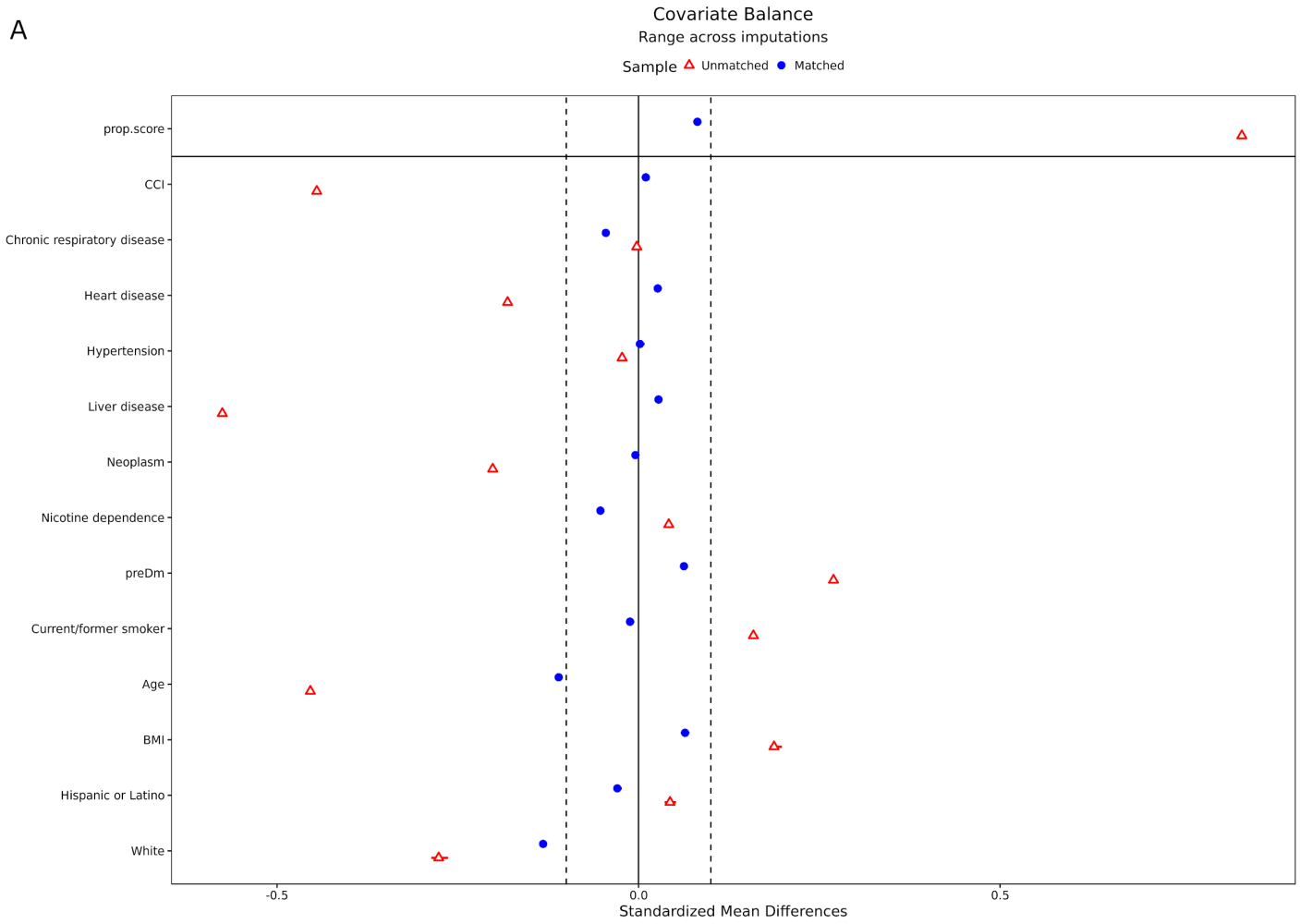
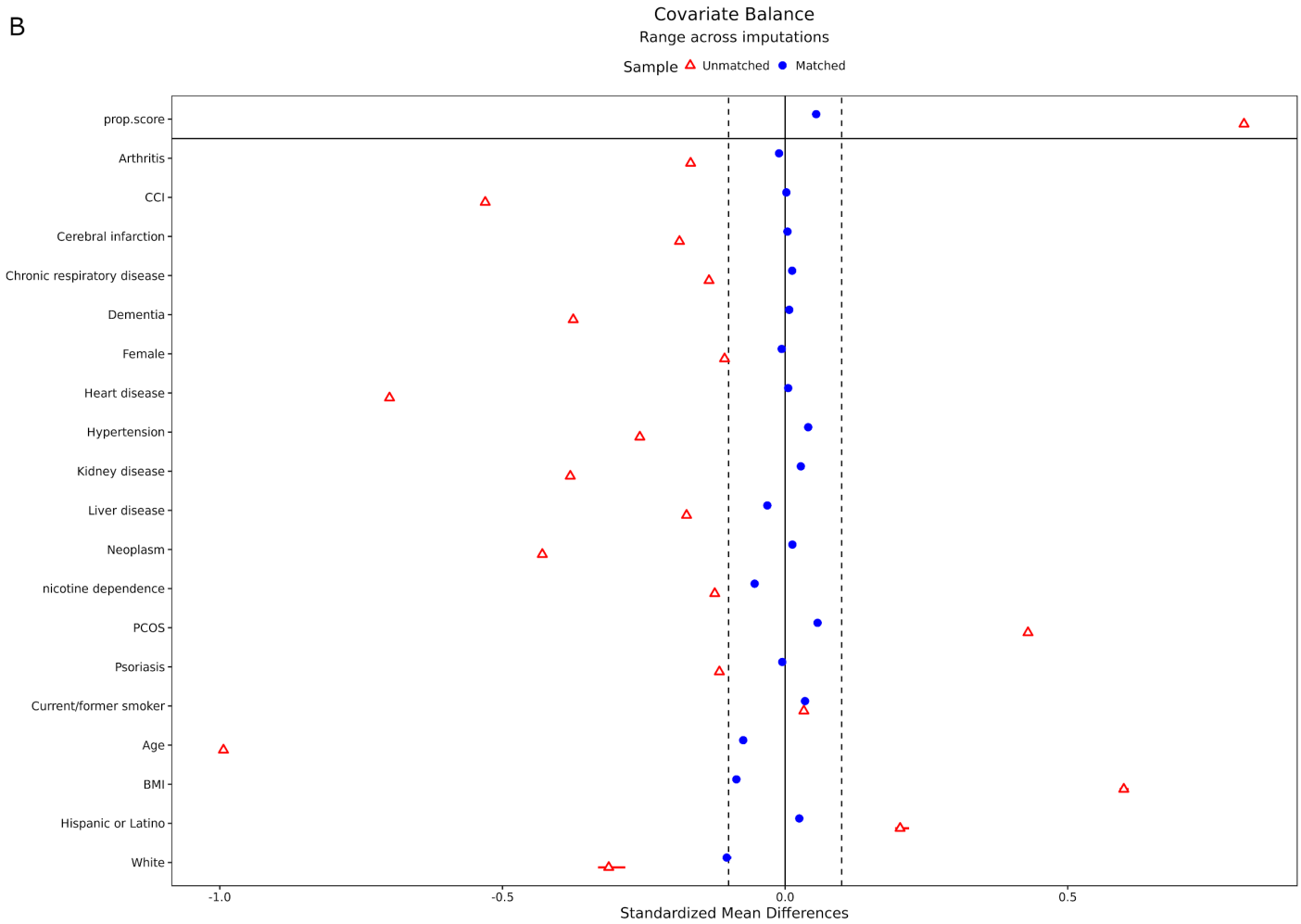
Supplemental Figures S1-S8, Supplemental Table 1

