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Supplementary Tables

Supplementary Table S1. RA treatment among the postmenopausal women included in the study

	All N=2,878	Early Menopause N=437	Usual Menopause N=2,441	p-value
Methotrexate	2,351 (81.7)	360 (82.4)	1,991 (81.6)	0.688
Hydroxychloroquine	1,051 (36.5)	149 (34.1)	902 (38.0)	0.135
Sulfasalazine	439 (15.3)	75 (17.2)	364 (14.9)	0.135
Leflunomide	932 (32.4)	153 (35.0)	779 (31.9)	0.233
Glucocorticoids	2,188 (76.0)	342 (78.3)	1,846 (75.6)	0.248
NSAIDs	2,375 (82.5)	361 (82.6)	2,014 (82.5)	>0.999
Biologic DMARDs	176 (6.1)	19 (4.3)	157 (6.4)	0.104

Values are presented as number (%).

NSAIDs, nonsteroidal anti-inflammatory drugs; DMARDs, disease-modifying anti-rheumatic drugs.

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Supplementary Table S2. Comorbidities according to age at menopause

	Early Menopause N=437	Usual Menopause N=2441	p-value
Cardiovascular disease	15 (3.4)	66 (2.7)	0.431
Hypertension	124 (28.4)	859 (35.2)	**0.006**
Diabetes mellitus	39 (8.9)	256 (10.5)	0.347
Thyroid disease	32 (7.3)	188 (7.7)	0.845
Pulmonary disease	34 (7.8)	195 (8.0)	0.924
Chronic liver disease	21 (4.8)	94 (3.9)	0.353
Gastrointestinal disease	102 (23.3)	540 (22.1)	0.575
Renal disease	17 (3.9)	66 (2.7)	0.212
Neurologic disease	14 (3.2)	54 (2.2)	0.229
Neoplastic disease	77 (17.6)	194 (7.9)	**<0.001**
Uterine/cervical neoplasm	51 (66.2)	74 (38.1)	**<0.001**
Ovarian neoplasm	7 (9.1)	18 (9.3)	>0.999
Breast neoplasm	6 (7.8)	25 (12.9)	0.293
Thyroid neoplasm	8 (10.4)	33 (17.0)	0.193
Gastric neoplasm	2 (2.6)	14 (7.2)	0.251
Colorectal neoplasm	0 (0.0)	12 (6.2)	**0.022**
Head & neck neoplasm	0 (0.0)	4 (2.1)	0.580
Lung/mediastinal neoplasm	1 (1.3)	3 (1.5)	>0.999
Urologic neoplasm	1 (1.3)	1 (0.5)	0.488
Haemato-oncological malignancies	1 (1.3)	4 (2.1)	>0.999
Brain neoplasm	0 (0.0)	3 (1.6)	0.561
Skin neoplasm	1 (1.3)	2 (1.0)	>0.999
Depression	12 (2.8)	44 (1.8)	0.257
Skin disease	6 (1.4)	66 (2.7)	0.132
Ophthalmologic disease	28 (6.4)	147 (6.0)	0.828
Osteoporosis	122 (51.5)	696 (53.3)	0.621
Previous fracture	107 (24.5)	479 (19.6)	**0.024**
Previous joint surgery	91 (20.8)	459 (18.8)	0.355

Values are presented as numbers (%).

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Supplementary Table S3. Longitudinal analysis of predictors of the SDAI, CDAI, DAS28, HAQ-DI, and EQ-5D utility values over time using a generalised estimating equation model in the entire study population

