THE LANCET
Healthy Longevity

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplementary Tables:

eTable 0. Association between home metformin use and mortality in unadjusted and adjusted analyses in patients with type 2 diabetes or obesity, hospitalized for Covid-19 (confirmed or presumed).[a]

Primary analyses, overall population	Odds Ratio (95% CI)
Unadjusted	0.802 (0.701, 0.917)
Logistic regression with full covariate list (Table 1)	0.911 (0.784, 1.060)
Logistic regression with Lasso selection variables[b]	0.904 (0.782, 1.045)
Mixed Effects Model[b]	0.898 (0.777, 1.038)
Subgroup analysis in females	
Logistic regression[b]	0.792 (0.640, 0.979)
With disease-medication interaction terms[d]	0.788 (0.637, 0.975)
Mixed Effects Model[b]	0.780 (0.631, 0.965)
With disease-medication interaction terms[d]	0.780 (0.631, 0.965)

[a]In patients with >6 months continuous coverage in 2019 and 90 days of metformin use.
[b]Adjusted for variables selected by Lasso: age, sex (in overall, not in subgroups by sex), comorbidities (hypertension, tobacco use, venous thromboembolism, neutropenia, chronic obstructive pulmonary disease, chronic kidney disease, alcohol abuse, HIV, asthma, inflammatory bowel disease, dementia, charlson comorbidity index, and the diabetes complications and severity index); and medications (ursodiol, angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), steroids, ivermectin, beta2agonists, mast cell stabilizers, allopurinol, azathioprine, mycophenolate mofetil), and state. [c]Matched on the same variables as the Logistic, Mixed effects, and Cox models.
[d]Hypertension with ACEi, ARB use; Asthma with beta2-agonist use

eTable 1. Associations between mortality and demographic and clinical characteristics by logistic regression model.[a]

Demographic characteristics	Odds Ratio (95% CI)
Age under 56	Reference group
Age 56-65 years	1.241 (0.829, 1.867)
Age 66-75 years	1.980 (1.370, 2.866)
Age 76-85 years	2.567 (1.775, 3.711)
Age > 85 years	3.042 (2.070, 4.470)
Male sex (female as reference group)	1.428 (1.210, 1.686)
Pre-existing Conditions	
Charlson comorbitidy index	1.023 (0.990, 1.057)
DCSI	0.981 (0.938, 1.0249
Venous Thromboembolism	0.647 (0.435, 0.964)
Essential HTN (no HTN, no ACE/ARB is ref)	1.108 (0.905, 1.356)
With ACEi	1.004 (0.807, 1.248)
With ARB	1.293 (1.040, 1.607)
With ACEi and ARB	0.722 (0.386, 1.370)
ACEi use, with no HTN	0.878 (0.671, 1.150)
ARB use, with no HTN	1.145 (0.873, 1.502)
Asthma (no asthma, no beta2agonist is ref)	1.242 (0.565, 2.730)
With beta2agonist	0.582 (0.373, 0.908)
Beta2agonist, no asthma	1.117 (0.942, 1.325)
Asthma (dichotomous variable)	0.620 (0.421, 0.912)
Neutropenia	2.061 (0.643, 6.605)
Chronic obstructive pulmonary disease	1.136 (0.926, 1.393)
Chronic kidney disease	1.143 (0.935, 1.408)
Alcohol abuse	0.632 (0.292, 1.371)
Human immunodeficiency virus	1.511 (0.618, 3.707)
Inflammatory bowel disease	0.318 (0.094, 1.325)
Dementia	1.195 (0.996, 1.434)
Home Medications	
Bile acid	2.032 (0.543, 7.614)
Steroids	1.120 (0.952, 1.318)
Ivermectin	1.415 (0.697, 2.870)
Mast cell stabilizer	0.661 (0.344, 1.272)
Allopurinol	1.513 (1.224, 1.870)
Azathioprine & Mycophenolate mofetil	3.307 (1.764, 6.201)

[a]Adjusted for variables in the table and state in which the hospitalization occurred
Abbreviations: DCSI=diabetes complications severity index; HTN=hypertension; ACEi = Angiotensin-converting enzyme inhibitors; ARB=angiotensin 2 receptor blocker

eTable 2. Associations between mortality and demographic and clinical characteristics by mixed-effects analysis.[a]