Love plots showing balancing results

A

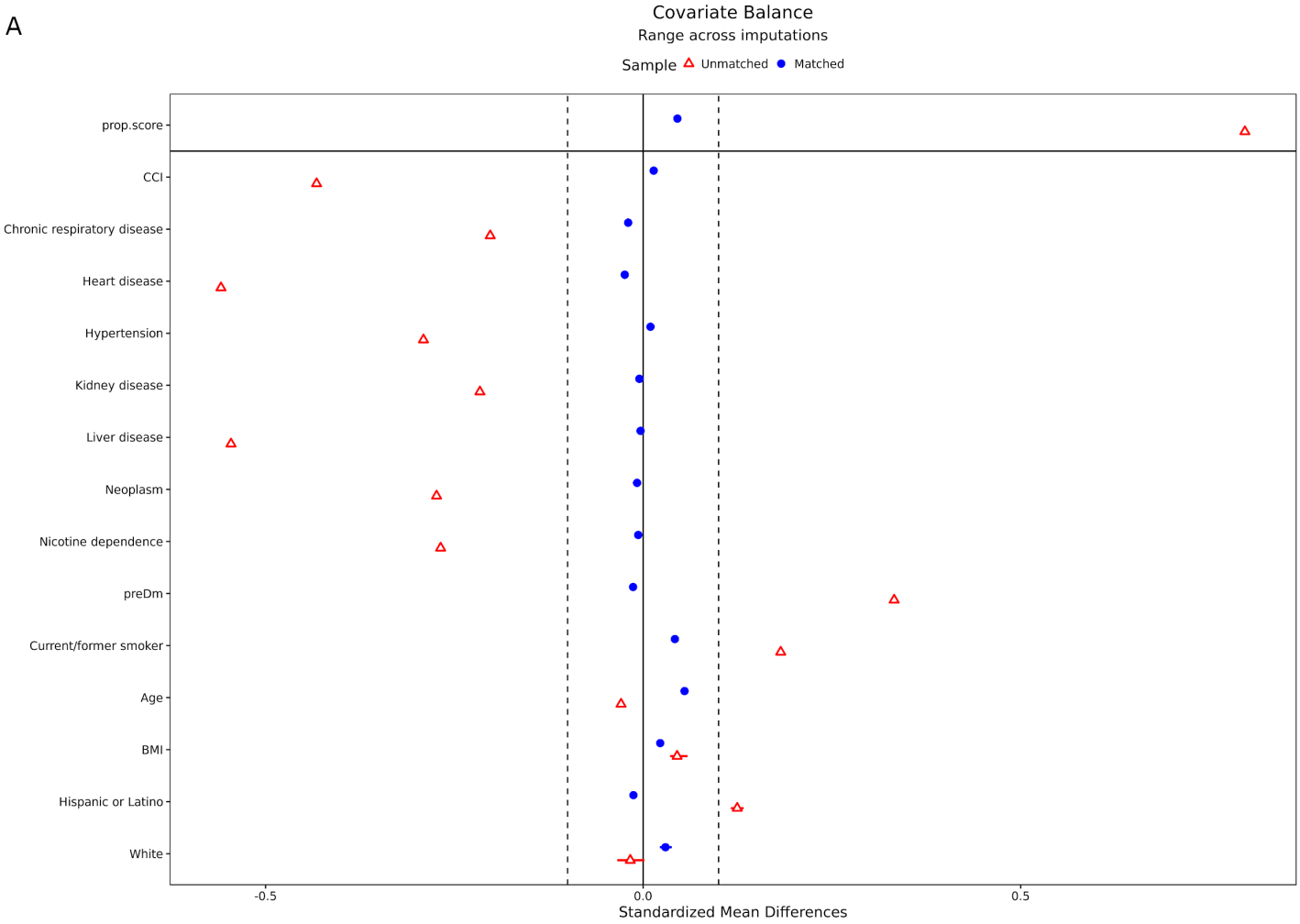


B

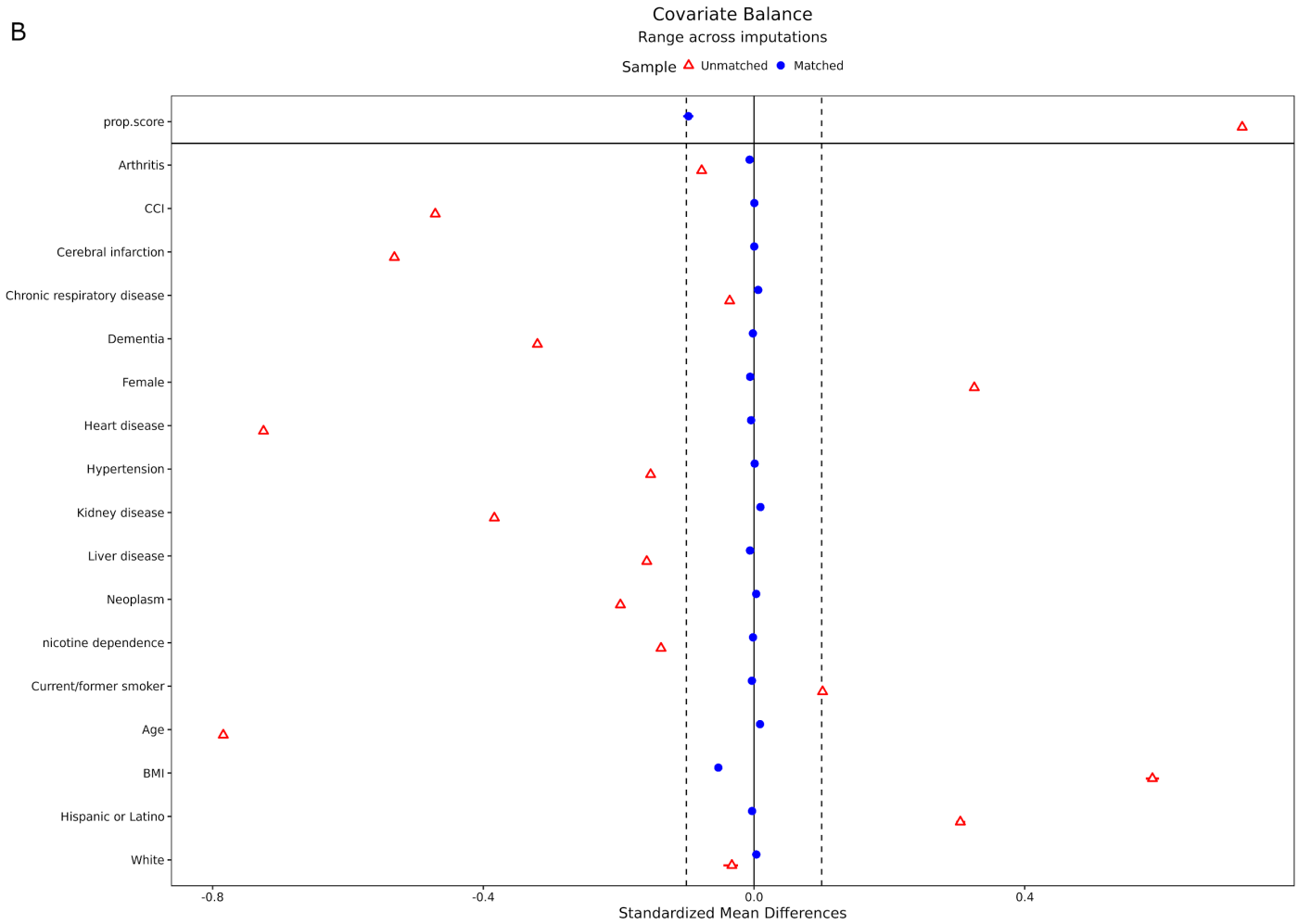


Supplemental Figure S1. Inverse probability weighting in PCOS and prediabetes cohorts for metformin versus levothyroxine. Both PCOS (A) and prediabetes (B) cohorts were balanced using an inverse probability weighting approach. The standardized mean difference (x axis) is shown for each of 19 covariates (y axis) and the overall propensity score. Red triangles indicate the original covariate balance and blue circles indicate the covariate balance after weighting.

