

Supplementary Online Contents

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Supplemental Table 1. Baseline patient characteristics in overall and stratified by biologic use in the overall cohort

Characteristics	Overall (<i>n</i> = 20,757)	Biologic use	
		No (<i>n</i> = 16,140)	Yes (<i>n</i> = 4,617)
Mean age (SD), y	63.2 (11.4)	64.8 (11.2)	57.6 (9.9)
Mean eGFR (SD), mL/min/1.73m ²	83.4 (14.8)	82.1 (14.4)	87.6 (15.4)
Male, <i>n</i> (%)	19,044 (91.7)	14,925 (92.5)	4,119 (89.2)
African American, <i>n</i> (%)	2,503 (12.1)	2,008 (12.4)	495 (10.7)
Hypertension, <i>n</i> (%)	13,289 (64.0)	10,687 (66.2)	2,602 (56.4)
Diabetes mellitus, <i>n</i> (%)	4,766 (23.0)	3,897 (24.1)	869 (18.8)
Coronary heart disease, <i>n</i> (%)	3,049 (14.7)	2,557 (15.8)	492 (10.7)
Congestive heart failure, <i>n</i> (%)	1,407 (6.8)	1,262 (7.8)	145 (3.1)
Cerebrovascular disease, <i>n</i> (%)	1,526 (7.4)	1,312 (8.1)	214 (4.6)
Peripheral arterial disease, <i>n</i> (%)	1,672 (8.1)	1,427 (8.8)	245 (5.3)
Chronic lung disease, <i>n</i> (%)	5,671 (27.3)	4,662 (28.9)	1,009 (21.9)
Dementia, <i>n</i> (%)	166 (0.8)	159 (1.0)	7 (0.2)
Liver disease, <i>n</i> (%)	248 (1.2)	205 (1.3)	43 (0.9)
Malignancies, <i>n</i> (%)	2,525 (12.2)	2,199 (13.6)	326 (7.1)
HIV/AIDS, <i>n</i> (%)	36 (0.2)	31 (0.2)	5 (0.1)
Depression, <i>n</i> (%)	1,886 (9.1)	1,429 (8.9)	457 (9.9)
Married, <i>n</i> (%)	12,515 (60.3)	9,781 (60.6)	2,734 (59.2)

Service connected, <i>n</i> (%)	9,021 (43.5)	6,775 (42.0)	2,246 (48.6)
Median per capita income (IQI), \$	24,131 (12704-34889)	23,997 (12550-35007)	24,840 (131616-34214)
Living in area with high housing stress, <i>n</i> (%)	6,258 (30.1)	4,778 (29.6)	1,480 (32.1)
Living in area with low education, <i>n</i> (%)	2,238 (10.8)	1,732 (10.7)	506 (11.0)
Living in area with low employment, <i>n</i> (%)	2,055 (9.9)	1,610 (10.0)	445 (9.6)
Living in area of persistent poverty, <i>n</i> (%)	1,110 (5.3)	870 (5.4)	240 (5.2)
Mean BMI (SD), <i>kg/m</i> ²	28.5 (5.5)	28.4 (5.5)	29.1 (5.5)
Mean systolic BP (SD), <i>mmHg</i>	134.6 (18.6)	134.9 (18.9)	133.4 (17.5)
Mean diastolic BP (SD), <i>mmHg</i>	75.9 (11.3)	75.5 (11.5)	77.3 (10.6)
Mean serum albumin (SD), <i>g/dL</i>	3.9 (0.4)	3.9 (0.5)	4.0 (0.4)
Mean articular procedures (SD), <i>n</i> (<i>per year</i>)	0.1 (0.4)	0.1 (0.4)	0.2 (0.4)
RASi use, <i>n</i> (%)	8,503 (41.0)	6,887 (42.7)	1,616 (35.0)
Statin use, <i>n</i> (%)	6,331 (30.5)	5,116 (31.7)	1,215 (26.3)
Methotrexate use, <i>n</i> (%)	7,672 (37.0)	5,389 (33.4)	2,283 (49.4)
Hydroxychloroquine use, <i>n</i> (%)	6,032 (29.1)	4,637 (28.7)	1,395 (30.2)
Sulfasalazine use, <i>n</i> (%)	3,071 (14.8)	2,147 (13.3)	924 (20.0)
Other non-biologic DMARD use, <i>n</i> (%)	585 (2.8)	406 (2.5)	179 (3.9)
NSAID use, <i>n</i> (%)	11,413 (55.0)	8,539 (52.9)	2,874 (62.2)
Glucocorticoid use, <i>n</i> (%)	8,517 (41.0)	6,122 (37.9)	2,395 (51.9)