Demographic characteristics	Odds Ratio (95% CI)
Age under 56	Reference group
Age 56-65 years	1.276 (0.857, 1.900)
Age 66-75 years	2.050 (1.426, 2.947)
Age 76-85 years	2.667 (1.856, 3.832)
Age > 85 years	3.190 (2.183, 4.661)
Male sex (female as reference group)	1.428 (1.210, 1.686)
Pre-existing Conditions	
Charlson comorbitidy index	1.021 (0.988, 1.055)
DCSI	0.979 (0.937, 1.0230
Venous Thromboembolism	0.656 (0.441, 0.975)
Essential HTN (no HTN, no ACE/ARB is ref)	1.113 (0.910, 1.360)
With ACEi	0.995 (0.802, 1.236)
With ARB	1.307 (1.054, 1.622)
With ACEi and ARB	0.718 (0.379, 1.360)
ACEi use, with no HTN	0.864 (0.661, 1.129)
ARB use, with no HTN	1.135 (0.867, 1.486)
Asthma (no asthma, no beta2agonist is ref)	1.250 (0.571, 2.737)
With Beta2agonist	0.586 (0.377, 0.913)
Beta2agonist, no asthma	1.116 (0.942, 1.321)
Asthma (dichotomous variable)	0.624 (0.424, 0.916)
Neutropenia	2.121 (0.665, 6.773)
Chronic obstructive pulmonary disease	1.116 (0.912, 1.367)
Chronic kidney disease	1.136 (0.930, 1.3870
Alcohol abuse	0.638 (0.295, 1.380)
Human immunodeficiency virus	1.499 (0.621, 3.622)
Inflammatory bowel disease	0.315 (0.093, 1.322)
Dementia	1.198 (0.999, 1.436)
Home Medications	
Bile acid	2.039 (0.546, 7.613)
Steroids	1.122 (0.955, 1.320)
Ivermectin	1.448 (0.720, 2.13)
Mast cell stabilizer	0.685 (0.357, 1.313)
Allopurinol	1.516 (1.229, 1.872)
Azathioprine & Mycophenolate mofetil	3.267 (1.753, 6.087)

[a]Adjusted for variables in the table and state in which the hospitalization occurred

Abbreviations: DCSI=diabetes complications severity index; HTN=hypertension; ACEi= Angiotensin-converting enzyme inhibitors; ARB=angiotensin 2 receptor blocker

eTable 3. Associations between mortality and demographic and clinical characteristics by Cox proportional-hazards, shared frailty model.[a]

Demographic characteristics	Hazard Ratio (95% CI)
Age < 56 years	Reference group
Age 56-65 years	1.259 (0.868, 1.827)
Age 66-75 years	1.895 (1.351, 2.659)
Age 76-85 years	2.426 (1.731, 3.399)
Age > 85 years	2.850 (2.009, 4.043)
Male sex (female as reference group)	1.464 (1.301, 1.648)
Pre-existing Conditions	
Charlson comorbidity index	1.022 (0.993, 1.051)
DCSI	0.937 (0.937, 1.011)
Venous Thromboembolism	0.699 (0.490, 0.996)
Essential HTN (no HTN is reference group)	1.087 (0.913, 1.293)
With ACEi	0.984 (0.814, 1.190)
With ARB	1.218 (1.011, 1.466)
With ACEi and ARB	0.769 (0.429, 1.379)
ACEi use, with no HTN	0.847 (0.667, 1.076)
ARB use, with no HTN	1.110 (0.877, 1.404)
Asthma (no asthma, no beta2agonist is ref)	1.146 (0.591, 2.22)
Asthma with beta2agonist	0.612 (0.408, 0.918)
Beta2agonist, no asthma	1.085 (0.937, 1.257)
Asthma, dichotomous variable	0.652 (0.461, 0.924)
Tobacco use	$1.11e^{13}$ (0, 0)
Chronic obstructive pulmonary disease	1.119 (0.938, 1.336)
Chronic kidney disease	1..113 (0.938, 1.320)
Alcohol abuse	0.724 (0.360, 1.457)
Human immunodeficiency virus	1.173 (0.571, 2.417)
Inflammatory bowel disease	0.335 (0.108, 1.057)
Dementia	1.172 (1.005, 1.368)
Home Medications	
Bile acid	1.921 (0.708, 5.211)
Angiotensin-converting enzyme inhibitors	0.869 (0.757, 0.997)
Angiotensin 2 receptor blockers	1.091 (0.952, 1.249)
Steroids	1.094 (0.951, 1.259)
Ivermectin	1.444 (0.809, 2.576)
Beta 2 agonist	1.066 (0.921, 1.233)
Mast cell stabilizer	0.674 (0.370, 1.227)
Allopurinol	1.384 (1.161, 1.649)
Azathioprine & Mycophenolate mofetil	2.485 (1.542, 4.004)