A


Covariate Balance
Range across imputations
Sample Unmatched Matched
prop.score
CCI
Chronic respiratory disease
Heart disease
Hypertension
Kidney disease
Liver disease
Neoplasm
Nicotine dependence
preDm
Current/former smoker
Age
BMI
Hispanic or Latino
White
-0.5
0.0
0.5
Standardized Mean Differences

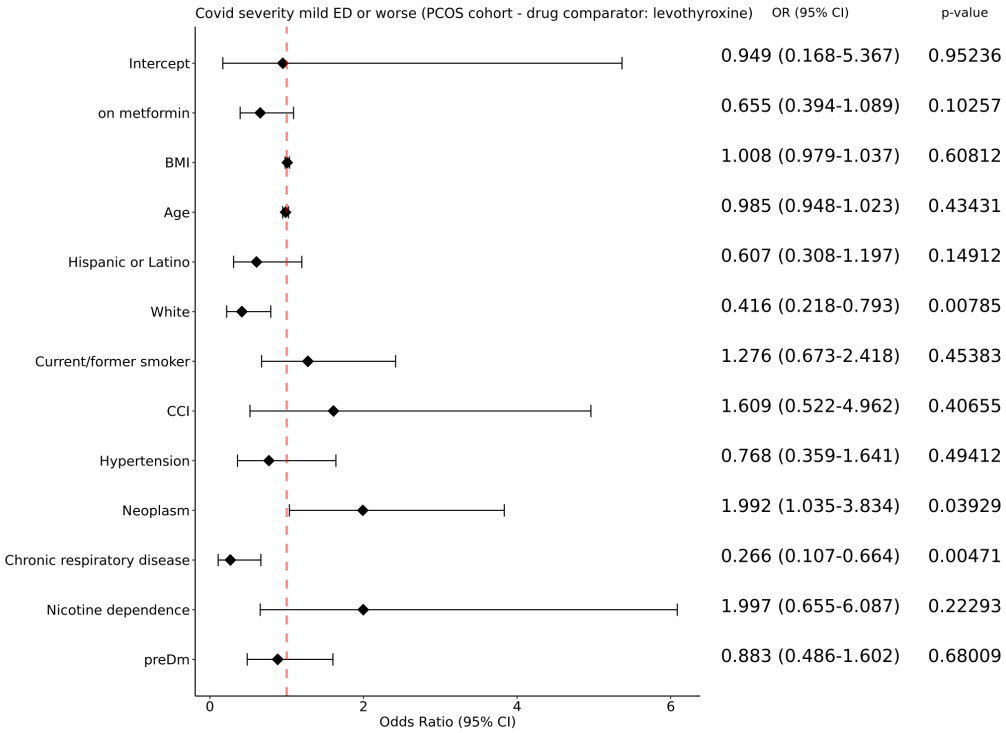
B



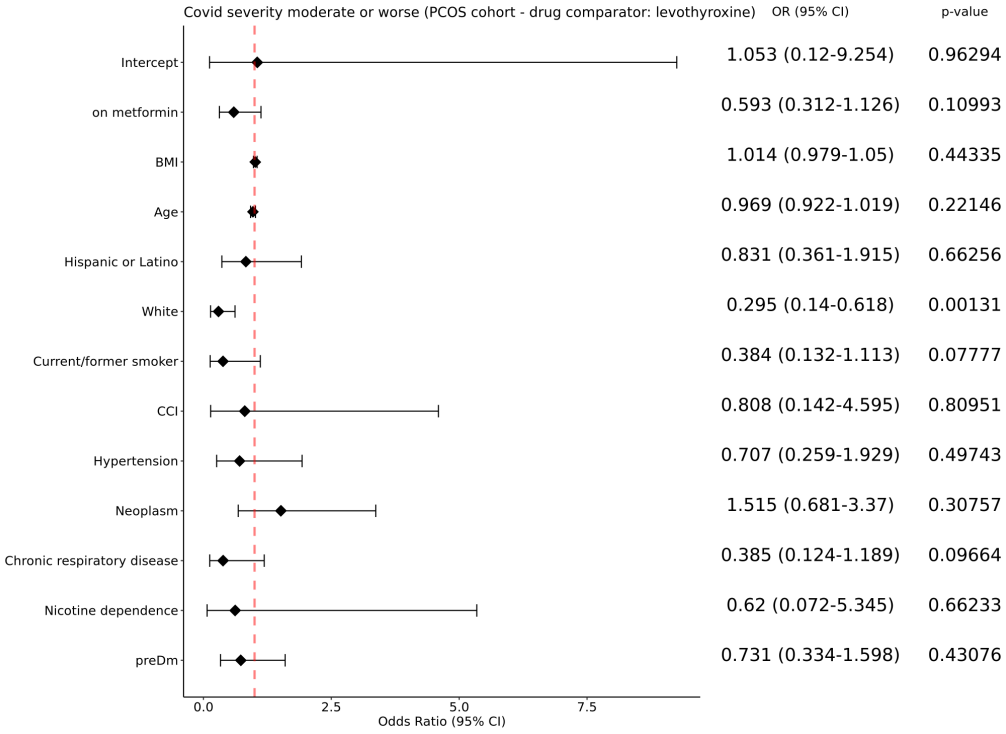
Supplemental Figure S2. Inverse probability weighting in PCOS and prediabetes cohorts for metformin versus ondansetron. Both PCOS (A) and prediabetes (B) cohorts were balanced using an inverse probability weighting approach. The standardized mean difference (x axis) is shown for each of 19 covariates (y axis) and the overall propensity score. Red triangles indicate the original covariate balance and blue circles indicate the covariate balance after weighting.