Note: Data are presented as number (percentage), mean (standard deviation), or median (interquartile interval). All *P*-values except liver disease (*P* = 0.06), HIV/AIDS (*P* = 0.23), low education (*P* = 0.66), low employment (*P* = 0.50), and persistent poverty (*P* = 0.61) for comparing differences between with and without biologic exposure were statistically significant.

Abbreviations: AIDS = acquired immunodeficiency syndrome; BMI = body mass index; BP = blood pressure; DMARD = disease-modifying anti-rheumatic drug; eGFR = estimated glomerular filtration rate; HIV = human immunodeficiency virus; NSAID = nonsteroidal anti-inflammatory drug; RASi = renin-angiotensin system inhibitor.

Supplemental Table 2. Types of initial biologics and number of patients treated with each biologic agent in the overall cohort (*n* = 4,617)

Type	Number	%
Etanercept	2,779	60.2
Adalimumab	990	21.4
Infliximab	441	9.6
Abatacept	189	4.1
Rituximab	160	3.5
Golimumab	25	0.5
Certolizumab	15	0.3
Anakinra	15	0.3
Tocilizumab	3	0.1

Supplemental Table 3. Predictive equation for the probability of biologic use

The multivariate logistic regression model underlying the odds ratios for biologic use in Table 2 has the following predictive equation:

$$\text{Probability for biologic use} = \exp(a)/(1 + \exp[a])$$

$$a = 0.5969 - 0.0530 \times \text{age} - 0.1850 \times I_{\text{female}} - 0.6024 \times I_{\text{African American}} + 0.0077 \times \text{eGFR} - 0.1785 \times I_{\text{diabetes}} - 0.1139 \times I_{\text{hypertension}} - 0.1481 \times I_{\text{coronary heart disease}} - 0.5425 \times I_{\text{congestive heart failure}} - 0.1687 \times I_{\text{cerebrovascular disease}} - 0.2668 \times I_{\text{peripheral vascular disease}} - 0.2580 \times I_{\text{chronic lung disease}} - 0.2405 \times I_{\text{liver disease}} - 1.1010 \times I_{\text{dementia}} - 0.3813 \times I_{\text{malignancy}} - 0.6538 \times I_{\text{HIV/AIDS}} - 0.2217 \times I_{\text{depression}} + 0.0154 \times \text{BMI} - 0.0018 \times \text{systolic blood pressure} + 0.0530 \times \text{log-income} - 0.0804 \times I_{\text{marital status}} + 0.0554 \times I_{\text{service connectedness}} + 0.1598 \times I_{\text{housing stress}} + 0.0298 \times I_{\text{low education}} - 0.0920 \times I_{\text{low employment}} - 0.0866 \times I_{\text{persistent poverty}} + 0.6077 \times I_{\text{methotrexate}} - 0.1684 \times I_{\text{hydroxychloroquine}} + 0.3387 \times I_{\text{sulfasalazine}} + 0.4173 \times I_{\text{other non-biologic DMARDs}} + 0.0807 \times I_{\text{NSAIDs}} + 0.4756 \times I_{\text{glucocorticoids}} - 0.0687 \times I_{\text{statin}} - 0.0073 \times I_{\text{RASi}} + 0.0118 \times \text{serum albumin} + 0.2549 \times \text{number of articular procedures per year}$$

Note: “I_” represents indicator variables taking value 0 or 1 depending on the absence or presence of the respective trait.