Outcome variable	Independent variables	Regression coefficient (β) (95% CI)	p-value
SDAI	Age	0.024 (0.001 – 0.047)	0.043
	RA duration	0.064 (0.039 – 0.089)	<0.001
	Baseline SDAI	0.578 (0.546 – 0.609)	<0.001
	Biologic use	-0.089 (-0.902 – 0.724)	0.83
	Early menopause	0.848 (0.291 – 1.404)	0.003
	Follow-up time	-0.734 (-0.837 – -0.630)	<0.001
CDAI	Age	0.022 (0.001 – 0.044)	0.039
	RA duration	0.062 (0.039 – 0.085)	<0.001
	Baseline CDAI	0.574 (0.543 – 0.605)	<0.001
	Biologic use	0.104 (-0.737 – 0.945)	0.809
	Early menopause	0.695 (0.182 – 1.208)	0.008
	Follow-up time	-0.738 (-0.831 – -0.645)	<0.001
DAS28	Age	0.003 (-0.001 – 0.007)	0.117
	RA duration	0.013 (0.009 – 0.018)	<0.001
	Baseline DAS28	0.566 (0.540 – 0.593)	<0.001
	Biologic use	0.056 (-0.074 – 0.187)	0.398
	Early menopause	0.080 (-0.017 – 0.177)	0.108
	Follow-up time	-0.161 (-0.179 – -0.144)	<0.001
HAQ-DI	Age	0.008 (0.006 – 0.010)	<0.001
	RA duration	0.008 (0.006 – 0.010)	<0.001
	Baseline HAQ-DI	0.693 (0.667 – 0.719)	<0.001
	Biologic use	0.011 (-0.048 – 0.070)	0.713
	Early menopause	0.077 (0.036 – 0.119)	<0.001
	Follow-up time	0.023 (0.016 – 0.031)	<0.001
EQ-5D utility values	Age	-0.002 (-0.003 – -0.001)	<0.001
	RA duration	-0.002 (-0.003 – -0.002)	<0.001
	Baseline EQ-5D utility value	0.569 (0.538 – 0.600)	<0.001
	Biologic use	-0.003 (-0.026 – 0.020)	0.784
	Early menopause	-0.026 (-0.043 – -0.009)	0.003
	Follow-up time	-0.002 (-0.005 – 0.001)	0.297

All covariates adjusted in the model were listed as independent variables.

SDAI, Simplified Disease Activity Index; CDAI, Clinical Disease Activity Index; DAS28, Disease Activity Score using 28 joint counts; HAQ-DI, Health Assessment Questionnaire-Disability Index; EQ-5D, EuroQol-5D.

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Supplementary Table S4. Longitudinal analysis of predictors of the SDAI, CDAI, DAS28, HAQ-DI, and EQ-5D utility values over time using a generalised estimating equation model among postmenopausal rheumatoid arthritis patients with a baseline CDAI >10

Outcome variable	Independent variables	Regression coefficient (β) (95% CI)	p-value
SDAI	Age	0.017 (-0.020 – 0.054)	0.368
	RA duration	0.083 (0.046 – 0.119)	<0.001
	Baseline SDAI	0.576 (0.528 – 0.624)	<0.001
	Biologic use	0.103 (-0.997 – 1.204)	0.854
	Early menopause	1.051 (0.208 – 1.894)	0.015
	Follow-up time	-1.702 (-1.859 – -1.546)	<0.001
CDAI	Age	0.018 (-0.016 – 0.052)	0.309
	RA duration	0.083 (0.049 – 0.117)	<0.001
	Baseline CDAI	0.574 (0.526 – 0.622)	<0.001
	Biologic use	0.121 (-1.005 – 1.246)	0.834
	Early menopause	0.857 (0.078 – 1.637)	0.031
	Follow-up time	-1.648 (-1.791 – -1.505)	<0.001
DAS28	Age	0.003 (-0.003 – 0.009)	0.355
	RA duration	0.017 (0.011 – 0.023)	<0.001
	Baseline DAS28	0.606 (0.557 – 0.655)	<0.001
	Biologic use	0.189 (0.018 – 0.359)	0.030
	Early menopause	0.140 (0.001 – 0.279)	0.048
	Follow-up time	-0.302 (-0.327 – -0.277)	<0.001
HAQ-DI	Age	0.006 (0.004 – 0.009)	<0.001
	RA duration	0.011 (0.008 – 0.013)	<0.001
	Baseline HAQ-DI	0.686 (0.651 – 0.721)	<0.001
	Biologic use	0.036 (-0.040 – 0.113)	0.354
	Early menopause	0.081 (0.021 – 0.141)	0.008
	Follow-up time	-0.004 (-0.015 – 0.007)	0.488
EQ-5D utility value	Age	-0.002 (-0.003 – -0.000)	0.006
	RA duration	-0.003 (-0.004 – -0.002)	<0.001
	Baseline EQ-5D utility value	0.532 (0.493 – 0.572)	<0.001
	Biologic use	-0.011 (-0.043 – 0.022)	0.519
	Early menopause	-0.031 (-0.056 – -0.005)	0.018
	Follow-up time	0.009 (0.004 – 0.014)	<0.001

All covariates adjusted in the model were listed as independent variables.