Forest Plots for PCOS cohort

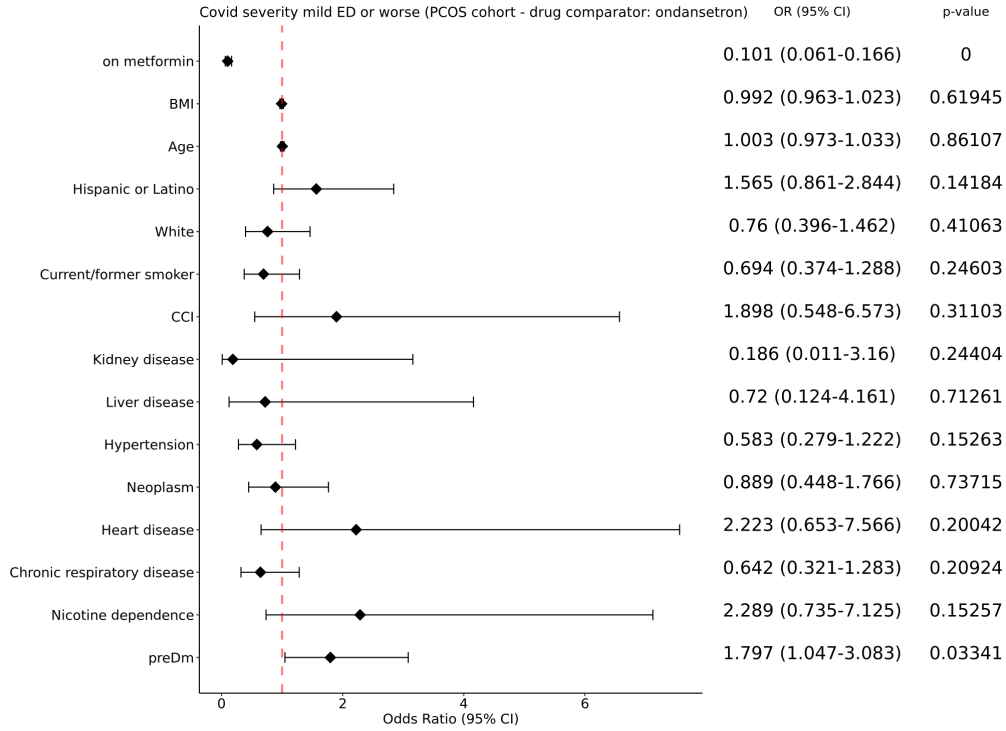
A



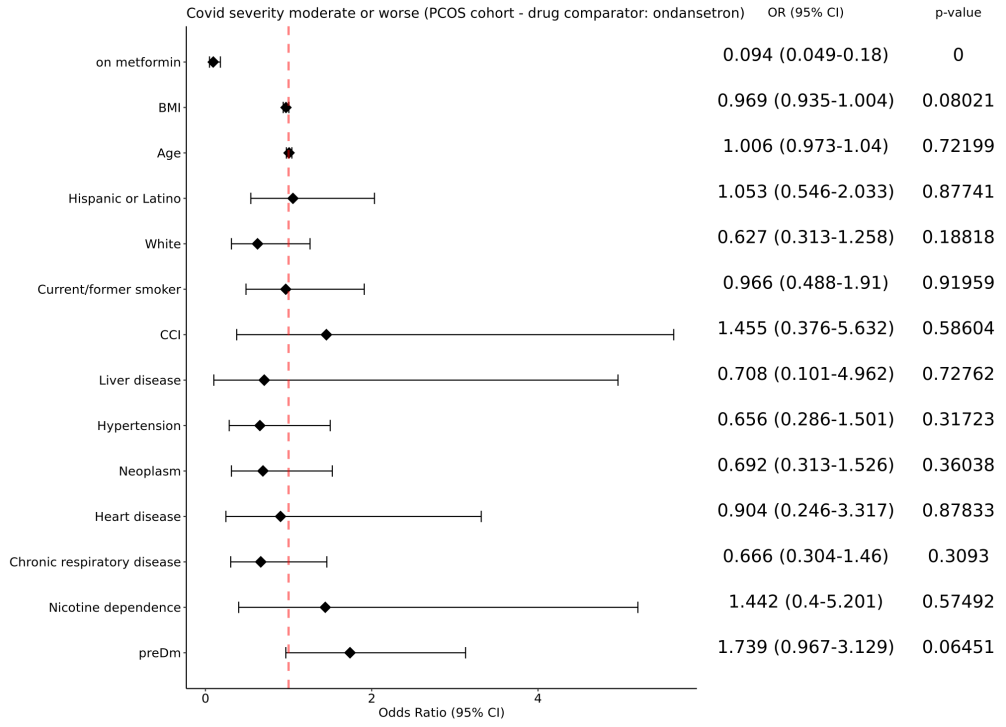
B



C


Covid severity mild ED or worse (PCOS cohort - drug comparator: ondansetron)
OR (95% CI)
p-value
on metformin
BMI
Age
Hispanic or Latino
White
Current/former smoker
CCI
Kidney disease
Liver disease
Hypertension
Neoplasm
Heart disease
Chronic respiratory disease
Nicotine dependence
preDm
0.101 (0.061-0.166)
0
0.992 (0.963-1.023)
0.61945
1.003 (0.973-1.033)
0.86107
1.565 (0.861-2.844)
0.14184
0.76 (0.396-1.462)
0.41063
0.694 (0.374-1.288)
0.24603
1.898 (0.548-6.573)
0.31103
0.186 (0.011-3.16)
0.24404
0.72 (0.124-4.161)
0.71261
0.583 (0.279-1.222)
0.15263
0.889 (0.448-1.766)
0.73715
2.223 (0.653-7.566)
0.20042
0.642 (0.321-1.283)
0.20924
2.289 (0.735-7.125)
0.15257
1.797 (1.047-3.083)
0.03341
0
2
4
6
Odds Ratio (95% CI)

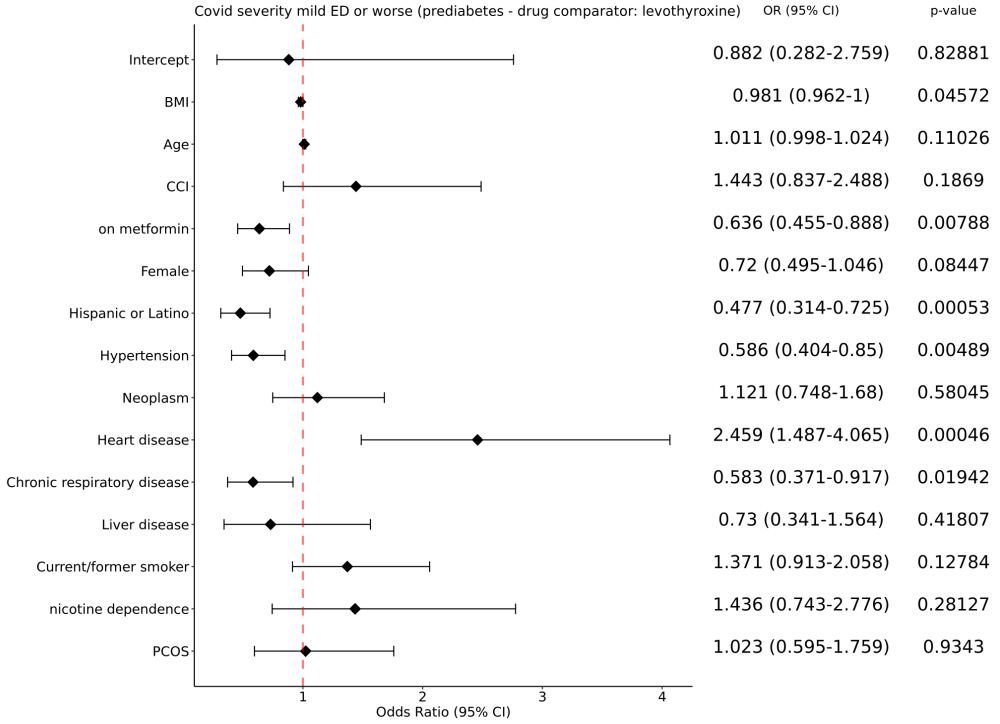
D


Covid severity moderate or worse (PCOS cohort - drug comparator: ondansetron)
OR (95% CI)
p-value
on metformin
BMI
Age
Hispanic or Latino
White
Current/former smoker
CCI
Liver disease
Hypertension
Neoplasm
Heart disease
Chronic respiratory disease
Nicotine dependence
preDm
0.094 (0.049-0.18)
0
0.969 (0.935-1.004)
0.08021
1.006 (0.973-1.04)
0.72199
1.053 (0.546-2.033)
0.87741
0.627 (0.313-1.258)
0.18818
0.966 (0.488-1.91)
0.91959
1.455 (0.376-5.632)
0.58604
0.708 (0.101-4.962)
0.72762
0.656 (0.286-1.501)
0.31723
0.692 (0.313-1.526)
0.36038
0.904 (0.246-3.317)
0.87833
0.666 (0.304-1.46)
0.3093
1.442 (0.4-5.201)
0.57492
1.739 (0.967-3.129)
0.06451
0
2
4
Odds Ratio (95% CI)

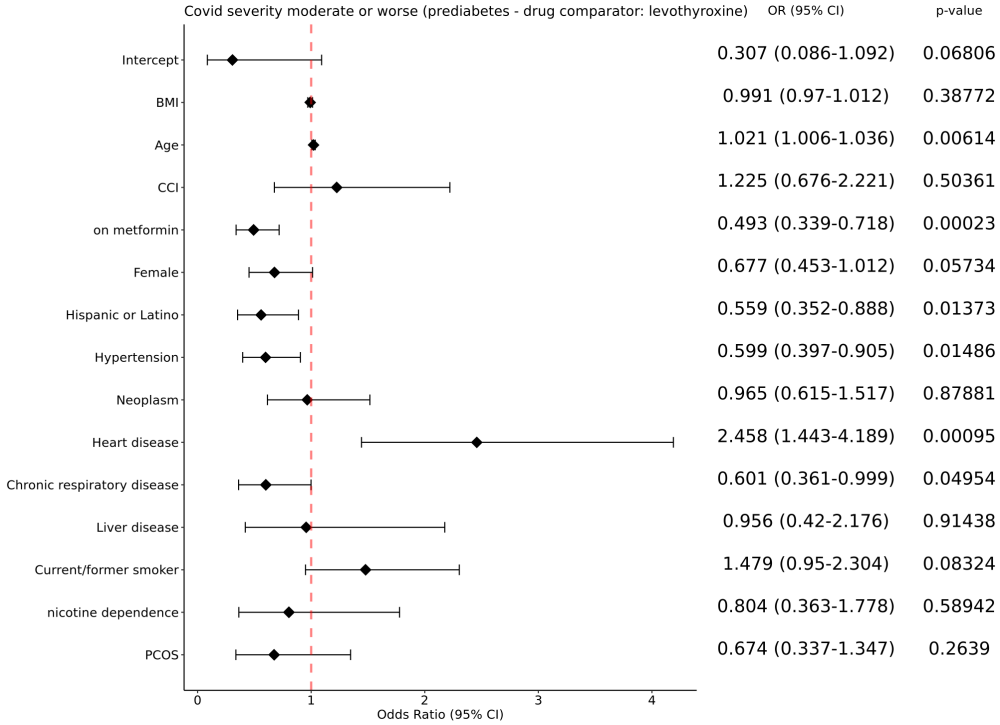
Supplementary Figure S3. Forest plots for the PCOS cohort. A: Mild vs Mild ED and worse, levothyroxine; B: Mild and Mild ED vs Moderate and worse, levothyroxine, C: Mild vs Mild ED and worse, ondansetron; D: Mild and Mild ED vs Moderate and worse, ondansetron.