Example for a 65 year old white married male with eGFR of 90 mL/min/1.73m², BMI of 29, systolic blood pressure of 140 mmHg, serum albumin of 3.2 g/dL, two articular procedures per year, log-income of 10.8 (USD 50,000) and using NSAIDs at baseline:

$$a = 0.5969 - 0.0530 \times 65 (\text{age}) + 0.0077 \times 90 (\text{eGFR}) + 0.0154 \times 29 (\text{BMI}) - 0.0018 \times 140 (\text{systolic blood pressure}) + 0.0530 \times 10.8 (\text{log-income}) + 0.0807 \times 1 (I_{\text{NSAIDs}}) + 0.0118 \times 3.2 (\text{serum albumin}) + 0.2549 \times 2 (\text{number of articular procedures per year}) = -0.75984$$

which gives Prob(biologic use) = $\exp(-0.75984)/(1+\exp[-0.75984]) = 0.32$.

Abbreviations: AIDS = acquired immunodeficiency syndrome; BMI = body mass index; DMARD = disease-modifying anti-rheumatic drug; eGFR = estimated glomerular filtration rate; HIV = human immunodeficiency virus; NSAID = nonsteroidal anti-inflammatory drug; RASi = renin-angiotensin system inhibitor.

Supplemental Table 4. Association of biologic treatment with incident CKD (decrease in eGFR [A] <60 and [B] <45 mL/min/1.73m²) in the overall cohort

	Decrease in eGFR (mL/min/1.73m ²)	
	HR (95% CI)	
	[A] <60	[B] <45
Treated (vs. untreated) with biologics	0.83 (0.72-0.96)	0.42 (0.32-0.56)

Estimates were calculated using time-dependent Cox models.

Data are adjusted for fixed (age, sex, race, prevalent comorbidities [diabetes mellitus, hypertension, coronary heart disease, congestive heart failure, cerebrovascular disease, peripheral vascular disease, chronic lung disease, liver disease, dementia, malignancy, depression, and HIV/AIDS], and socioeconomic parameters [mean per capita income, marital status, service connectedness, housing stress, low education, low employment, and persistent poverty]) and time-dependent covariates (eGFR, BMI, systolic blood pressure, serum albumin, number of articular procedures per year, and medications [statins, RASi, methotrexate, hydroxychloroquine, sulfasalazine, leflunomide, other non-biologic DMARDs, NSAIDs, and glucocorticoids]).

Abbreviations: AIDS = acquired immunodeficiency syndrome; BMI = body mass index; CI = confidence interval; DMARD = disease-modifying anti-rheumatic drug; eGFR = estimated glomerular filtration rate; HIV = human immunodeficiency virus; HR = hazard ratio; NSAID = nonsteroidal anti-inflammatory drug; RASi = renin-angiotensin system inhibitor.

Supplemental Table 5. Association of biologic treatment with change in eGFR in the overall cohort

	Change in eGFR (mL/min/1.73m ² /year)		
	<-3	MOR (95% CI) -3 to <0	≥0
Treated (vs. untreated) with biologics	0.82 (0.72-0.95)	1 [reference]	1.03 (0.95-1.12)

Estimates were calculated using multinomial logistic regression models.

Data are adjusted for fixed (age, sex, race, prevalent comorbidities [diabetes mellitus, hypertension, coronary heart disease, congestive heart failure, cerebrovascular disease, peripheral vascular disease, chronic lung disease, liver disease, dementia, malignancy, depression, and HIV/AIDS], and socioeconomic parameters [mean per capita income, marital status, service connectedness, housing stress, low education, low employment, and persistent poverty]) and time-dependent covariates (eGFR, BMI, systolic blood pressure, serum albumin, number of articular procedures per year, and medications [statins, RASi, methotrexate, hydroxychloroquine, sulfasalazine, leflunomide, other non-biologic DMARDs, NSAIDs, and glucocorticoids]).

