SUPPLEMENTARY MATERIAL FOR:

Cardiovascular risk factors and outcomes in early rheumatoid arthritis: a population-based study

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Appendix 1. The Read codes used to define RA cases and the study outcomes

The Read codes and drug lists used to identify cases of RA, exclusion conditions and study outcomes are listed below. We used the validated case definition approach used by Muller et al:

Criterion 1: At least one diagnostic Read code for RA and at least one appropriate prescription of a disease modifying antirheumatic drug (DMARD) with no alternative indication for the DMARD;

or

Criterion 2: all three of the following:

- a) two or more diagnostic Read codes for RA (on different dates);
- b) no alternative diagnosis after the final RA code;
- c) RA code in group A, opposed to only group B.

Muller S, Hider SL, Raza K, et al. An algorithm to identify rheumatoid arthritis in primary care: a Clinical Practice Research Datalink study. *BMJ open* 2015; 5: e009309.

Rheumatoid arthritis	
Group A codes	
N040.	Rheumatoid arthritis
N0400	Rheumatoid arthritis of cervical spine
N0401	Other rheumatoid arthritis of spine
N0402	Rheumatoid arthritis of shoulder
N0403	Rheumatoid arthritis of sternoclavicular joint
N0404	Rheumatoid arthritis of acromioclavicular joint
N0405	Rheumatoid arthritis of elbow
N0406	Rheumatoid arthritis of distal radio-ulnar joint
N0407	Rheumatoid arthritis of wrist
N0408	Rheumatoid arthritis of metacarpophalangeal joint
N0409	Rheumatoid arthritis of proximal interphalangeal joint of finger
N040A	Rheumatoid arthritis of distal interphalangeal joint of finger
N040B	Rheumatoid arthritis of hip
N040C	Rheumatoid arthritis of sacro-iliac joint
N040D	Rheumatoid arthritis of knee
N040E	Rheumatoid arthritis of tibio-fibular joint
N040F	Rheumatoid arthritis of ankle
N040G	Rheumatoid arthritis of subtalar joint
N040H	Rheumatoid arthritis of talonavicular joint
N040J	Rheumatoid arthritis of other tarsal joint
N040K	Rheumatoid arthritis of 1st metatarsophalangeal joint
N040L	Rheumatoid arthritis of lesser metatarsophalangeal joint

N040M	Rheumatoid arthritis of interphalangeal joint of toe
N040S	Rheumatoid arthritis - multiple joint
N040T	Flare of rheumatoid arthritis
Nyu10	[X]Rheumatoid arthritis with involvement of other organs or systems
Nyu11	[X]Other seropositive rheumatoid arthritis
Nyu12	[X]Other specified rheumatoid arthritis
N047.	Seropositive errosive rheumatoid arthritis
N04X.	Seropositive rheumatoid arthritis, unspecified
Group B codes	
N040N	Rheumatoid vasculitis
N040P	Seronegative rheumatoid arthritis
N040Q	Rheumatoid bursitis
N040R	Rheumatoid nodule
H570.	Rheumatoid lung
G5yA.	Rheumatoid carditis
N041.	Felty's syndrome
N042.	Other rheumatoid arthropathy with visceral or systemic involvement
N0420	Rheumatic carditis
N0422	Rheumatoid nodule
N042z	Rheumatoid arthropathy with visceral or systemic involvement NOS
N043.	Juvenile rheumatoid arthritis - Still's disease
N0430	Juvenile rheumatoid arthropathy unspecified
N0431	Acute polyarticular juvenile rheumatoid arthritis
N0432	Pauciarticular juvenile rheumatoid arthritis
N0433	Monarticular juvenile rheumatoid arthritis
N043z	Juvenile rheumatoid arthritis NOS
N04y0	Rheumatoid lung
66H..	Rheumatol. disorder monitoring
66H1.	Rheumat. initial assessment
66H2.	Rheumat. follow-up assessment
66H3.	Rheumat.dis.- joints affected
66H4.	Rheumat. symptom change
66H5.	Rheumat. drug side effect
66H6.	Rheumat. treatment change
66H7.	Rheumat.dis.treatment started
66H8.	Rheumat.dis.treatment stopped
66H9.	Rheumatology management plan given
66HA.	Rheumatology drug monitoring
66HB.	Rheumatology disorder annual review
66HB0	Rheumatoid arthritis annual review
66HC.	Rheumatic disorder annual review invitation
66HZ.	Rheumatol.dis. monitoring NOS
F3964	Myopathy due to rheumatoid arthritis