SDAI, Simplified Disease Activity Index; CDAI, Clinical Disease Activity Index; DAS28, Disease Activity Score using 28 joint counts; HAQ-DI, Health Assessment Questionnaire-Disability Index; EQ-5D, EuroQol-5D.

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Supplementary Table S5. Longitudinal analysis of predictors of the SDAI, CDAI, DAS28, HAQ-DI, and EQ-5D utility values over time using a generalised estimating equation model among postmenopausal rheumatoid arthritis patients with a baseline DAS28 ≥3.2

Outcome variable	Independent variables	Regression coefficient (β) (95% CI)	p-value
SDAI	Age	0.018 (-0.015 – 0.051)	0.279
	RA duration	0.064 (0.034 – 0.094)	<0.001
	Baseline SDAI	0.569 (0.529 – 0.610)	<0.001
	Biologic use	0.169 (-0.862 – 1.199)	0.748
	Early menopause	1.236 (0.480 – 1.992)	0.001
	Follow-up time	-1.264 (-1.396 – -1.133)	<0.001
CDAI	Age	0.014 (-0.017 – 0.044)	0.382
	RA duration	0.067 (0.038 – 0.095)	<0.001
	Baseline CDAI	0.558 (0.517 – 0.598)	<0.001
	Biologic use	0.443 (-0.646 – 1.531)	0.426
	Early menopause	1.092 (0.381 – 1.803)	0.003
	Follow-up time	-1.213 (-1.335 – -1.092)	<0.001
DAS28	Age	0.002 (-0.003 – 0.008)	0.368
	RA duration	0.015 (0.010 – 0.021)	<0.001
	Baseline DAS28	0.582 (0.535 – 0.629)	<0.001
	Biologic use	0.116 (-0.040 – 0.272)	0.144
	Early menopause	0.117 (-0.004 – 0.238)	0.058
	Follow-up time	-0.260 (-0.281 – -0.240)	<0.001
HAQ-DI	Age	0.007 (0.005 – 0.009)	<0.001
	RA duration	0.010 (0.007 – 0.012)	<0.001
	Baseline HAQ-DI	0.675 (0.642 – 0.708)	<0.001
	Biologic use	0.048 (-0.024 – 0.119)	0.192
	Early menopause	0.111 (0.055 – 0.168)	<0.001
	Follow-up time	0.013 (0.003 – 0.023)	0.011
EQ-5D utility value	Age	-0.001 (-0.002 – -0.000)	0.012
	RA duration	-0.003 (-0.004 – -0.002)	<0.001
	Baseline EQ-5D utility value	0.549 (0.509 – 0.589)	<0.001
	Biologic use	-0.013 (-0.042 – 0.015)	0.356
	Early menopause	-0.038 (-0.062 – -0.015)	0.001
	Follow-up time	0.003 (-0.001 – 0.007)	0.180

All covariates adjusted in the model were listed as independent variables.

SDAI, Simplified Disease Activity Index; CDAI, Clinical Disease Activity Index; DAS28, Disease Activity Score using 28 joint counts; HAQ-DI, Health Assessment Questionnaire-Disability Index; EQ-5D, EuroQol-5D.

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Supplementary Table S6. Univariate and multivariate Cox proportional hazard regression analysis of sustained and point clinical remission in postmenopausal women with baseline CDAI >10 (N=1,585)