Abbreviations: AIDS = acquired immunodeficiency syndrome; BMI = body mass index; CI = confidence interval; DMARD = disease-modifying anti-rheumatic drug; eGFR = estimated glomerular filtration rate; HIV = human immunodeficiency virus; MOR = multinomial odds ratio; NSAID = nonsteroidal anti-inflammatory drug; RASi = renin-angiotensin system inhibitor.

Supplemental Table 6. ICD-9 and procedure (CPT) codes used to define prevalent comorbid conditions and RA-related articular procedures

Comorbid condition	ICD-9 code
Rheumatoid arthritis	714.0
Hypertension	401-405
Diabetes mellitus	250.x
Coronary artery disease	414.0, 414.8, 414.9
Angina	411, 413
Myocardial infarction	410-410.9, 412
PCI	36.03, 36.04, 36.06, 36.07, 36.09
CABG	36.10-36.17, 36.19
Congestive heart failure	428-428.9
Cerebrovascular disease	430-438
Peripheral arterial disease	440.0-440.9, 443, 443.x, 38.0, 38.1, 39.50, 39.22, 39.24, 39.25, 39.26, 39.28
Chronic lung disease	490-496, 500-505, 506.4
Dementia	290-290.9
Liver disease	571.x, 572.x, 456.0-456.21
Malignancy	140-172.9, 174-195.8, 200-208.9, 196-199.1
HIV/AIDS	042, V08, 795.71
Depression	296.x
CPT codes used to define coronary interventions and RA-related articular procedures	
Procedure	CPT code
PCI	92980 92981 92982 92984 92985 92986 92987 92988 92989 92990 92991 92992 92993 92994 92995 92996
CABG	33510 33511 33512 33513 33514 33515 33516 33517 33518 33519 33521 33522 33523 33533 33534 33535 33536 22532 22533 22534 22548 22554 22556 22558 22585 22590 22595 22600 22610 22612 22614 22630 22632 22800 22802 22804 22808 22810 22812 23470 23472 23800 23802 24360 24361 24362 24363 24365 24366 24800 24802 25332 25441 25442 25443 25444 25445 25446 25447 25800 25805 25810 25820 25825 25830 26131 26135 26140 26145 26530 26531 26535 26536 26820 26841 26842 26843 26844 26850 26852 26860 26861 26862 26863 27130 27280 27282 27284 27286 27334 27437 27438 27440 27441 27442 27443 27445 27446 27447 27580 27700 27702 27703 27870 27871 28270 28272 28292 28293 28294 28296 28297 28298 28299 28705 28715
RA-related articular procedures	

28725 28730 28735 28737 28740 28750 28755 28760 29899
20551 20552 20553 20600 20605 20610

Abbreviations: AIDS = acquired immunodeficiency syndrome; CABG = coronary artery bypass grafting; CPT = Current Procedural Terminology; HIV = human immunodeficiency virus; ICD = International Classification of Diseases; PCI = percutaneous coronary intervention; RA = rheumatoid arthritis

