associated with age (p = 0.007). There was an association

with obesity (p = 0.031) and with hypertension (p = 0.041). Homocysteine had a borderline association (0.053).

Table 2 shows the association between semiquantified NCP and patient history of serologic results and past treatments. Only a history of anti-dsDNA was significantly associated with semiquantified noncalcified plaque (p = 0.03). Note, however, that based on the confidence interval, even in the absence of low p values, we cannot rule out the possibility of a moderate association between some of the predictors and mean NCP.

Table 3 shows the association of semiquantified NCP with serologies and treatments at the time of the NCP assessment. There was a strong association between semiquantified NCP and the current use of methotrexate (MTX; p = 0.0001), but not with other treatments [including prednisone, hydroxychloroquine, azathioprine, mycophenolate mofetil, or nonsteroidal antiinflammatory drugs (NSAID)]. There was also an association between current anticardiolipin antibodies (aCL) immunoglobulin G > 20 IU and semiquantified NCP (p = 0.026). Complement levels (C3, C4) and lupus anticoagulant (by dilute Russell's viper venom time) were not associated.

In the multivariate analysis (Table 4), semiquantified NCP was associated with age (p = 0.0001), current MTX use (p = 0.0005), BMI (p = 0.058), and anti-dsDNA history (p = 0.019). Hypertension, aCL, and homocysteine were no longer significant in the multivariate analysis.

DISCUSSION

To our knowledge, ours is the first study of semiquantified NCP in SLE. In our previous analysis of presence or absence of noncalcified plaque in SLE, we found that noncalcified plaque was present more often in those with higher disease activity, current immunosuppressive use, and current NSAID use[10]. Our current study enrolled a larger number of patients and used new technology to quantify the burden of noncalcified plaque.

We found that 53% of patients with SLE who had no coronary calcification had noncalcified plaque. Hausleiter, *et al* found noncalcified plaque in only 16% of patients with a coronary artery calcium score of 0, Cheng, *et al* 6.5%, Sosnowski, *et al* 12%, and Rubinshtein, *et al* 7%[31,32,33,34]. We believe that the higher prevalence in SLE represents the increased inflammatory burden of SLE.

Obesity has been shown to be associated with noncalcified plaque in the general population[35]. In one study, those with higher BMI were 2.76 times more likely to have noncalcified plaque compared with those with a normal BMI[36]. We have previously shown higher BMI to be associated with coronary artery calcium, as well[10]. Rupture of vulnerable plaque may be associated with metabolic syndrome, especially in the setting of abdominal obesity[37]. However, the association of obesity with semiquantified noncalcified plaque was only borderline in the multivariate model.

Our quantitative analysis of noncalcified plaque failed to show an association with measures of SLE disease activity, contrary to our previous qualitative analysis[19]. In our quantitative analysis, noncalcified plaque was not associated with either the physician global assessment or SELENA-SLEDAI. Several other studies have failed to show an association of SLE disease activity with subclinical measures of atherosclerosis[38,39,40]. A recent study of 139 patients with SLE found that a longer period with moderate to severe activity (as measured by SLEDAI) was associated with coronary artery calcium[41]. A Canadian study also found that disease activity as measured by SLEDAI was associated with risk for coronary artery

disease[42]. Finally, our own longitudinal study did find that disease activity, measured by SELENA-SLEDAI, increased the risk of cardiovascular events[4].

It is surprising that aCL, rather than the lupus anticoagulant, was the significant antiphospholipid antibody (aPL) in our models. The lupus anticoagulant has been a more specific predictor of thrombosis in multiple studies, including our own[43]. However, aCL[44] and other aPL[45], including low-density lipoprotein[46], have been associated with atherosclerotic cardiovascular disease in some studies. In our previous study of coronary artery calcium, however, aCL was not associated with atherosclerotic cardiovascular disease[10].