[a]Adjusted for the variables in this table and state in which the hospitalization occurred.
Abbreviations: DCSI=diabetes complications severity index. HTN=hypertension; ACEi= Angiotensin-converting enzyme inhibitors; ARB=angiotensin 2 receptor blocker

eTable 4. Association between persons with home TNFα use (n=38) and mortality in persons hospitalized for Covid-19 (confirmed or presumed).[a]

Cox proportional-hazards, HR, stratified model[b]	0.361 (0.0894, 1.414)
Cox proportional-hazards, HR, shared frailty model[b]	0.350 (0.087, 1.415)
Propensity Matched Model,[c] caliper 0.2	0.483 (0.082, 2.844)
Log-Rank test, p-value	0.31
Propensity Matched Model[d], caliper 0.2	0.193 (0.038, 0.983)
Log-Rank test, p-value	0.03

[a]In patients with at least 6 months of continuous coverage in 2019 and 90 days of metformin use.
[b]Adjusted for variables selected by Lasso: age, sex (in overall, not in subgroups by sex), comorbidities (hypertension, tobacco use, venous thromboembolism, neutropenia, chronic obstructive pulmonary disease, chronic kidney disease, alcohol abuse, HIV, asthma, inflammatory bowel disease, dementia, charlson comorbidity index, and the diabetes complications and severity index); and medications (ursodiol, angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), steroids, ivermectin, beta2agonists, mast cell stabilizers, allopurinol, azathioprine, mycophenolate mofetil), and state. [c]Matched on the same variables as the Logistic, Mixed effects, and Cox models.
[d]Matched on only for age, sex, charlson co-morbidity index, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease.

eTable 5. E-values for the associations between metformin use and mortality in persons hospitalized with Covid-19[a]

Overall population	OR (95% CI)	E value	E value, CI
Unadjusted	0.802 (0.701, 0.917)	1.478	1.259
Logistic regression with full covariate list (Table 1)	0.911 (0.784, 1.060)	1.271	1
Logistic regression with Lasso selection variables[b]	0.904 (0.782, 1.045)	1.285	1
Mixed Effects Model[b]	0.898 (0.777, 1.038)	1.297	1
Cox proportional-hazards, HR, stratified model[b]	0.887 (0.782, 1.008)	1.318	1
Cox proportional-hazards, HR, shared frailty model[b]	0.884 (0.778, 1.003)	1.323	1
Propensity Matched Model,[c] exact matching	0.912 (0.777, 1.071)	1.269	1
Propensity Matched Model, caliper 0.2[c]	0.898 (0.768, 1.051)	1.297	1
Subanalyses in females			
Logistic regression[b]	0.792 (0.640, 0.979)	1.496	1.115
Mixed Effects Model[b]	0.780 (0.631, 0.965)	1.519	1.153
Cox proportional-hazards, HR, shared frailty model[b]	0.785 (0.650, 0.951)	1.510	1.187
Propensity Matched Model,[c] caliper 0.2	0.759 (0.601, 0.960)	1.560	1.166
Sensitivity analyses in females with Covid-19 confirmed by PCR			
Cox proportional-hazards, HR, shared frailty model[b]	0.808 (0.651, 1.003)	1.466	1
Cox proportional-hazards, HR, shared frailty model[e]	0.790 (0.637, 0.978)	1.500	1.118
Propensity Matched Model,[c]	0.744 (0.565, 0.980)	1.589	1.111
Association between home TNFa use and mortality, n=38 persons hospitalized with Covid-19			
Cox proportional-hazards, HR, stratified model[b]	0.361 (0.0894, 1.414)	2.716	1
Cox proportional-hazards, HR, shared frailty model[b]	0.350 (0.087, 1.415)	2.771	1
Propensity Matched Model,[e] caliper 0.2	0.483 (0.082, 2.844)	2.234	1
Propensity Matched Model,[f] caliper 0.2	0.193 (0.038, 0.983)	3.981	1.102