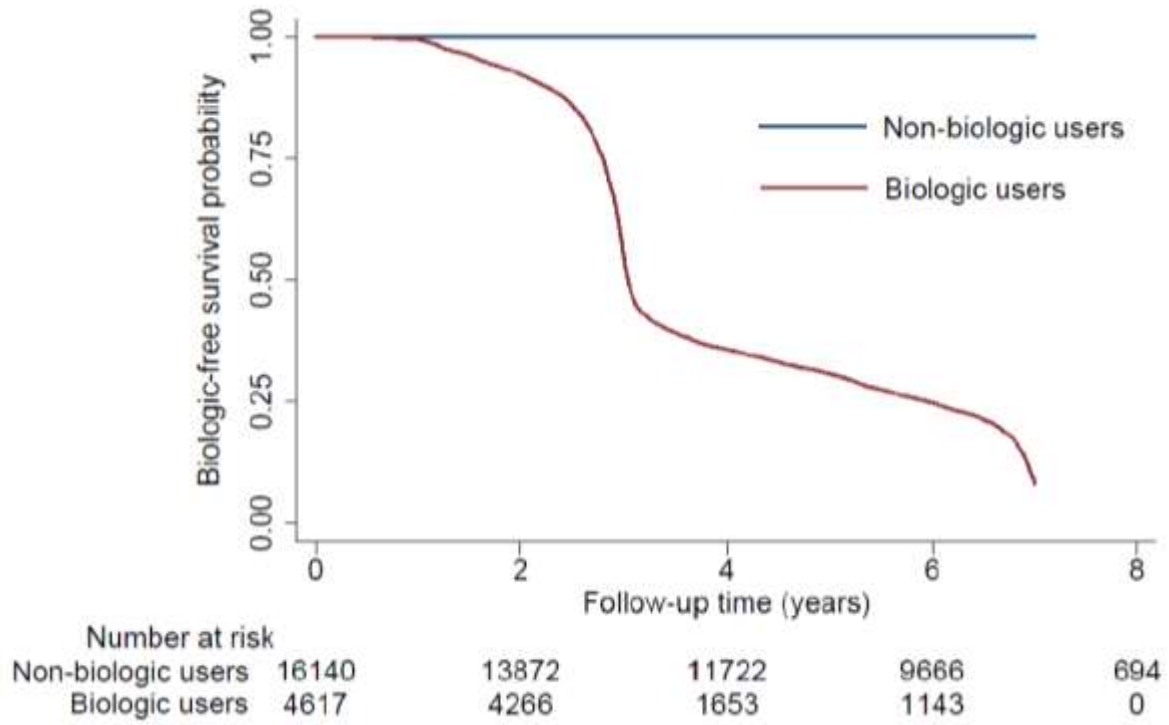
Supplemental Table 7. Area-based socio-economic indicators

The Area Health Resources Files (AHRF, <http://ahrf.hrsa.gov/>) system is issued by the National Center for Health Workforce Analysis, Bureau of Health Workforce, Health Resources and Services Administration.

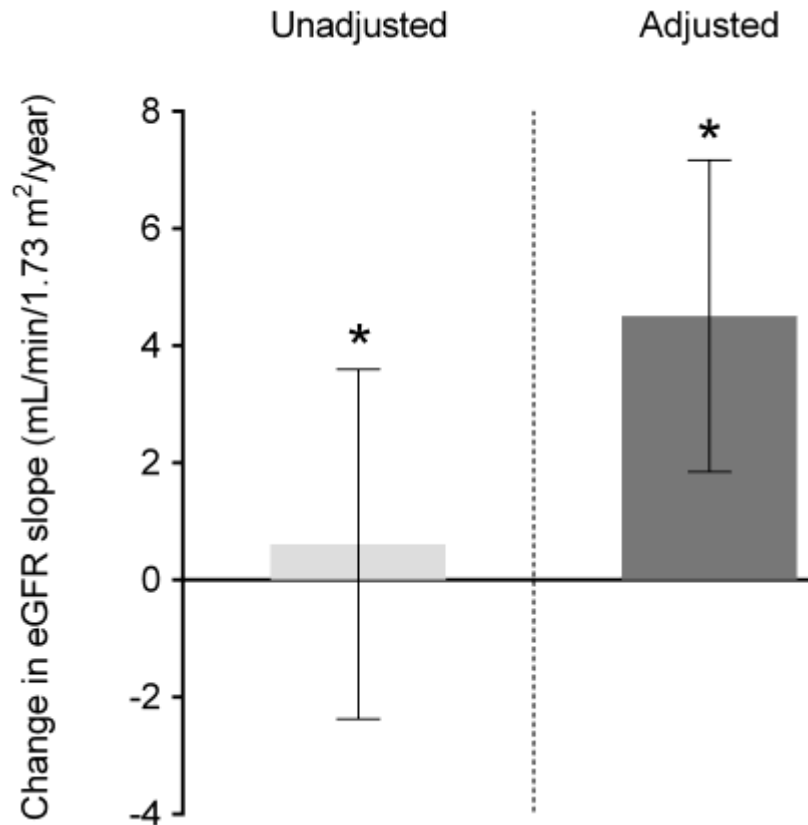
Within the AHRF, we used select **2004 County Typology Codes** from the Economic Research Service (ERS), U.S. Department of Agriculture, www.ers.usda.gov. The 2004 County Typology Codes were developed for all 3,141 counties, county equivalents, and independent cities in the United States.