Forest plots for prediabetes cohort

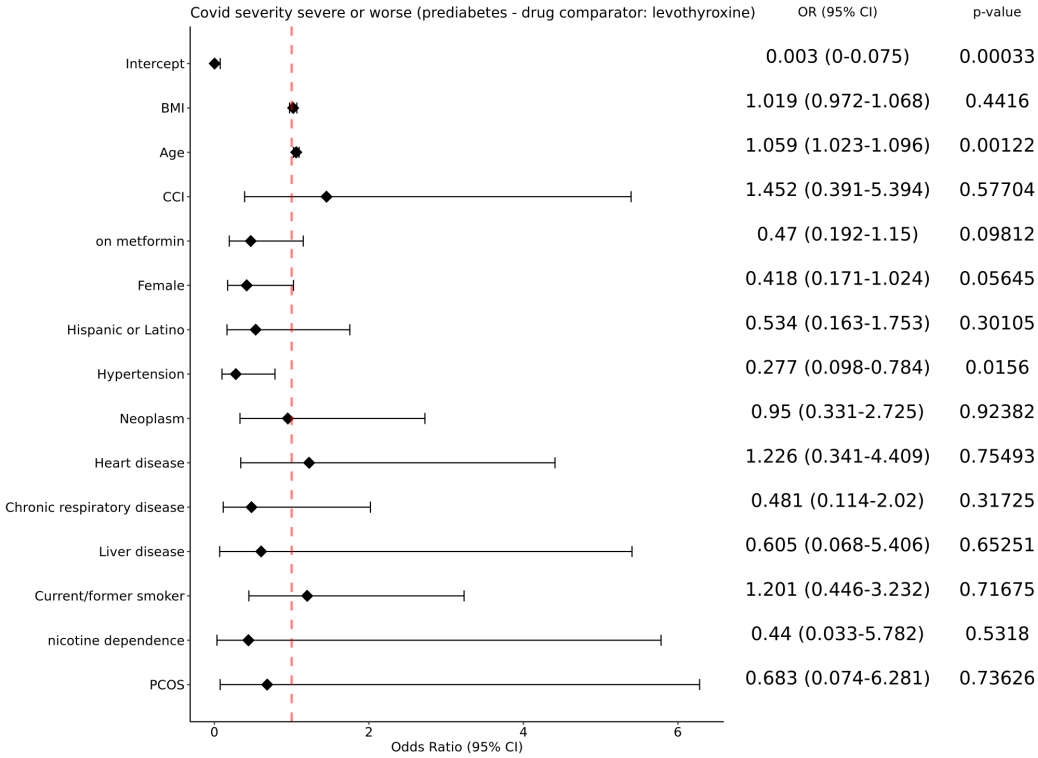
A



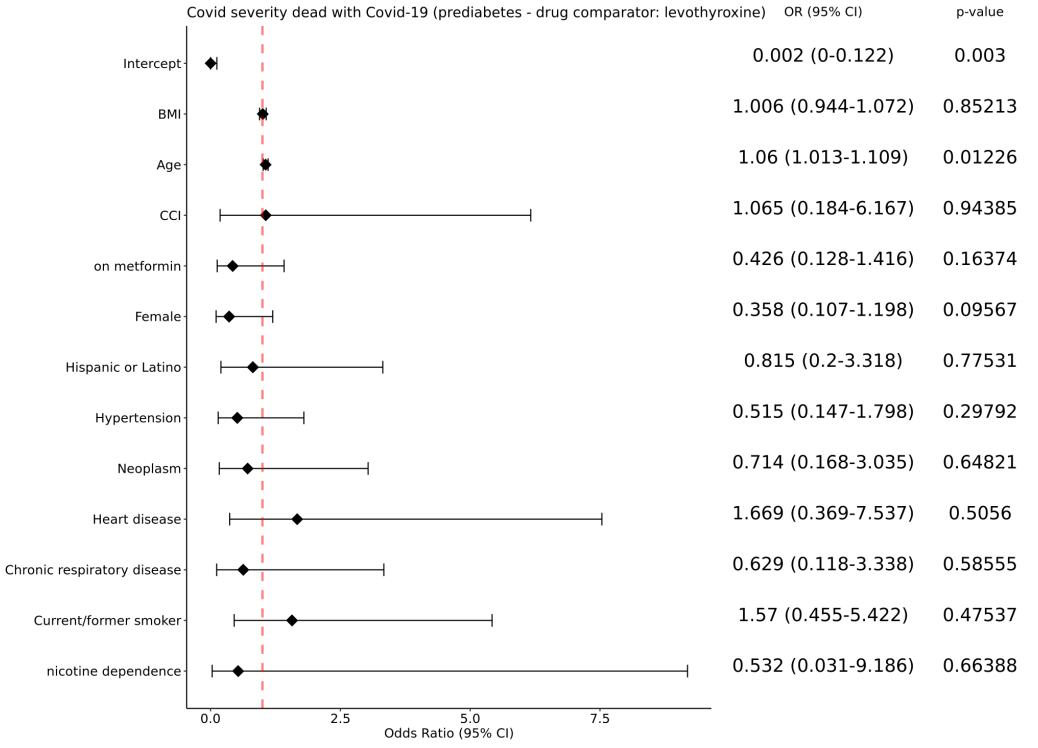
B



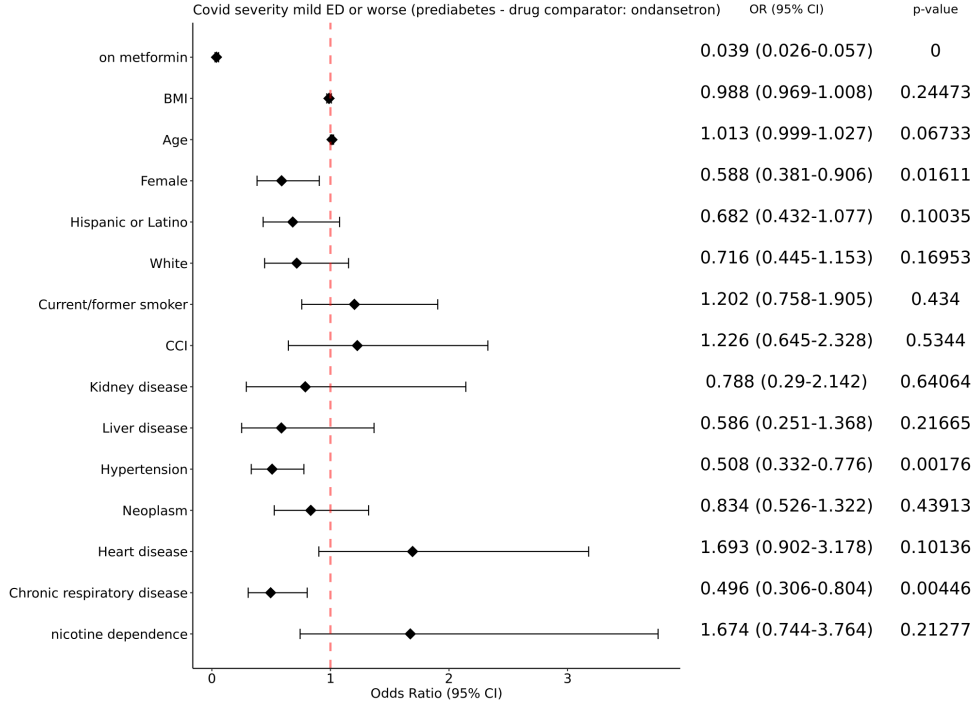
C


Covid severity severe or worse (prediabetes - drug comparator: levothyroxine)
OR (95% CI)
p-value
Intercept
BMI
Age
CCI
on metformin
Female
Hispanic or Latino
Hypertension
Neoplasm
Heart disease
Chronic respiratory disease
Liver disease
Current/former smoker
nicotine dependence
PCOS
0.003 (0-0.075)
0.00033
1.019 (0.972-1.068)
0.4416
1.059 (1.023-1.096)
0.00122
1.452 (0.391-5.394)
0.57704
0.47 (0.192-1.15)
0.09812
0.418 (0.171-1.024)
0.05645
0.534 (0.163-1.753)
0.30105
0.277 (0.098-0.784)
0.0156
0.95 (0.331-2.725)
0.92382
1.226 (0.341-4.409)
0.75493
0.481 (0.114-2.02)
0.31725
0.605 (0.068-5.406)
0.65251
1.201 (0.446-3.232)
0.71675
0.44 (0.033-5.782)
0.5318
0.683 (0.074-6.281)
0.73626
0
2
4
6
Odds Ratio (95% CI)