[a]In patients with >6 months continuous coverage in 2019 and 90 days of metformin use.
[b]Adjusted for variables selected by Lasso: age, sex (in overall, not in subgroups by sex), comorbidities (hypertension, tobacco use, venous thromboembolism, neutropenia, chronic obstructive pulmonary disease, chronic kidney disease, alcohol abuse, HIV, asthma, inflammatory bowel disease, dementia, charlson comorbidity index, and the diabetes complications and severity index); and medications (ursodiol, angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), steroids, ivermectin, beta2agonists, mast cell stabilizers, allopurinol, azathioprine, mycophenolate mofetil), and state.[c] Matched on the same variables as the Logistic, Mixed effects, and Cox models.
[c]Matched on the same variables as the Logistic, Mixed effects, and Cox models.
[e]Matched on the same variables as the Logistic, Mixed effects, and Cox models.
[f]Matched on only for age, sex, charlson co-morbidity index, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease.

Supplemental Materials 1.

**Prescription Medications Assessed:**

ACE inhibitors; angiotensin receptor blockers; statin; antiplatelet agents (defined as aspirin, clopidogrel, ticagrelor, ticlopidine, and eptifibatide); anticoagulant agents (defined as warfarin, heparin, rivaroxaban, dabigatran, apixaban, enoxaparin, fondaparinux); anti-tumor necrosis factor medications (defined as infliximab, adalimumab, certolizumab, golimumab, etanercept); tenofovir alone; highly active antiretroviral therapy (HAART); systemic steroids (defined as prednisone, dexamethasone, or prednisolone); hydroxychloroquine or chloroquine; JAK inhibitors (tofacitinib was the only JAK inhibitor identified with a claim in the database); calcineurin inhibitors (defined as cyclosporine or tacrolimus); mTOR inhibitors (defined as sirolimus or everolimus); insulin, GLP-1 receptor agonists; beta blockers; ivermectin; beta 2 agonists; allopurinol; purine synthesis inhibitors (defined as azathioprine or mycophenolate); anti-viral herpes medications (acyclovir, ganciclovir, and valganciclovir); montelukast sodium; NSAIDs (defined as ibupropfen, naproxen, indomethacin, or celecoxib); diuretics (defined as by furosemide, bumetanide, torsemide, metolazone, or ethacrynic acid); azithromycin; ursodiol; tumor-necrosis alpha inhibitors.

Comorbidities Assessed:

Type 2 Diabetes (ICD10, e11.0-9); Type 1 Diabetes (ICD10, e10.0-9); Essential Hypertension (ICD10, i10); Tobacco Use (ICD10, z71.6, z72.0); Coronary Artery Disease (ICD10, i25.0-9); Heart Failure with Preserved Ejection Fraction (ICD10, i50.30-33)/ Systolic Heart Failure (ICD10, i50.20-23 and i50.40-43); Liver Disease (ICD10, k70.0-k70.9, k71.0-k71.9, k72.0-k72.91, k73.0-k73.9, k74.0-k74.69, k75.0-k75.9, k76.0-k76.9, k77); Class 2 Obesity defined as BMI ≥ 35 (ICD10, z68.35-39, z68.40-45, e66.01, e66.2, e66.8, e66.9); Prior venous thromboembolism (ICD10, i27.82, z86.711, z86.718, i82.A, i82.B, i82.C, i82.0-9); Neutropenia (ICD10, d70.0-9); Cancer (ICD10, C00-96); Coagulation Disorder (ICD10, d68.0-9); Heart Valve (ICD10, z95.2, z95.5, z95.9); COPD (ICD10, j41.0, j41.1, j41.8, j43.0-9, j44.0, j44.1, j44.9); Interstitial Lung Disease (ICD10, j84.0-9); Chronic Kidney Disease Stage 3 or 4 (ICD10, n18.3, n18.4); End Stage Renal Disease (ICD10, n18.5, n18.6); Atrial Fibrillation or Flutter (ICD10, i48.0-92); CVA/TIA (ICD10, g45.0-9, g46.0-8, g97.31-32, i60.0-9, i61.0-9, i62.0-9, i63.0-9, i97.81-82); ETOH Abuse (ICD10, f10.0-99, k70.0-9, g62.1, i42.6, k29.2, o35.4, o99.31); HIV (ICD10, b20, b97.35, r75, z21); Asthma (ICD10, j45.2-998); Prior General Flu (ICD10, j10.0-89, j11.0-89); Prior Avian or Swine Flu (ICD10, j09.X1-X9); Inflammatory bowel disease (ICD10, k50.0-919, k51.0-919); Lupus or Rheumatoid Arthritis (ICD10, l93.0-.2, m32.0-9, m06.0-9); Dementia (ICD10, f03.90, f03.91, f01.5, g30.0-9, g31.0-9).
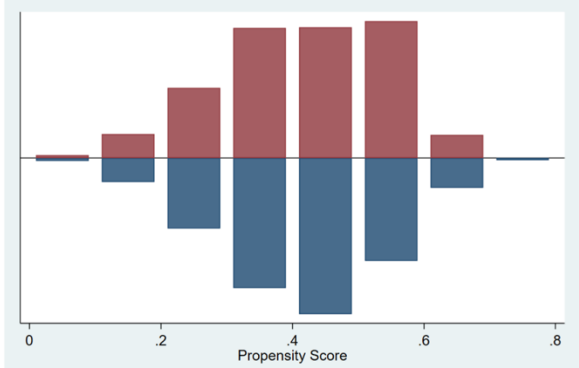
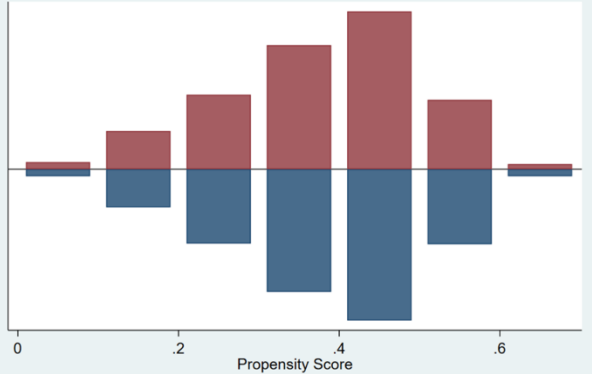**eFigure 1.** Log log plot assessing the proportionality assumption
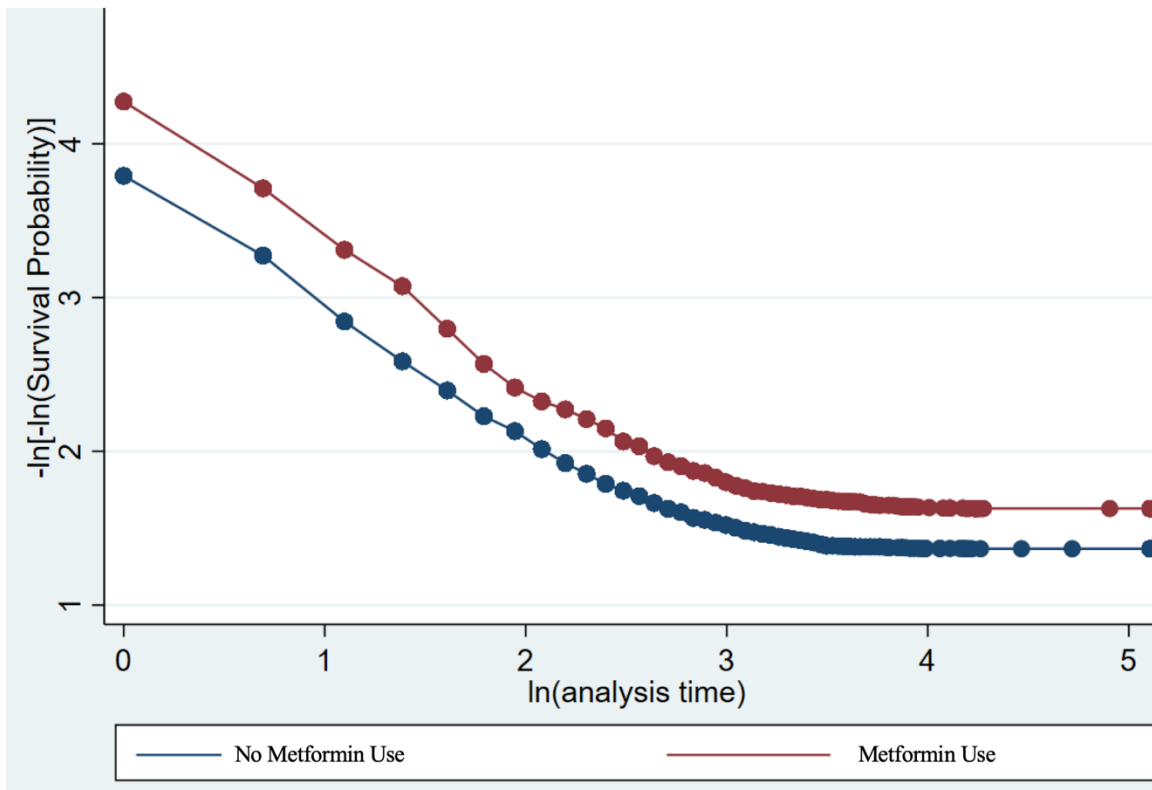
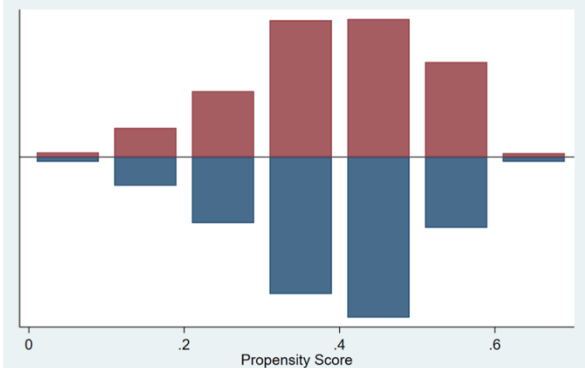**eFigure 2.** Balance of matching with caliper 0.2