Indicators	Definition
Housing stress	30 percent or more of households had one or more of these housing conditions in 2000: lacked complete plumbing, lacked complete kitchen, paid 30 percent or more of income for owner costs or rent, or had more than 1 person per room.
Low-education	25 percent or more of residents 25 through 64 years old had neither a high school diploma nor GED in 2000.
Low-employment	Less than 65 percent of residents 21 through 64 years old were employed in 2000.
Persistent poverty	20 percent or more of residents were poor as measured by each of the last 4 censuses: 1970, 1980, 1990 and 2000.

Supplemental Figure 1. Kaplan-Meier curve for initiation of biologics in the overall cohort



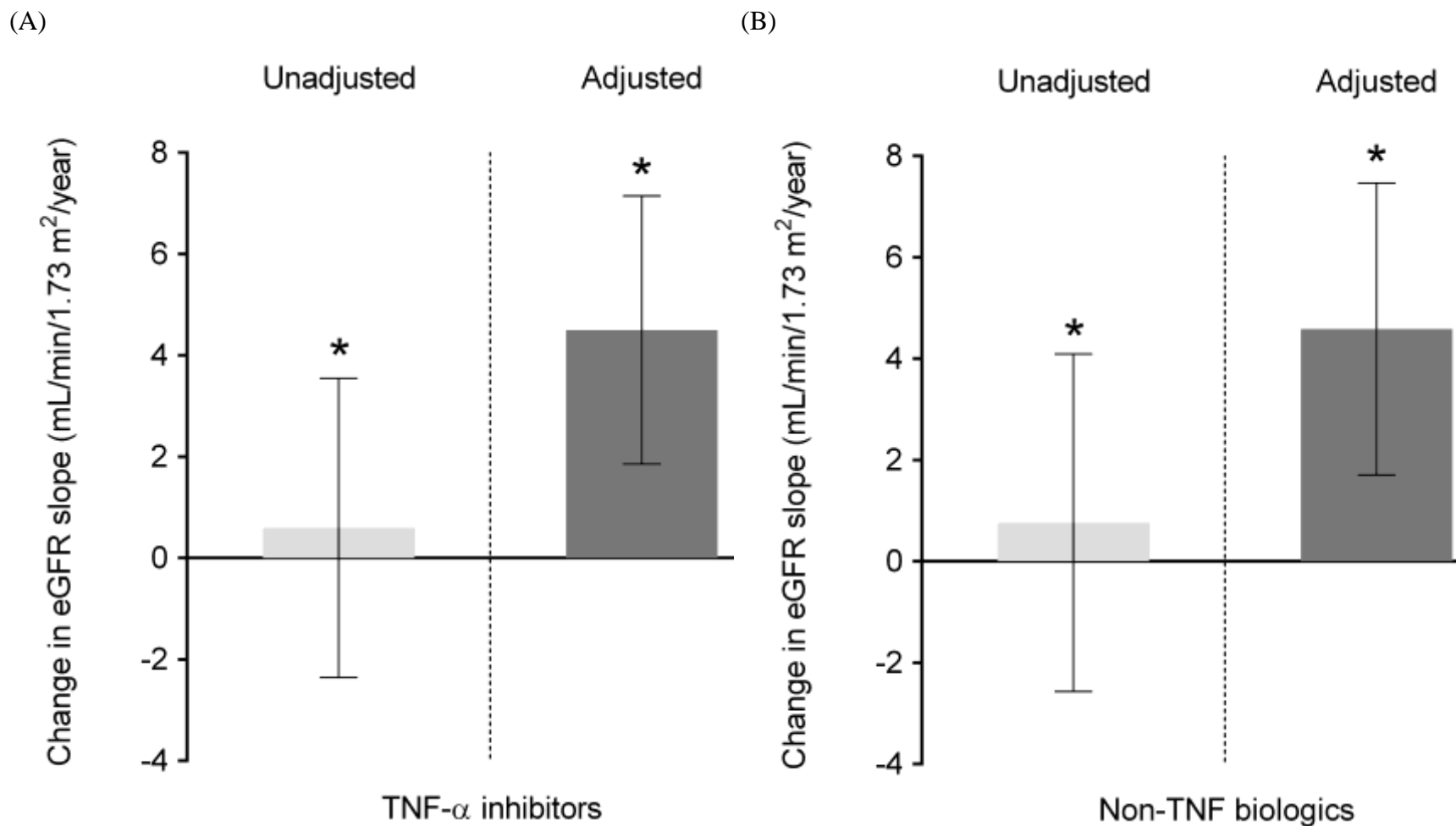
Supplemental Figure 2. Change in eGFR slopes (mean, SD) before and after biologic administration in patients treated with biologics in the overall cohort