	Point remission				Sustained remission			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
Variable	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Early Menopause	0.905 (0.631–1.296)	0.585	-	-	0.733 (0.332–1.620)	0.443	-	-
Age	0.990 (0.974–1.006)	0.213	-	-	1.001 (0.968–1.035)	0.954	-	-
RA duration	0.958 (0.939–0.978)	<0.001	0.961 (0.942–0.981)	<0.001	0.894 (0.846–0.945)	<0.001	0.902 (0.853–0.953)	<0.001
Level of education[a]	1.279 (0.981–1.666)	0.069	-	-	1.142 (0.662–1.967)	0.633	-	-
Economic status[b]	1.733 (1.338–2.245)	<0.001	1.487 (1.121–1.973)	0.006	2.465 (1.430–4.247)	0.001	2.146 (1.195–3.853)	0.011
Baseline pain VAS	0.986 (0.981–0.991)	<0.001	0.995 (0.989–1.002)	0.182	0.981 (0.971–0.991)	<0.001	0.996 (0.983–1.009)	0.566
Baseline fatigue VAS	0.990 (0.985–0.994)	<0.001	0.994 (0.989–1.000)	0.069	0.976 (0.966–0.986)	<0.001	0.988 (0.976–0.999)	0.040
Baseline sleep disturbance VAS	0.991 (0.986–0.995)	<0.001	0.995 (0.990–1.001)	0.083	0.979 (0.969–0.990)	<0.001	0.985 (0.972–0.998)	0.027
Baseline CRP	0.970 (0.888–1.059)	0.492	-	-	0.984 (0.824–1.176)	0.86	-	-
Baseline CDAI score	0.958 (0.938–0.977)	<0.001	0.982 (0.961–1.005)	0.122	0.960 (0.919–1.002)	0.063	-	-
Seropositivity	1.210 (0.620–2.363)	0.576	-	-	0.811 (0.251–2.616)	0.725	-	-

[a]The reference group received a middle school education or less.

[b]The reference group had a monthly income of <US$ 1700.

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Supplementary Table S7. Univariate and multivariate Cox proportional hazard regression analyses of sustained and point clinical remission in postmenopausal women with a baseline DAS28 ≥3.2 (N=1,827)

	Point remission				Sustained remission			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
Variable	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Early Menopause	0.928 (0.750–1.148)	0.493	-	-	0.932 (0.644–1.350)	0.710	-	-
Age	0.989 (0.979–0.999)	0.026	0.990 (0.979–1.001)	0.066	0.996 (0.979–1.013)	0.636	-	-
RA duration	0.974 (0.963–0.986)	<0.001	0.978 (0.966–0.989)	<0.001	0.955 (0.935–0.976)	<0.001	0.956 (0.936–0.977)	<0.001
Level of education[a]	1.043 (0.891–1.221)	0.599	-	-	1.004 (0.764–1.319)	0.977	-	-
Economic status[b]	1.216 (1.043–1.418)	0.013	1.051 (0.881–1.254)	0.578	1.361 (1.044–1.775)	0.023	1.215 (0.912–1.620)	0.183
Baseline pain VAS	0.996 (0.993–0.999)	0.008	1.005 (1.001–1.009)	0.025	0.998 (0.993–1.003)	0.337	-	-
Baseline fatigue VAS	0.996 (0.994–0.999)	0.008	0.998 (0.995–1.002)	0.381	0.995 (0.991–1.000)	0.049	0.998 (0.993–1.004)	0.538
Baseline sleep disturbance VAS	0.996 (0.994–0.999)	0.005	0.998 (0.995–1.001)	0.241	0.997 (0.993–1.002)	0.227	-	-
Baseline Physician's VAS	1.000 (0.996–1.004)	0.927	-	-	0.999 (0.992–1.006)	0.721	-	-
Baseline CRP	0.948 (0.899–0.999)	0.045	0.990 (0.937–1.046)	0.710	0.941 (0.854–1.038)	0.224	-	-
Baseline DAS28 score	0.728 (0.666–0.796)	<0.001	0.715 (0.639–0.800)	<0.001	0.735 (0.626–0.861)	<0.001	0.753 (0.630–0.900)	0.002
Seropositivity	0.939 (0.634–1.393)	0.756	-	-	0.685 (0.382–1.230)	0.205	-	-

[a] The reference group received a middle school education or less.

[b]The reference group had a monthly income of <US$ 1700.