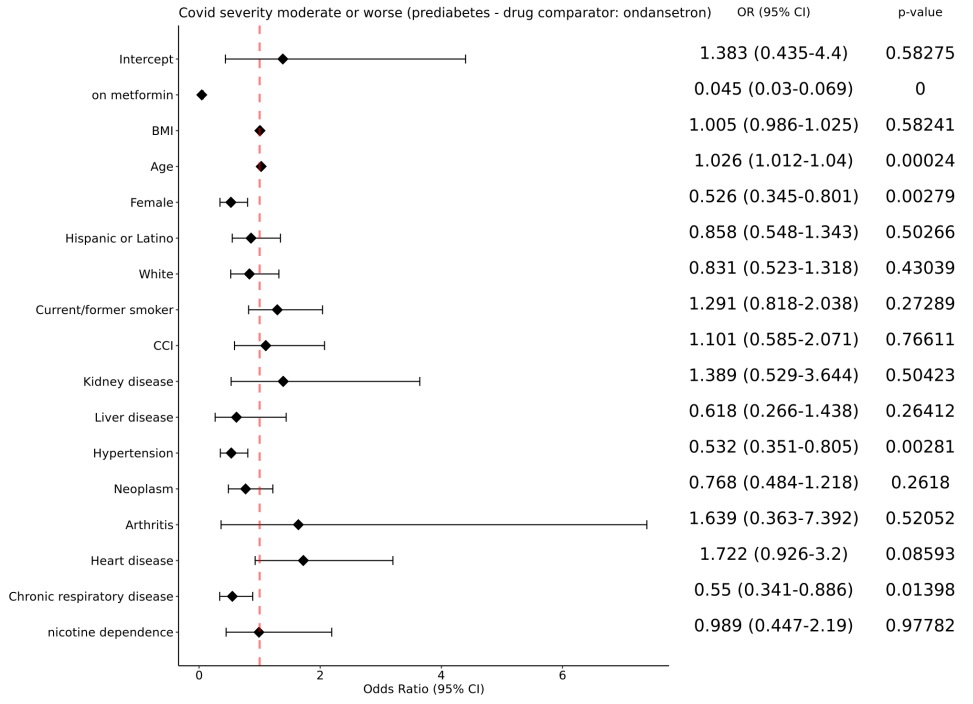
D


Covid severity dead with Covid-19 (prediabetes - drug comparator: levothyroxine)
OR (95% CI)
p-value
Intercept
BMI
Age
CCI
on metformin
Female
Hispanic or Latino
Hypertension
Neoplasm
Heart disease
Chronic respiratory disease
Current/former smoker
nicotine dependence
0.002 (0-0.122)
0.003
1.006 (0.944-1.072)
0.85213
1.06 (1.013-1.109)
0.01226
1.065 (0.184-6.167)
0.94385
0.426 (0.128-1.416)
0.16374
0.358 (0.107-1.198)
0.09567
0.815 (0.2-3.318)
0.77531
0.515 (0.147-1.798)
0.29792
0.714 (0.168-3.035)
0.64821
1.669 (0.369-7.537)
0.5056
0.629 (0.118-3.338)
0.58555
1.57 (0.455-5.422)
0.47537
0.532 (0.031-9.186)
0.66388
0.0
2.5
5.0
7.5
Odds Ratio (95% CI)

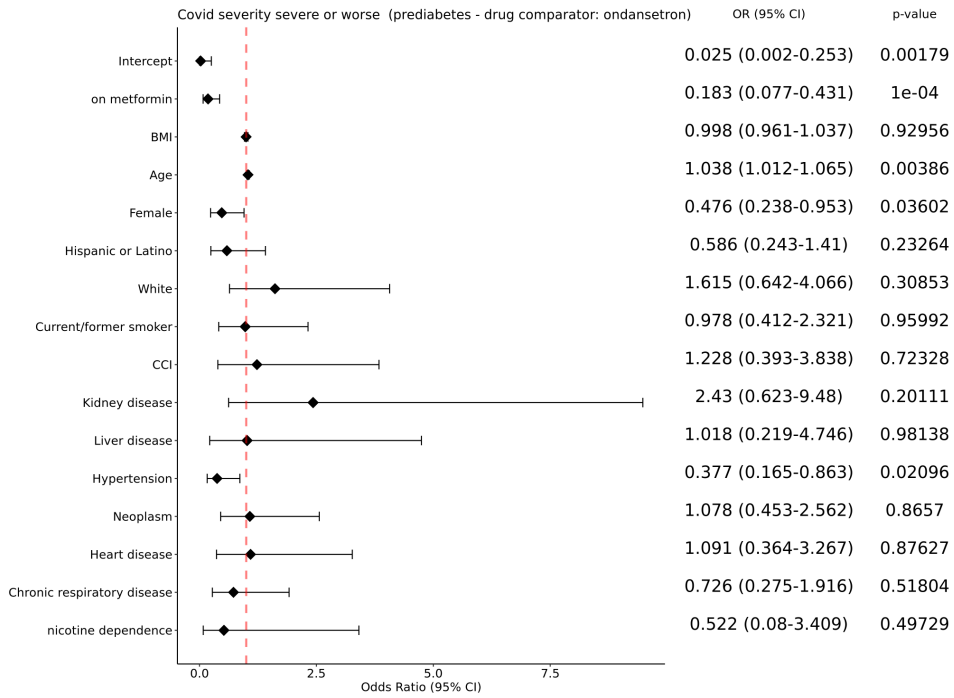
E


Covid severity mild ED or worse (prediabetes - drug comparator: ondansetron)
OR (95% CI)
p-value
on metformin
BMI
Age
Female
Hispanic or Latino
White
Current/former smoker
CCI
Kidney disease
Liver disease
Hypertension
Neoplasm
Heart disease
Chronic respiratory disease
nicotine dependence
0.039 (0.026-0.057)
0
0.988 (0.969-1.008)
0.24473
1.013 (0.999-1.027)
0.06733
0.588 (0.381-0.906)
0.01611
0.682 (0.432-1.077)
0.10035
0.716 (0.445-1.153)
0.16953
1.202 (0.758-1.905)
0.434
1.226 (0.645-2.328)
0.5344
0.788 (0.29-2.142)
0.64064
0.586 (0.251-1.368)
0.21665
0.508 (0.332-0.776)
0.00176
0.834 (0.526-1.322)
0.43913
1.693 (0.902-3.178)
0.10136
0.496 (0.306-0.804)
0.00446
1.674 (0.744-3.764)
0.21277
0
1
2
3
Odds Ratio (95% CI)

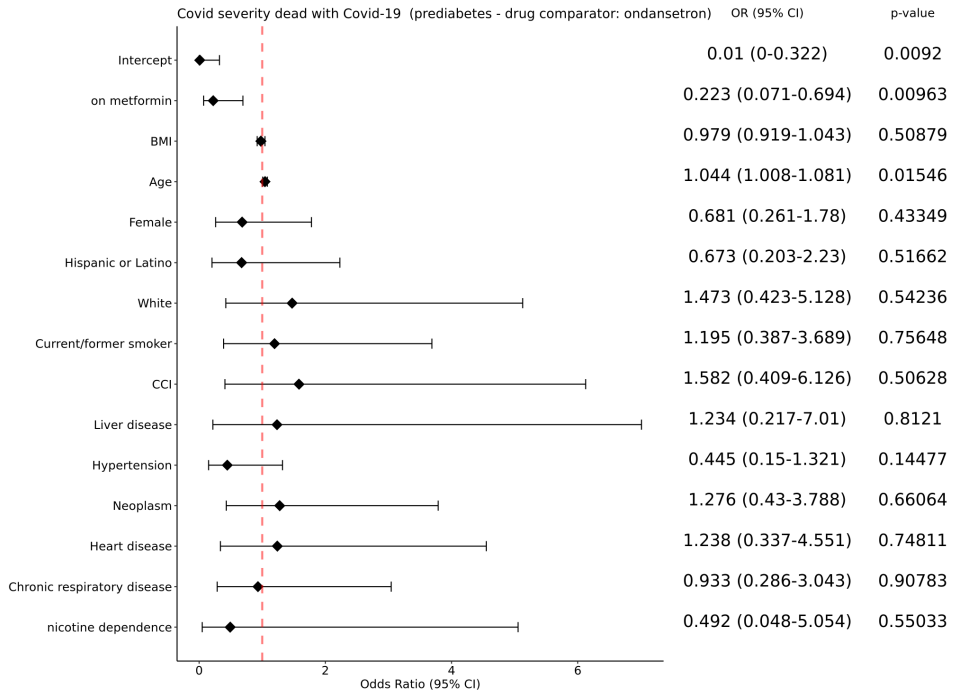
F


Covid severity moderate or worse (prediabetes - drug comparator: ondansetron)
OR (95% CI)
p-value
Intercept
on metformin
BMI
Age
Female
Hispanic or Latino
White
Current/former smoker
CCI
Kidney disease
Liver disease
Hypertension
Neoplasm
Arthritis
Heart disease
Chronic respiratory disease
nicotine dependence
1.383 (0.435-4.4)
0.58275
0.045 (0.03-0.069)
0
1.005 (0.986-1.025)
0.58241
1.026 (1.012-1.04)
0.00024
0.526 (0.345-0.801)
0.00279
0.858 (0.548-1.343)
0.50266
0.831 (0.523-1.318)
0.43039
1.291 (0.818-2.038)
0.27289
1.101 (0.585-2.071)
0.76611
1.389 (0.529-3.644)
0.50423
0.618 (0.266-1.438)
0.26412
0.532 (0.351-0.805)
0.00281
0.768 (0.484-1.218)
0.2618
1.639 (0.363-7.392)
0.52052
1.722 (0.926-3.2)
0.08593
0.55 (0.341-0.886)
0.01398
0.989 (0.447-2.19)
0.97782
0
2
4
6
Odds Ratio (95% CI)