Ankylosing spondylitis	
N100.	Ankylosing spondylitis
N0450	Juvenile ankylosing spondylitis

Psoriatic arthritis	
M160.	Psoriatic arthropathy
M1601	Distal interphalangeal psoriatic arthropathy
M160z	Psoriatic arthropathy NOS
Nyu13	[X]Other psoriatic arthropathies
M1600	Psoriasis spondylitica
M1602	Arthritis mutilans

Myocardial infarction	
323..	ECG: myocardial infarction
3233.	ECG: antero-septal infarct.
3234.	ECG:posterior/inferior infarct
3235.	ECG: subendocardial infarct
3236.	ECG: lateral infarction
323Z.	ECG: myocardial infarct NOS
G30..	Acute myocardial infarction
G300.	Acute anterolateral infarction
G301.	Other specified anterior myocardial infarction
G3010	Acute anteroapical infarction
G3011	Acute anteroseptal infarction
G301z	Anterior myocardial infarction NOS
G302.	Acute inferolateral infarction
G303.	Acute inferoposterior infarction
G304.	Posterior myocardial infarction NOS
G305.	Lateral myocardial infarction NOS
G306.	True posterior myocardial infarction
G307.	Acute subendocardial infarction
G3070	Acute non-Q wave infarction
G3071	Acute non-ST segment elevation myocardial infarction
G308.	Inferior myocardial infarction NOS
G309.	Acute Q-wave infarct
G30B.	Acute posterolateral myocardial infarction
G30X.	Acute transmural myocardial infarction of unspecified site
G30X0	Acute ST segment elevation myocardial infarction
G30y.	Other acute myocardial infarction
G30y0	Acute atrial infarction
G30y1	Acute papillary muscle infarction
G30y2	Acute septal infarction
G30yz	Other acute myocardial infarction NOS
G30z.	Acute myocardial infarction NOS

G310.	Postmyocardial infarction syndrome
G32..	Old myocardial infarction
G35..	Subsequent myocardial infarction
G350.	Subsequent myocardial infarction of anterior wall
G351.	Subsequent myocardial infarction of inferior wall
G353.	Subsequent myocardial infarction of other sites
G35X.	Subsequent myocardial infarction of unspecified site
G36..	Certain current complications following acute myocardial infarction
G360.	Haemopericardium as current complication following acute myocardial infarction
G361.	Atrial septal defect as current complication following acute myocardial infarction
G362.	Ventricular septal defect as current complication following acute myocardial infarction
G363.	Rupture of cardiac wall without haemopericardium as current complication following acute myocardial infarction
G364.	Rupture of chordae tendinae as current complication following acute myocardial infarction
G365.	Rupture of papillary muscle as current complication following acute myocardial infarction
G366.	Thrombosis of atrium, auricular appendage, and ventricle as current complications following acute myocardial infarction
G38..	Postoperative myocardial infarction
G380.	Postoperative transmural myocardial infarction of anterior wall
G381.	Postoperative transmural myocardial infarction of inferior wall
G382.	Postoperative transmural myocardial infarction of other sites
G383.	Postoperative transmural myocardial infarction of unspecified site
G384.	Postoperative subendocardial myocardial infarction
G38z.	Postoperative myocardial infarction, unspecified