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Supplementary Table S8. Baseline characteristics of postmenopausal women with RA who had never-used hormone replacement therapy (N=2,199)

	Early Menopause **N=314**	Usual Menopause N=1,885	P-value
Age at enrolment	59.0±9.9	61.1±8.2	**<0.001**
Age at disease onset	46.7±12.5	50.1±11.0	**<0.001**
Disease duration, year	9.3±8.5	8.7±7.6	0.242
Education, high school or more	126 (40.3)	625 (33.4)	**0.021**
Monthly income, ≥1700 US$	127 (40.6)	748 (40.0)	0.852
Current-smoker	12 (3.8)	45 (2.4)	0.318
Current alcohol drinking	49 (15.6)	207 (11.0)	**0.047**
BMI, kg/m^2	22.8±3.3	23.1±3.3	0.174
Reproductive variables			
Age at menopause, years	35.2±4.1	49.4±3.9	**<0.001**
Time since menopause, years	22.1±11.2	11.1±8.1	**<0.001**
Age at menarche, years	15.9±2.1	16.2±2.2	0.114
Number of pregnancies	3.8±2.3	4.4±2.3	0.429
Number of deliveries	2.5±1.5	2.7±1.3	0.832
Breastfeeding	261 (88.5)	1,648 (90.3)	0.347
Duration of breastfeeding, months	40.6±32.1	40.5±33.1	0.939
Patient-reported outcomes			
Morning stiffness >1 hour	298 (94.9)	1,749 (92.8)	0.432
Pain VAS	44.5±29.5	41.5±28.2	0.076
Global assessment VAS	46.6±27.3	43.6±26.1	0.061
Fatigue VAS	48.7±30.1	45.5±29.0	0.067
Sleep disturbance VAS	33.6±32.5	28.9±29.4	**0.016**
EQ-5D-VAS	59.3±22.7	63.0±19.4	**0.007**
EQ-5D utility value	0.6±0.3	0.6±0.3	0.189
HAQ-DI	0.9±0.7	0.9±0.7	0.505
Physician's VAS	27.6±19.4	27.9±18.8	0.769
Laboratory findings			
Seropositivity	229 (72.9)	1,437 (76.2)	0.451
RF-positive	147 (69.7)	934 (77.4)	**0.018**
RF titre	137.5±200.3	142.6±245.3	0.808
ACPAs-positive	179 (57.0)	1,144 (60.7)	0.407
ESR	33.3±27.4	32.3±25.0	0.533
CRP	1.0±2.1	0.9±1.5	0.155
28 tender joint count	4.7±6.2	4.1±5.2	0.091
28 swollen joint count	2.6±4.0	2.1±3.3	0.056
SDAI	15.8±12.3	14.1±10.2	**0.028**
CDAI	14.7±11.7	13.3±9.9	**0.049**
DAS28	4.1±1.4	3.9±1.3	**0.047**
Moderate to high disease activity			
SDAI >11	174 (57.8)	943 (52.6)	0.104
Erosion on hand x-ray	61 (19.4)	357 (18.9)	0.858

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Values are presented as mean (standard deviation) or number (%).

BMI, body mass index; HRT, hormone replacement therapy; VAS, visual analogue scale; EQ-5D, EuroQol-5D; HAQ-DI, Health Assessment Questionnaire-Disability Index; RF, rheumatoid factor; ACPAs, anti-citrullinated protein antibodies; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; SDAI, Simplified Disease Activity Index; CDAI, Clinical Disease Activity Index; DAS28, Disease Activity Score using 28 joint counts