* $P < 0.001$ for comparing differences between pre- and post-biologic administration. Slopes were estimated from unadjusted (left bar) and multivariable-adjusted (right bar) mixed-effects models. Models were adjusted for fixed (age, sex, race, comorbidities [diabetes mellitus, hypertension, coronary heart disease, congestive heart failure, cerebrovascular disease, peripheral vascular disease, chronic lung disease, liver disease, dementia, malignancy, depression, and HIV/AIDS], and socioeconomic parameters [mean per capita income, marital status, service connectedness, housing stress, low education, low employment, and persistent poverty]) and time-dependent confounders (eGFR, BMI, systolic blood pressure, serum albumin, number of articular procedures per year, and medications [statins, RASi, methotrexate, hydroxychloroquine, sulfasalazine, leflunomide, other non-biologic DMARDs, NSAIDs, and glucocorticoids]).

Abbreviations: AIDS = acquired immunodeficiency syndrome; BMI = body mass index; DMARD = disease-modifying anti-rheumatic drug; eGFR = estimated glomerular filtration rate; HIV = human immunodeficiency virus; NSAID = nonsteroidal anti-inflammatory drug; RASi = renin-angiotensin system inhibitor; SD = standard deviation.

Supplemental Figure 3. Change in eGFR slopes (mean, SD) before and after biologic administration in patients treated with (A) TNF- α inhibitors and (B) non-TNF biologics in the overall cohort