Stroke	
Fyu56	[X]Other lacunar syndromes
G63y0	Cerebral infarct due to thrombosis of precerebral arteries
G63y1	Cerebral infarction due to embolism of precerebral arteries
G64..	Cerebral arterial occlusion
G640.	Cerebral thrombosis
G6400	Cerebral infarction due to thrombosis of cerebral arteries
G641.	Cerebral embolism
G6410	Cerebral infarction due to embolism of cerebral arteries
G64z.	Cerebral infarction NOS
G64z0	Brainstem infarction
G64z1	Wallenberg syndrome
G64z2	Left sided cerebral infarction
G64z3	Right sided cerebral infarction
G64z4	Infarction of basal ganglia
G66..	Stroke and cerebrovascular accident unspecified
G660.	Middle cerebral artery syndrome

G661.	Anterior cerebral artery syndrome
G662.	Posterior cerebral artery syndrome
G663.	Brain stem stroke syndrome
G664.	Cerebellar stroke syndrome
G665.	Pure motor lacunar syndrome
G666.	Pure sensory lacunar syndrome
G667.	Left sided CVA
G668.	Right sided CVA
G6760	Cerebral infarction due to cerebral venous thrombosis, nonpyogenic
G6W..	Cerebral infarction due to unspecified occlusion or stenosis of precerebral arteries
G6X..	Cerebral infarction due to unspecified occlusion or stenosis of cerebral arteries
Gyu63	[X]Cerebral infarction due to unspecified occlusion or stenosis of cerebral arteries
Gyu64	[X]Other cerebral infarction
Gyu65	[X]Occlusion and stenosis of other precerebral arteries
Gyu66	[X]Occlusion and stenosis of other cerebral arteries
Gyu6G	[X]Cerebral infarction due to unspecified occlusion or stenosis of precerebral arteries

Heart failure	
1O1..	Heart failure confirmed
662f.	New York Heart Association classification - class I
662g.	New York Heart Association classification - class II
662h.	New York Heart Association classification - class III
662i.	New York Heart Association classification - class IV
662p.	Heart failure 6 month review
662T.	Congestive heart failure monitoring
662W.	Heart failure annual review
679W1	Education about deteriorating heart failure
679X.	Heart failure education
67D4.	Heart failure information given to patient
7900.	Transplantation of heart and lung
79000	Allotransplantation of heart and lung
79001	Revision of transplantation of heart and lung
7900y	Other specified transplantation of heart and lung
7900z	Transplantation of heart and lung NOS
7901.	Other transplantation of heart
79010	Allotransplantation of heart NEC
79011	Xenotransplantation of heart
79013	Piggyback transplantation of heart
79014	Revision of implantation of prosthetic heart
79015	Revision of transplantation of heart NEC
7901y	Other specified other transplantation of heart
7901z	Other transplantation of heart NOS
7933.	Transluminal heart assist operations
79330	Transluminal insertion of pulsation balloon into aorta

79331	Transluminal insertion of heart assist system NEC
79332	Transluminal maintenance of heart assist system
79334	Implantation of ventricular assist device
79335	Implantation of right ventricular assist device
79336	Implantation of left ventricular assist device
79337	Implantation of biventricular assist device
7933y	Other specified transluminal heart assist operation
7933z	Transluminal heart assist operation NOS
7936J	Implantation of intravenous biventricular cardiac pacemaker system
79379	Implantation of biventricular cardiac pacemaker system
793L.	Open heart assist operations
793L0	Open implantation of ventricular assist device
793Ly	Other specified open heart assist operations
793Lz	Open heart assist operations NOS
8B29.	Cardiac failure therapy
8CeC.	Preferred place of care for next exacerbation of heart failure
8CL3.	Heart failure care plan discussed with patient
8CMK.	Has heart failure management plan
8CMW8	Heart failure clinical pathway
8H2S.	Admit heart failure emergency
8HBE.	Heart failure follow-up
8HHb.	Referral to heart failure nurse
8HHz.	Referral to heart failure exercise programme
8Hk0.	Referred to heart failure education group
8HTL.	Referral to heart failure clinic
8HTL0	Referral to rapid access heart failure clinic
9N0k.	Seen in heart failure clinic
9N2p.	Seen by community heart failure nurse
9Or0.	Heart failure review completed
G1yz1	Rheumatic left ventricular failure
G2101	Malignant hypertensive heart disease with congestive cardiac failure
G2111	Benign hypertensive heart disease with congestive cardiac failure
G21z1	Hypertensive heart disease NOS with congestive cardiac failure
G232.	Hypertensive heart and renal disease with (congestive) heart failure
G234.	Hypertensive heart and renal disease with both (congestive) heart failure and renal failure
G58..	Heart failure
G580.	Congestive heart failure
G5800	Acute congestive heart failure
G5801	Chronic congestive heart failure
G5802	Decompensated cardiac failure
G5803	Compensated cardiac failure
G5804	Congestive heart failure due to valvular disease
G581.	Left ventricular failure
G5810	Acute left ventricular failure