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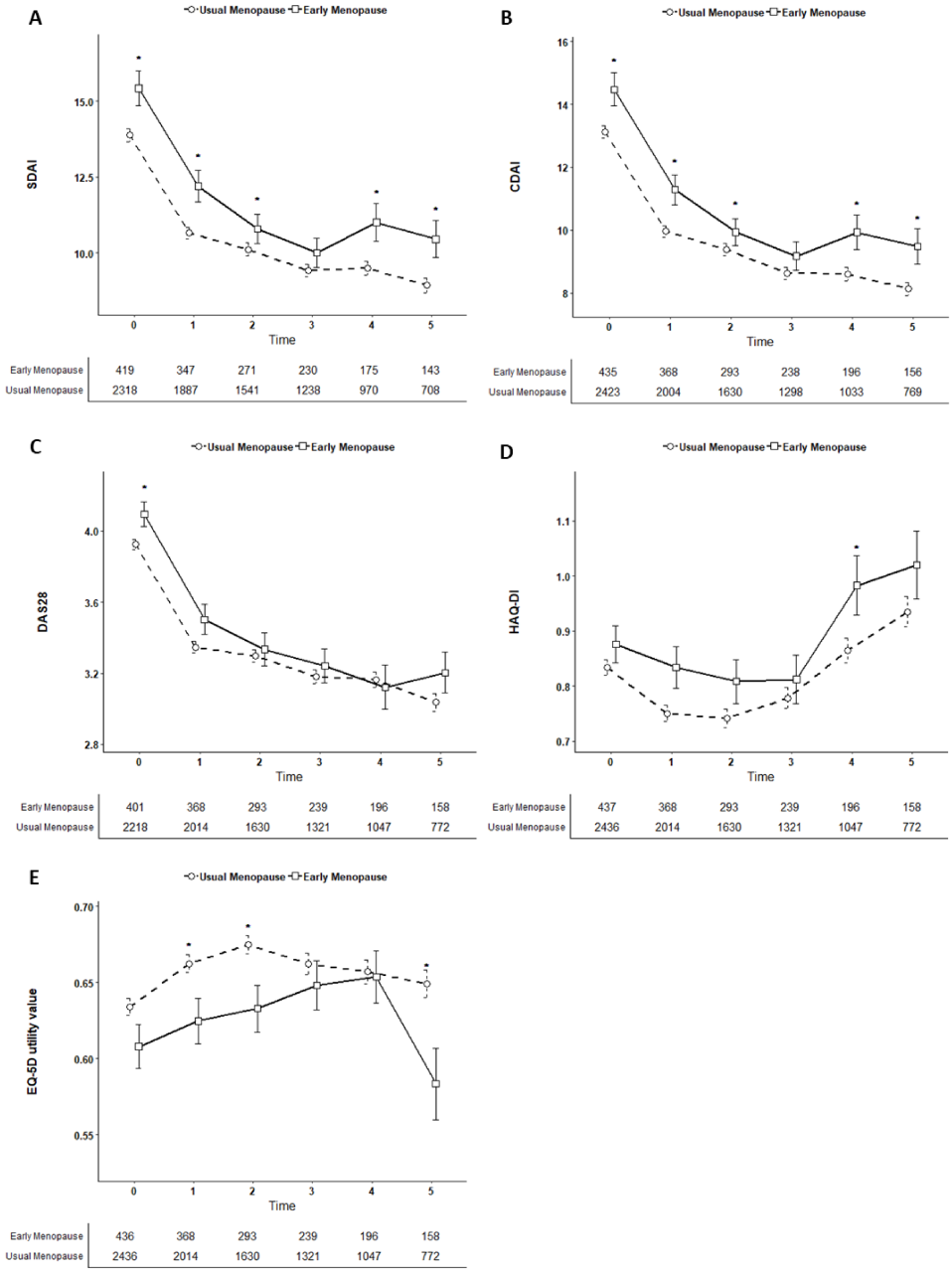
Supplementary Figures

Supplementary Figure 1. Longitudinal changes in disease activity indices and patient-reported outcomes between the early menopause and usual menopause groups over the 5-year follow-up among rheumatoid arthritis patients with a baseline SDAI >11 (N=1,448)



Time trend graphs of the SDAI, CDAI, DAS28, HAQ-DI, and EQ-5D utility values are shown as mean ± standard error. The numbers of women in the early and usual menopause groups with available data at each time point are shown in the bottom table. The mean difference between the two groups was analysed using the Wilcoxon rank-sum test with *p<0.05 at each time point.