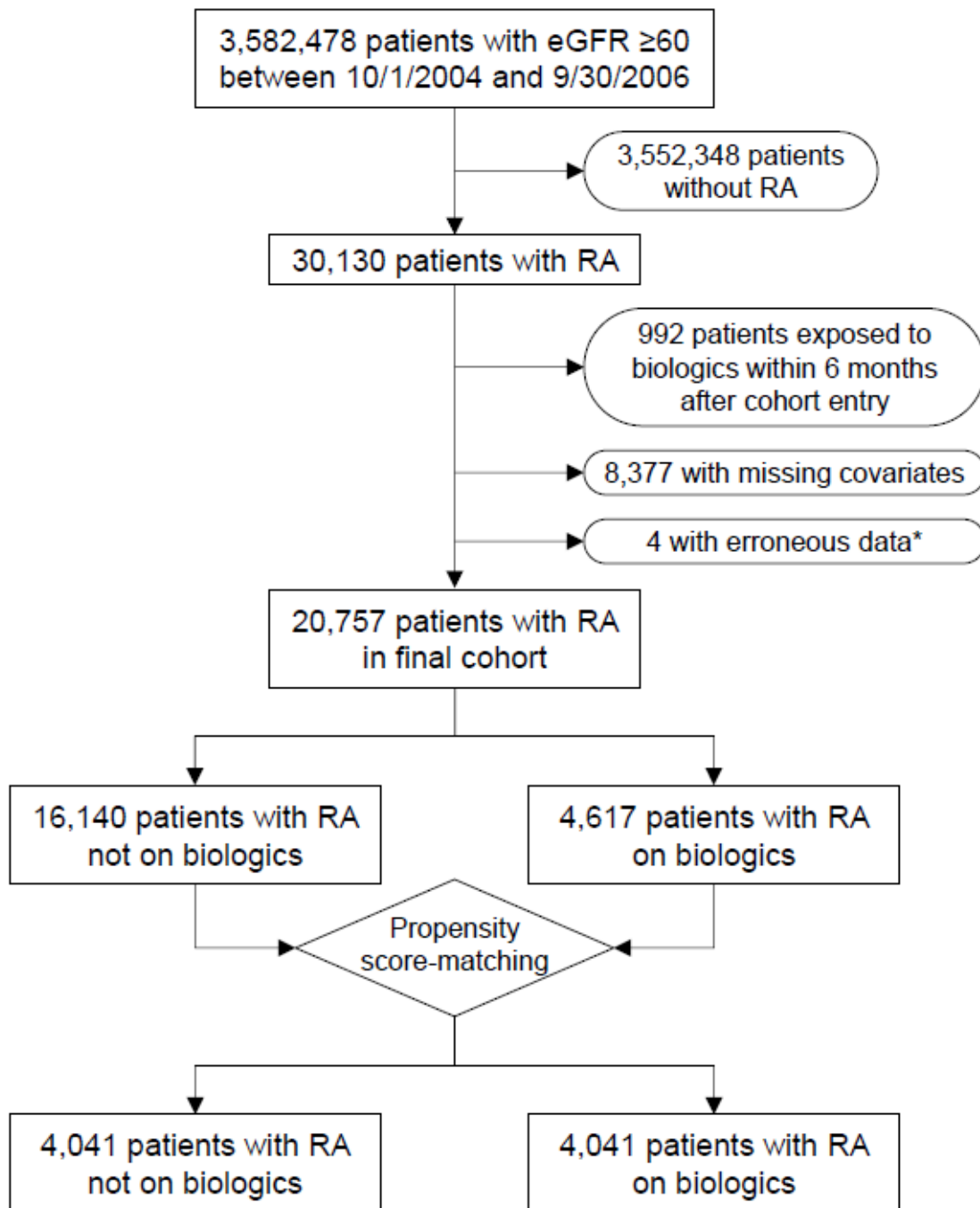


* $P < 0.001$ for comparing differences between pre- and post-biologic administration.

Slopes were estimated from unadjusted (left bar) and multivariable-adjusted (right bar) mixed-effects models. Models were adjusted for fixed (age, sex, race, comorbidities [diabetes mellitus, hypertension, coronary heart disease, congestive heart failure,

cerebrovascular disease, peripheral vascular disease, chronic lung disease, liver disease, dementia, malignancy, depression, and HIV/AIDS], and socioeconomic parameters [mean per capita income, marital status, service connectedness, housing stress, low education, low employment, and persistent poverty]) and time-dependent confounders (eGFR, BMI, systolic blood pressure, serum albumin, number of articular procedures per year, and medications [statins, RASi, methotrexate, hydroxychloroquine, sulfasalazine, leflunomide, other non-biologic DMARDs, NSAIDs, and glucocorticoids]).

Abbreviations: AIDS = acquired immunodeficiency syndrome; BMI = body mass index; DMARD = disease-modifying anti-rheumatic drug; eGFR = estimated glomerular filtration rate; HIV = human immunodeficiency virus; NSAID = nonsteroidal anti-inflammatory drug; RASi = renin-angiotensin system inhibitor; SD = standard deviation.

Supplemental Figure 4. Algorithm used to define study cohort

*Patients with the date of start of follow-up later than the date of last encounter.

Abbreviations: eGFR = estimated glomerular filtration rate; RA = rheumatoid arthritis.