G582.	Acute heart failure
G583.	Heart failure with normal ejection fraction
G584.	Right ventricular failure
G58z.	Heart failure NOS
Q48y1	Congenital cardiac failure
Q490.	Neonatal cardiac failure

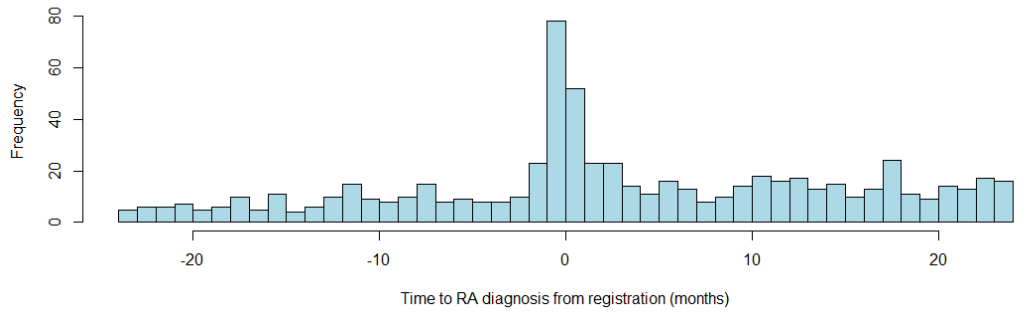
Drug Class	**Medications**
Conventional synthetic disease modifying anti-rheumatic drugs (DMARDs)	Azathioprine, Chloroquine, Ciclosporin, Gold, Hydroxychloroquine, Leflunomide, Methotrexate, Mycophenolate, Penicillamine, Sirolimus, Sulfasalazine, Tacrolimus
Biologic/ targeted synthetic DMARDs	Abatacept*, Adalimumab, Baricitinib*, Certolizumab*, Etanercept, Golimumab*, Infliximab, Rituximab, Tocilizumab*, Tofacitinib*

* These medications were searched for but no prescriptions were found in the primary care record during the study period.

Appendix 2. The exclusion of false incident cases of RA and case matching approach

Incident cases

We have found that the majority of newly registered patients with RA commonly have their historic records transferred from their previous primary care practice and therefore have historic diagnosis codes recorded with their current primary care practice which demonstrate that their RA diagnosis precedes their registration. These patients do not however have data on historic blood test results or prescriptions and are therefore excluded from our analysis. Furthermore, primary care providers can input diagnosis codes retrospectively into the record enabling them to capture the historic onset of disease prior to registration even if these records are not transferred from a previous practice. These patients are also not included in our cohort. False incident cases are therefore unlikely after the GP practice registration date and we see only a small excess of probable false incident cases after the practice registration date and these occur before or during the first three months of registration (supplementary figure 1). We have excluded incident cases within this three-month period.



Supplementary figure 1. The apparent incident rate of RA relative to the patient's registration date with their GP (at time = 0). A false incidence peak can be seen around this time but the incidence has fallen to the background level within three months of the registration date.

Notes on the matching approach used

Patients with RA were matched by age and gender at GP practice level with individuals without RA who were registered at the same time that their case counterpart was diagnosed with RA. The index date for controls was defined as the RA diagnosis date of their matched counterpart. The pool of available controls for each case was therefore those people registered at their own GP practice at the time of their diagnosis. We elected to use a matching ratio of 1:1 for cases and controls. Whilst a higher ratio of controls would have increased precision of estimates in this group and also comparison estimates we found that by increasing the matching ratio we began to lose some of the RA cases. As this effect predominantly affected smaller GP practices (with a small available pool of controls) and therefore potentially introduced an additional source of bias we therefore elected to use a 1:1 matching ratio.