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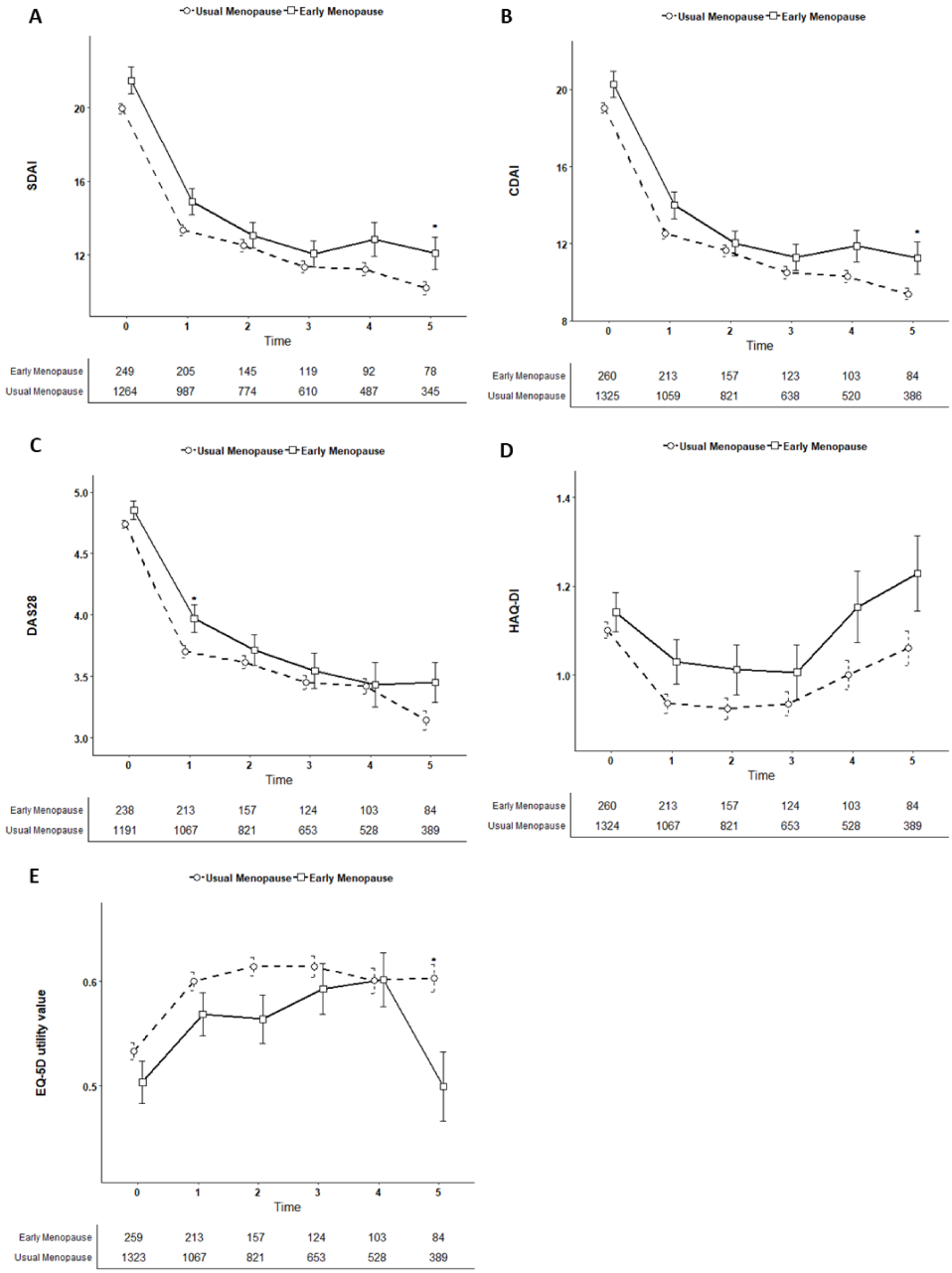
Supplementary Figure 2. Longitudinal changes in disease activity indices and patient-reported outcomes between the early menopause and usual menopause groups over the 5-year follow-up among rheumatoid arthritis patients with a baseline CDAI >10 (N=1,587)



Time trend graphs of the SDAI, CDAI, DAS28, HAQ-DI, and EQ-5D utility values are shown as mean ± standard error. The numbers of women in the early and usual menopause groups with available data at each time point are shown in the bottom table. The mean difference between the two groups was analysed using the Wilcoxon rank-sum test with *p<0.05 at each time point.