The finding of the association of noncalcified plaque with current MTX treatment is based on 9 SLE patients with noncalcified plaque who were taking MTX. In our study, the weekly MTX dosage ranged from 15 to 25 mg. At the time of the scan, the patients taking MTX had mild to moderate arthritis activity. In our study, 9 patients who were taking MTX did not differ from the other patients in their homocysteine levels. There are several studies in rheumatoid arthritis (RA) showing that MTX use is associated with a reduced risk of cardiovascular events[47,48,49,50]. In a study of 1240 patients with RA, deaths due to cardiovascular disease were reduced 70% by MTX[47]. Another large multinational study of 4363 patients with RA showed an 18% reduction in the risk of myocardial infarction in those treated with MTX for 1 year[48]. In a small study of 39 patients with RA, treatment with MTX decreased carotid intima-media thickness by 17.6%[51]. Our finding is counterintuitive, because MTX has antiinflammatory effects due to its capacity to release adenosine. This increases the expression of enzymes involved in metabolizing cholesterol and of transporters involved in the reverse transport of cholesterol[52].

In our analysis, semiquantified noncalcified plaque was associated with homocysteine in univariate but not multivariate analysis. We have previously shown homocysteine to be a risk factor for atherosclerotic events and stroke in SLE[53]. Elevated levels of homocysteine are common in SLE[54,55]. The role of homocysteine as a determinant of atherosclerotic events has been controversial[56,57,58].

Our study has several limitations. When we did not find statistically significant relationships, we could not rule out moderate associations, as demonstrated by the size of the confidence intervals. These show the range of associations consistent with our data and indicate that in many cases, even though we did not detect significance, we cannot rule out clinically relevant associations. Analysis of outcomes (death from cardiac causes, cardiac arrest, myocardial infarction, or rehospitalization because of unstable or progressive angina) was not possible, given the short followup after CTA. Our study population was also limited to SLE patients with no chronic kidney disease.

Our study of semiquantified noncalcified plaque in SLE found that NCP is common in SLE, increases with age, and contributes to the overall atherosclerotic burden. Age, obesity, homocysteine, and possibly hypertension and SLE-specific factors (aCL, history of anti-dsDNA) are associated with the extent of noncalcified plaque at the univariate or multivariate level. The association with current MTX therapy is unexplained and of concern. The quantification of NCP is a major research advance, but its value for clinical management has not been established at present.

Acknowledgments

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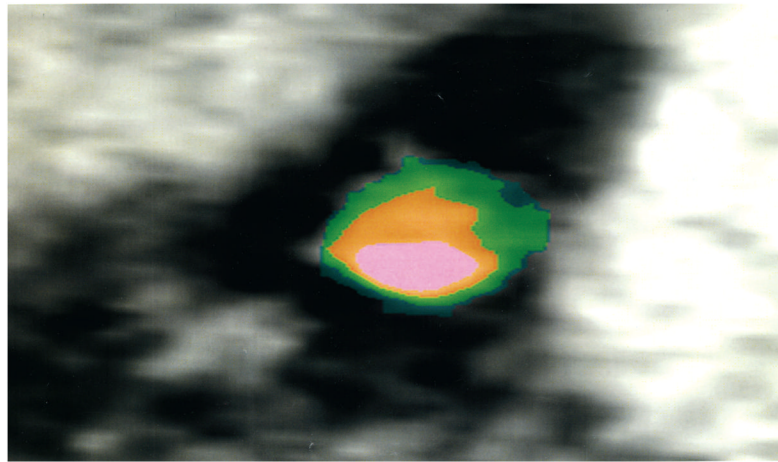
Figure 1.
Cross section of the left anterior descending coronary artery, showing calcium (pink), vessel lumen (orange), and noncalcified plaque (green).

Table 1

Association of noncalcified coronary plaque with demographics and cardiovascular risk factors in our study group (n = 147). Data were missing for some variables.