Appendix 3. Medication use among individuals with RA within 30 days of diagnosis and at 3 years after diagnosis.

	Diagnosis (n=6591) n (%)	**3 years after diagnosis (n=4646)** n (%)	**p**
Glucocorticoids	393 (6.0)	2,498 (53.8)	<0.001
Methotrexate	260 (3.9)	2,090 (45.0)	<0.001
csDMARD	398 (6.0)	2,158 (46.4)	<0.001
bDMARD	10 (0.2)	122 (2.6)	<0.001

csDMARD=conventional synthetic disease-modifying anti-rheumatic drug; bDMARD= biologic disease-modifying anti-rheumatic drug.

Appendix 4. Cardiovascular events preceding a diagnosis of rheumatoid arthritis

	RA (n=6,591) n (%)	**No RA (n=6,591)** n (%)	**p**
Cardiovascular event*			
Within 5 years of diagnosis	226 (3.4)	184 (2.8)	0.036
Within 5 to 10 years of diagnosis	124 (1.9)	118 (1.8)	0.741
More than 10 years prior to diagnosis	154 (2.3)	128 (1.9)	0.123

RA = rheumatoid arthritis. *Myocardial infarction, heart failure or stroke

Appendix 5. Association of cardiovascular risk factors and the composite endpoint (myocardial infarction, stroke, or heart failure) among individuals with and without RA

	RA HR (95% CI)	**P value**	**No RA HR (95% CI)**	**P value**
Age (years)	1.06 (1.05-1.07)	<0.001	1.07 (1.05-1.08)	<0.001
Male	1.71 (1.43-2.05)	<0.001	1.63 (1.29-2.07)	<0.001
Non-white ethnicity	0.67 (0.39-1.15)	0.144	1.22 (0.56-2.62)	0.629
Current smoker	1.51 (1.14-1.98)	0.003	1.34 (0.92-1.93)	0.125
BMI (kg/m^2)	1.03 (1.02-1.05)	<0.001	1.02 (0.99-1.04)	0.123
LDL (mmol/L)	0.91 (0.83-1.00)	0.049	0.92 (0.80-1.05)	0.217
Systolic BP (mmHg)	1.00 (0.99-1.00)	0.285	1.01 (1.00-1.01)	0.185
CKD	1.54 (1.20-1.98)	0.001	1.41 (1.07-1.84)	0.013
Diabetes	1.39 (1.10-1.77)	0.006	1.07 (0.78-1.48)	0.662
Steroid use	1.30 (1.02-1.65)	0.033	1.15 (0.61-2.17)	0.667
csDMARD	1.06 (0.81-1.38)	0.674	1.08 (0.15-7.77)	0.943
Seropositivity	1.03 (0.84-1.27)	0.752	1.90 (1.08-3.34)	0.026
CRP (mg/dL)	1.00 (1.00-1.00)	0.294	1.00 (1.00-1.01)	0.327

BMI=body mass index; BP= blood pressure; CRP= C-reactive protein; LDL= low-density lipoprotein; csDMARD=conventional synthetic disease-modifying anti-rheumatic drug.

Appendix 6. Association of cardiovascular risk factors and the primary composite endpoint (myocardial infarction, stroke, or heart failure) adjusted for the presence of CVD (stroke, myocardial infarction and heart failure) at baseline in people with rheumatoid arthritis