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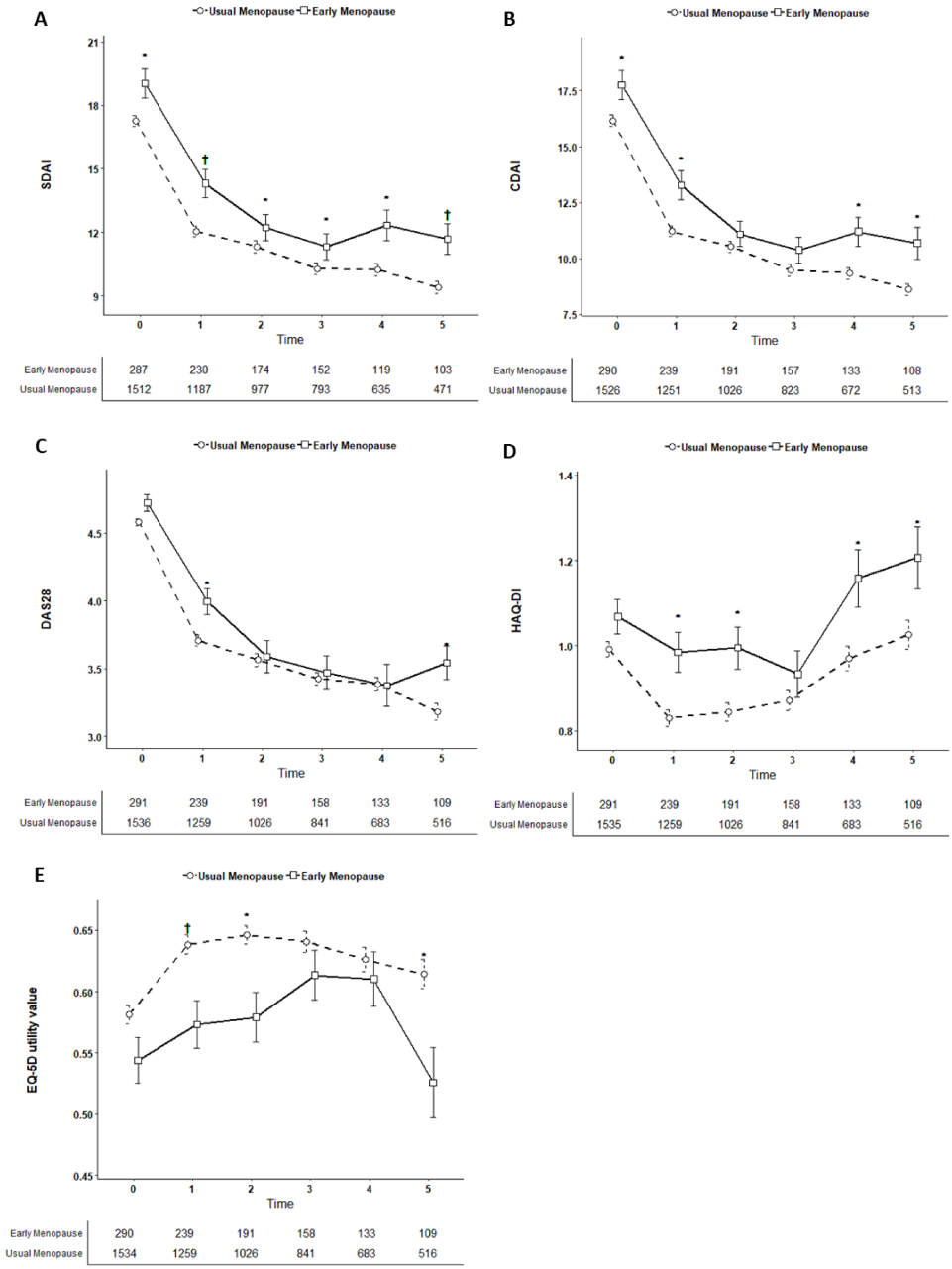
Supplementary Figure 3. Longitudinal changes in disease activity indices and patient-reported outcomes between the early menopause and usual menopause groups over the 5-year follow-up among rheumatoid arthritis patients with a baseline DAS28 ≥3.2 (N=1,827)



Time trend graphs of the SDAI, CDAI, DAS28, HAQ-DI, and EQ-5D utility values are shown as mean ± standard error. The numbers of women in the early and usual menopause groups with available data at each time point are shown in the bottom table. The mean difference between the two groups was analysed using the Wilcoxon rank-sum test with *p<0.05 and †p<0.001 at each time point.