Characteristic	Mean Noncalcified Plaque Score (SD)	p	Differences Between Subgroups in Mean Plaque Score Controlling for Age (95% CI)	p Controlling for Age
Age, yrs				
< 45, n = 50	0.14 (0.20)	0.007	Reference group	
45–55, n = 53	0.22 (0.31)		0.09 (−0.02, 0.20)	
55+, n = 42	0.36 (0.33)		0.23 (0.11, 0.34)	
Ethnicity				
White, n = 102	0.24 (0.32)	0.96	Reference group	0.99
Black, n = 39	0.23 (0.23)		−0.00 (−0.11, 0.10)	
Other, n = 6	0.21 (0.23)		0.02 (−0.24, 0.27)	
Sex				
Female, n = 126	0.22 (0.26)	0.11	Reference group	0.14
Male, n = 20	0.33 (0.43)		0.10 (−0.03, 0.23)	
Smoking history				
No, n = 95	0.22 (0.30)		Reference group	
Yes, n = 51	0.26 (0.27)	0.42	0.02 (−0.08, 0.11)	0.75
Menopause (women only)				
No, n = 52	0.17 (0.22)	0.060	Reference group	0.19
Yes, n = 70	0.26 (0.29)		−0.08 (−0.04, 0.20)	
Body mass index				
< 25, n = 34	0.14 (0.23)		Reference group	
25–29, n = 36	0.26 (0.34)	0.016 [*]	0.11 (−0.01, 0.22)	0.031 [**]
30+, n = 34	0.31 (0.29)		0.14 (0.03, 0.25)	
History of hypertension				
No, n = 47	0.13 (0.18)	0.0044	Reference group	0.041
Yes, n = 99	0.28 (0.32)		0.10 (−0.20, −0.00)	
Homocysteine				
Low, n = 66	0.19 (0.22)	0.022	Reference group	0.053
High, n = 64	0.31 (0.35)		0.10 (−0.00, 0.20)	
History of diabetes				
No, n = 137	0.24 (0.29)	0.44	Reference group	0.63
Yes, n = 9	0.16 (0.26)		−0.05 (−0.23, 0.14)	
History of high cholesterol				
No, n = 53	0.15 (0.20)	0.0075	Reference group	0.18
Yes, n = 93	0.28 (0.33)		0.07 (−0.03, 0.17)	

[*]
p = 0.016 for trend with body mass index as a continuous predictor.

[**]
p = 0.031 for trend with body mass index as a continuous predictor, controlling for age.

Table 2

Association of noncalcified coronary plaque with history of serologic findings and treatment history in our study group (n = 147). Data were missing for some variables.

Factor	Mean Noncalcified Plaque Score (SD)	p	Differences Between Subgroups in Mean Plaque Score Controlling for Age (95% CI)	p Controlling for Age
Lupus nephritis (biopsy confirmed)				
No, n = 115	0.24 (0.31)	0.41	Reference group	0.76
Yes, n = 32	0.20 (0.23)		0.02 (−0.09, 0.13)	
Anti-dsDNA				
No, n = 46	0.20 (0.22)	0.32	Reference group	0.030
Yes, n = 100	0.25 (0.32)		0.11 (0.01, 0.21)	
Anticardiolipin antibody				
No, n = 50	0.18 (0.27)		Reference group	
Yes, n = 96	0.26 (0.30)	0.11	0.06 (−0.04, 0.15)	0.26
Lupus anticoagulant				
No, n = 89	0.20 (0.26)	0.090	Reference group	0.12
Yes, n = 57	0.28 (0.34)		0.07 (−0.02, 0.16)	
Corticosteroids				
No, n = 23	0.26 (0.36)		Reference group	
Yes, n = 123	0.23 (0.28)	0.66	−0.00 (−0.12, 0.12)	0.99
Hydroxychloroquine				
No, n = 4	0.28 (0.31)		Reference group	
Yes, n = 142	0.23 (0.29)	0.76	−0.08 (−0.20, 0.35)	0.58
Azathioprine				
No, n = 108	0.25 (0.31)		Reference group	
Yes, n = 37	0.18 (0.23)	0.36	−0.02 (−0.12, 0.08)	0.72
Cytoxan				
No, n = 115	0.24 (0.31)		Reference group	
Yes, n = 30	0.19 (0.22)	0.33	−0.03 (−0.14, 0.08)	0.59
Methotrexate				
No, n = 121	0.22 (0.27)	0.18	Reference group	0.12
Yes, n = 24	0.31 (0.40)		0.10 (−0.02, 0.22)	
NSAID				
No, n = 27	0.19 (0.19)	0.38	Reference group	0.57
Yes, n = 119	0.25 (0.24)		0.03 (−0.08, 0.15)	
Anti-Ro				
No, n = 87	0.25 (0.31)	0.084	Reference group	0.20
Yes, n = 19	0.15 (0.19)		−0.07 (−0.18, 0.04)	
Anti-Sm				
No, n = 122	0.24 (0.30)	0.38	Reference group	0.96
Yes, n = 24	0.18 (0.23)		0.00 (−0.12, 0.13)	
Anti-RNP				
No, n = 115	0.24 (0.30)		Reference group	

Factor	Mean Noncalcified Plaque Score (SD)	p	Differences Between Subgroups in Mean Plaque Score Controlling for Age (95% CI)	p Controlling for Age
Yes, n = 31	0.19 (0.25)	0.35	−0.02 (−0.13, 0.86)	0.70
Anti-La				
No, n = 131	0.24 (0.30)	0.29	Reference group	0.39
Yes, n = 15	0.16 (0.17)		−0.07 (−0.22, 0.87)	

NSAID: nonsteroidal antiinflammatory drugs.