	HR (95% CI)	P value
Age (years)	1.06 (1.05-1.07)	<0.001
Male	1.60 (1.31-1.96)	<0.001
Non-white ethnicity	0.95 (0.36-2.51)	0.919
Current smoker	1.44 (1.07-1.96)	0.018
BMI (kg/m^2)	1.02 (1.01-1.04)	0.009
LDL (mmol/L)	0.89 (0.78-1.02)	0.112
Systolic BP (mmHg)	1.00 (0.99-1.00)	0.627
CKD	1.61 (1.22-2.11)	0.001
Diabetes	1.46 (1.11-1.91)	0.007
Steroid use	1.19 (0.91-1.55)	0.200
DMARD	0.97 (0.72-1.32)	0.869
Seropositivity	1.09 (0.87-1.37)	0.432
CRP (mg/dL)	1.00 (1.00-1.01)	0.163
Myocardial infarction	0.87 (0.56-1.37)	0.556
Stroke	0.95 (0.64-1.42)	0.802
Heart failure	1.14 (0.63-2.06)	0.660

BMI = body mass index; BP = blood pressure; CKD = chronic kidney disease; CRP = C-reactive protein; LDL= low-density lipoprotein; HR = hazard ratio; DMARD = disease-modifying anti-rheumatic drug.

Appendix 7. Association of cardiovascular risk factors and the extended composite endpoint (myocardial infarction, stroke, heart failure, coronary artery disease, percutaneous coronary intervention, and angina) among individuals with and without RA

	RA		No RA	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**
Age (years)	1.06 (1.05-1.07)	<0.001	1.06 (1.05-1.08)	<0.001
Male	1.67 (1.40-2.01)	<0.001	1.47 (1.19-1.81)	<0.001
Non-white ethnicity	1.09 (0.47-2.52)	0.847	1.12 (0.51-2.50)	0.781
Current smoker	1.56 (1.20-2.04)	0.001	1.36 (0.98-1.89)	0.068
BMI (kg/m^2)	1.03 (1.01-1.05)	<0.001	1.03 (1.01-1.05)	0.008
LDL (mmol/L)	0.87 (0.78-0.97)	0.017	0.90 (0.80-1.02)	0.091
Systolic BP (mmHg)	1.00 (0.99-1.00)	0.277	1.00 (1.00-1.01)	0.365
CKD	1.51 (1.18-1.93)	0.001	1.35 (1.06-1.72)	0.015
Diabetes	1.32 (1.04-1.69)	0.025	1.08 (0.81-1.43)	0.606
Steroid use	1.28 (1.01-1.62)	0.041	1.66 (0.97-2.86)	0.067
DMARD	1.03 (0.79-1.35)	0.817	1.08 (0.60-1.93)	0.796
Seropositivity	1.01 (0.83-1.25)	0.887	1.81 (0.44-7.33)	0.409
CRP (mg/dL)	1.00 (1.00-1.00)	0.347	1.00 (1.00-1.01)	0.176

BMI = body mass index; BP = blood pressure; CKD = chronic kidney disease; CRP = C-reactive protein; DMARD = disease-modifying anti-rheumatic drug; LDL= low-density lipoprotein; HR = hazard ratio; RA = rheumatoid arthritis.

Appendix 8. Association of RA with the composite endpoint (myocardial infarction, stroke, or heart failure) in the overall cohort in an adjusted model with stratification by matched set.

	HR (95% CI)	p
RA	1.33 (1.07-1.65)	0.010
Non-white ethnicity	1.33 (0.65-2.73)	0.440
Current smoker	1.41 (0.95-2.11)	0.092
BMI (kg/m^2)	1.02 (0.99-1.04)	0.191
LDL (mmol/L)	0.89 (0.78-1.01)	0.075
Systolic BP (mmHg)	1.00 (0.99-1.01)	0.540
CKD	1.52 (1.09-2.12)	0.013
Diabetes	1.36 (0.96-1.93)	0.084
Glucocorticoid use	0.89 (0.58-1.36)	0.592
DMARD use	0.88 (0.53-1.45)	0.621
Seropositivity	1.19 (0.82-1.74)	0.352
CRP (mg/dL)	1.00 (1.00-1.01)	0.246

Parameter estimates for covariates are shown for completeness. BMI = body mass index; BP = blood pressure; CKD = chronic kidney disease; CRP = C-reactive protein; DMARD = disease-modifying anti-rheumatic drug; LDL= low-density lipoprotein; HR = hazard ratio; RA = rheumatoid arthritis.