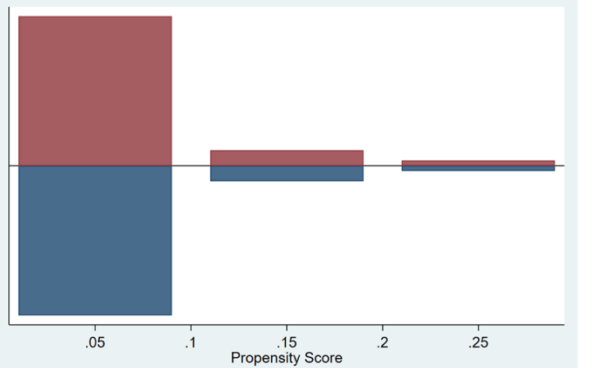Overall sample of persons with type 2 diabetes and obesity:

Persons with type 2 diabetes or obesity, males only:

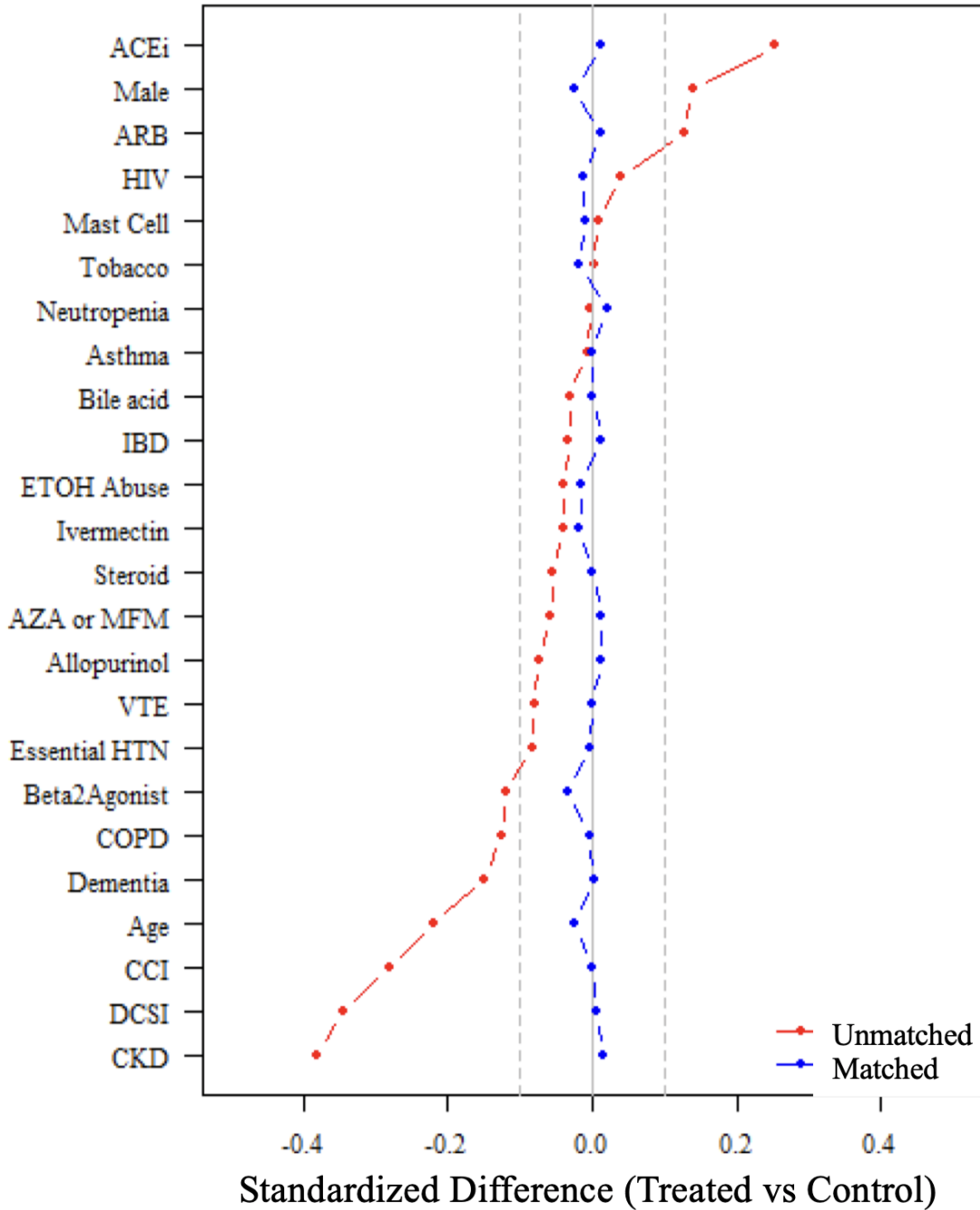Persons with type 2 diabetes or obesity, females only:

Balance of matching in persons with TNF-alpha:

No Metformin use

Metformin use

eFigure 3. Propensity matched covariate balance

Abbreviations: ACEi=angiotensin converting enzyme inhibitor; ARB=angiotensin 2 receptor blocker; IBD=inflammatory bowel disease; ETOH=alcohol; AZA=azathioprine; MFM=mycophenolate mofetil; VTE=venous thromboembolism; HTN=hypertension; COPD=chronic obstructive pulmonary disease; CCI=charlson comorbitidy index; DCSI=diabetes complications and severity index; CKD=chronic kidney disease.

eFigure 4. Kaplan Meier curve by TNF-alpha inhibitor use, with propensity matching in persons hospitalized for Covid-19.

Top panel: exact propensity matching on all 32 variables by LASS0

p = 0.30

Kaplan Meier Curve for Anti-TNF

p = 0.032

Bottom panel: exact propensity matching on age, gender, charlson comorbidity score, state, and presence of systemic lupus erythematosus, inflammatory bowel disease, rheumatoid arthritis.

No TNF-alpha inhibitor use   TNF-alpha inhibitor use