Table 3

Association of noncalcified coronary plaque with serologic findings and treatment from the same day (current) visit in our study group (n = 147). Data were missing for some variables.

Factor	Mean Noncalcified Plaque Score (SD)	p	Differences Between Subgroups in Mean Plaque Score Controlling for Age (95% CI)	p Controlling for Age
C3 < 79 mg/dl				
No, n = 114	0.23 (0.30)	0.90	Reference group	0.53
Yes, n = 25	0.22 (0.27)		0.04 (−0.08, 0.16)	
C4 < 2 mg/dl				
No, n = 119	0.24 (0.30)	0.85	Reference group	0.32
Yes, n = 20	0.23 (0.29)		0.07 (−0.07, 0.20)	
Lupus anticoagulant (dRVVT)				
No, n = 107	0.23 (0.30)	0.59	Reference group	0.62
Yes, n = 23	0.26 (0.30)		0.03 (−0.10, 0.16)	
Anticardiolipin IgG > 20				
No, n = 126	0.22 (0.29)		Reference group	
Yes, n = 9	0.42 (0.37)	0.046	0.22 (0.03, 0.41)	0.026
Current anti-dsDNA				
No, n = 109	0.25	0.20	Reference group	0.80
Yes, n = 27	0.17		−0.02 (−0.14, 0.11)	
Corticosteroids				
No, n = 98	0.25 (0.30)	0.29	Reference group	0.66
Yes, n = 48	0.20 (0.27)		−0.02 (−0.12, 0.08)	
Hydroxychloroquine				
No, n = 24	0.22 (0.23)	0.79	Reference group	0.99
Yes, n = 122	0.24 (0.30)		0.00 (−0.12, 0.12)	
Azathioprine				
No, n = 134	0.24 (0.30)	0.53	Reference group	0.61
Yes, n = 13	0.18 (0.19)		−0.04 (−0.20, 0.12)	
Methotrexate				
No, n = 138	0.21 (0.26)	0.0001	Reference group	0.0001
Yes, n = 9	0.59 (0.50)		0.38 (0.19, 0.56)	
Mycophenolate mofetil				
No, n = 128	0.25	0.097	Reference group	0.52
Yes, n = 19	0.13		−0.04 (−0.18, 0.09)	
NSAID				
No, n = 91	0.25	0.45	Reference group	0.37
Yes, n = 55	0.21		−0.04 (−0.13, 0.05)	
Physical global assessment				
< 0.5	0.19	0.37	Reference group	0.27
0.5–0.99	0.27		0.08 (−0.02, 0.19)	
1+	0.24		0.07 (−0.06, 0.19)	
Current SLEDAI				

Factor	Mean Noncalcified Plaque Score (SD)	p	Differences Between Subgroups in Mean Plaque Score Controlling for Age (95% CI)	p Controlling for Age
0–2	0.23	0.71	Reference group	0.34
3+	0.25		0.05 (−0.05, −0.15)	

dRVVT: dilute Russell's viper venom test; NSAID: nonsteroidal antiinflammatory drugs; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index.

Table 4

Multivariable model to predict mean semiquantified noncalcified coronary plaque.

Variable	Effect on Mean Noncalcified Plaque Score (95% CI)	p
Age (per 10 yrs)	0.08 (0.04, 0.12)	< 0.0001
Body mass index (per unit change)	0.03 (0.00, 0.07)	0.058
Hypertension	0.08 (−0.02, 0.17)	0.11
Anti-dsDNA history	0.10 (0.01, 0.20)	0.032
Male gender	0.11 (−0.01, 0.23)	0.067
Current methotrexate use	0.34 (0.15, 0.53)	0.0005