G



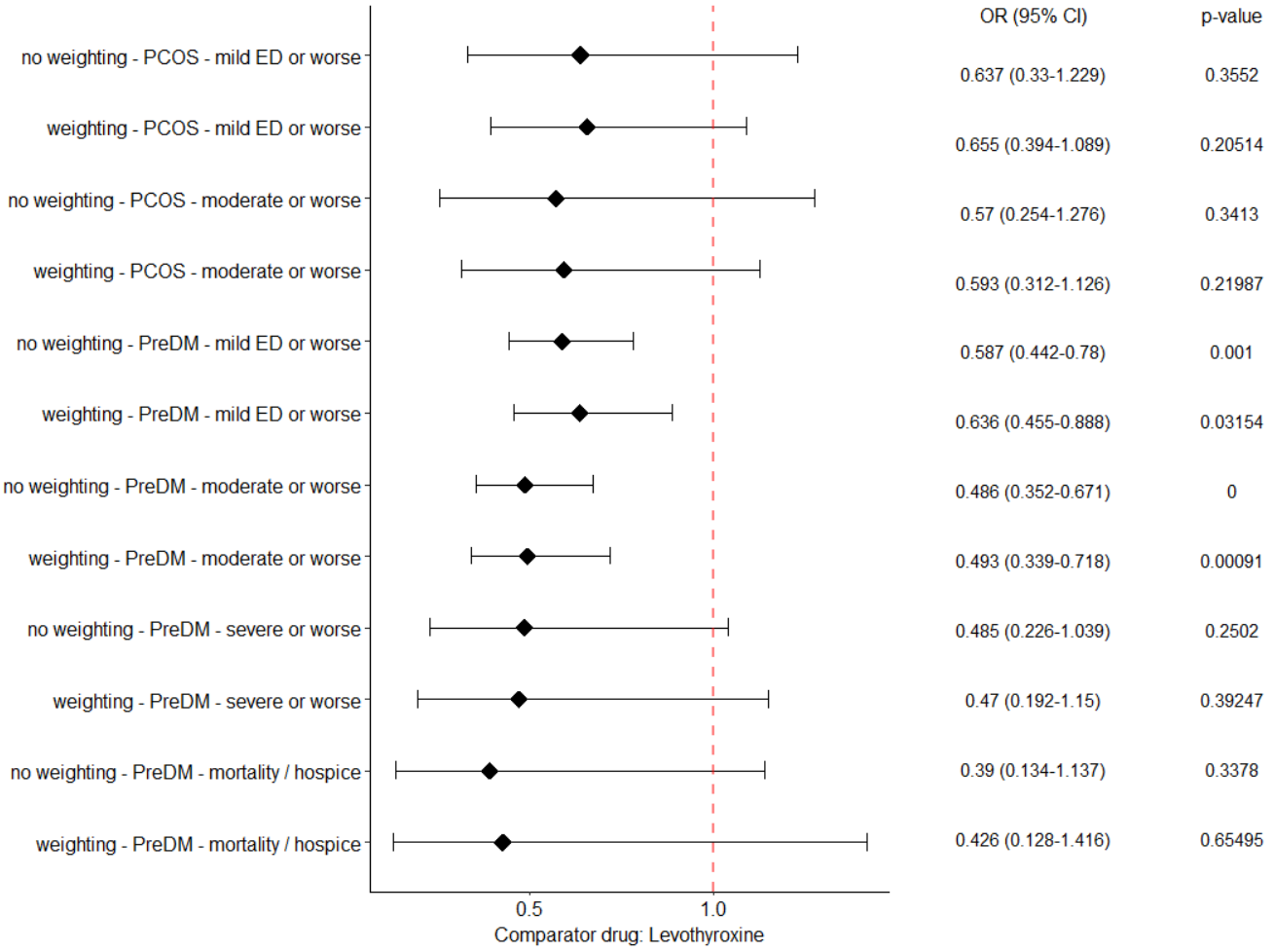
H



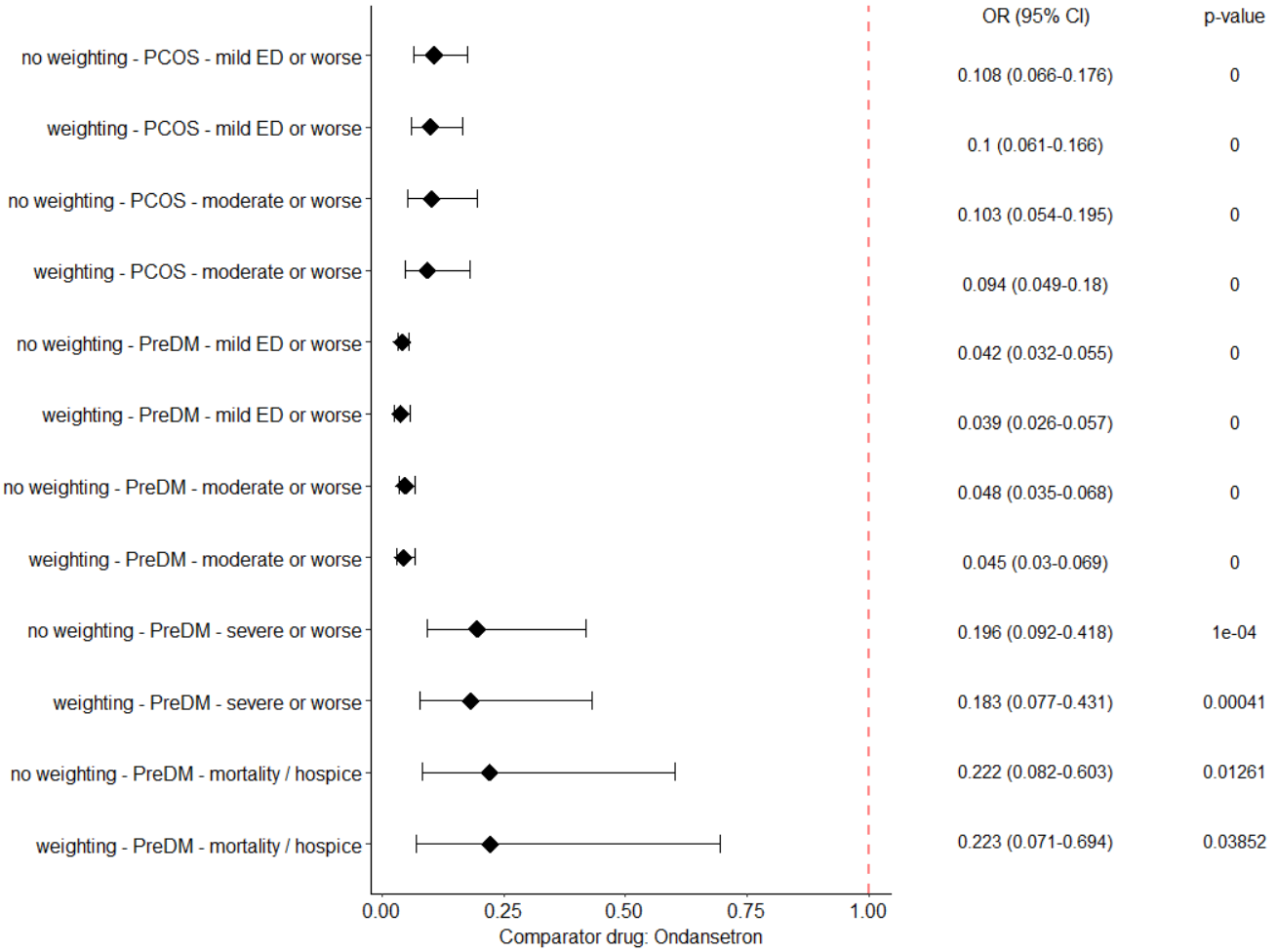
Supplementary Figure S4. Forest Plots for Prediabetes. A: Mild vs Mild ED and worse, levothyroxine, B: Mild and mild ED vs moderate and worse, levothyroxine, C: Mild, mild ED, and moderate vs severe and worse, levothyroxine, D: Mild, mild ED, moderate, and severe vs death with COVID-19, levothyroxine, E: Mild vs Mild ED and worse, ondansetron, F: Mild and mild ED vs moderate and worse, ondansetron, G: Mild, mild ED, and moderate vs severe and worse, ondansetron, H: Mild, mild ED, moderate, and severe vs death with COVID-19, ondansetron.

Comparison of ORs (and 95% CI) between weighted and unweighted cohorts

A. Levothyroxine



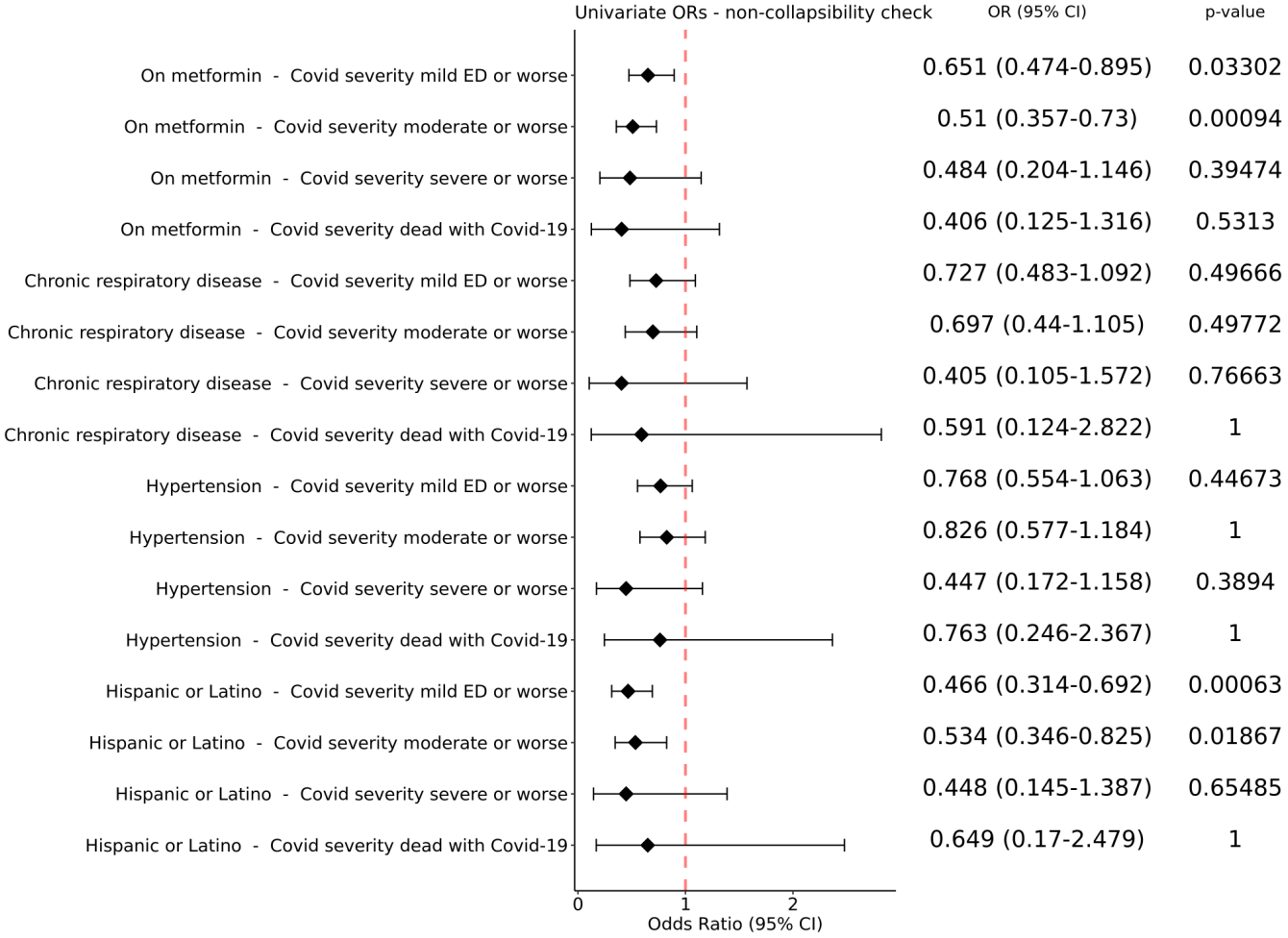
B. ondansetron



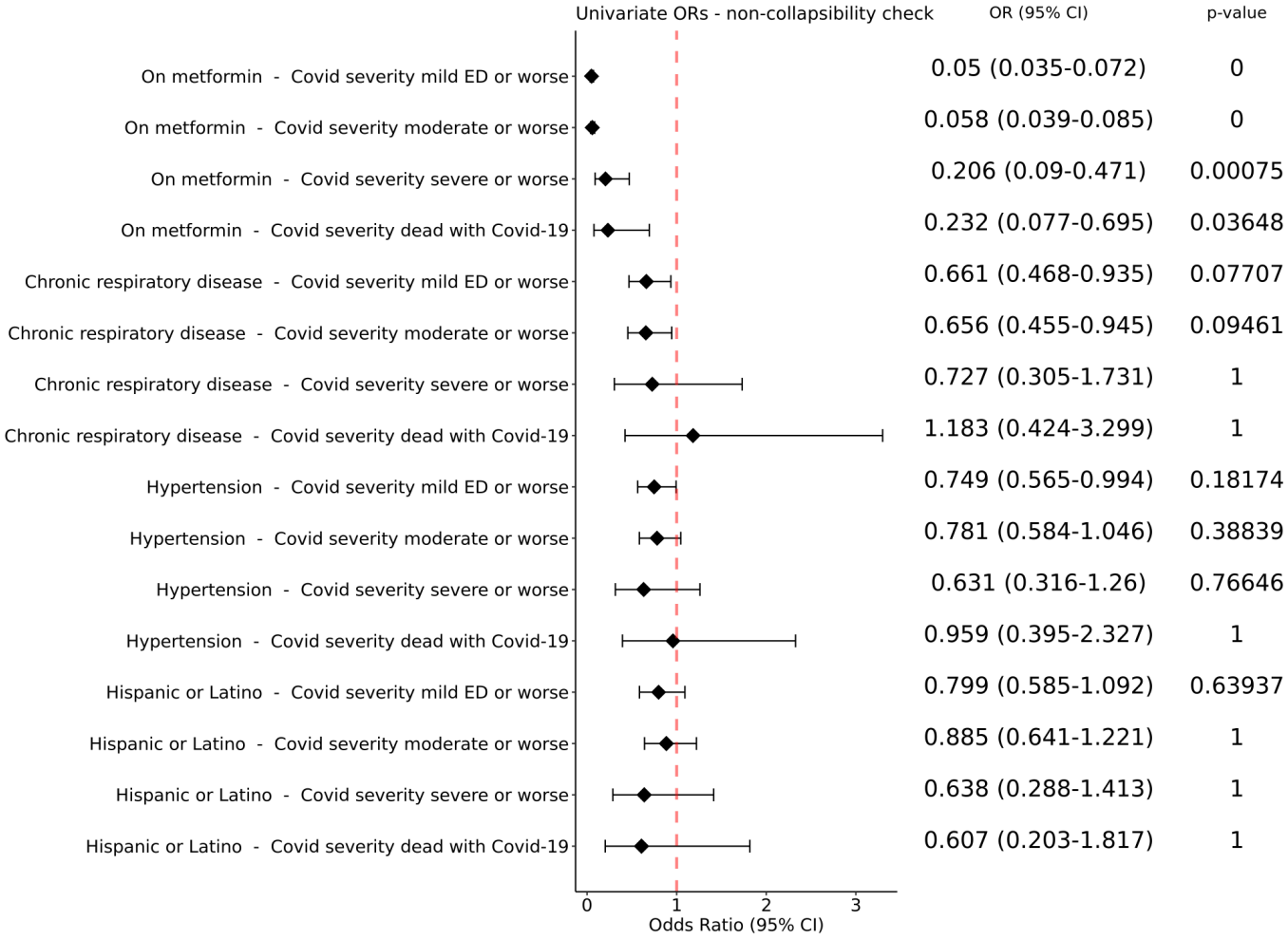
Supplementary Figure S5 A-B. Comparison between ORs (95% CI) estimates obtained on the unweighted and weighted cohorts.

Non-collapsibility tests

A. Levothyroxine



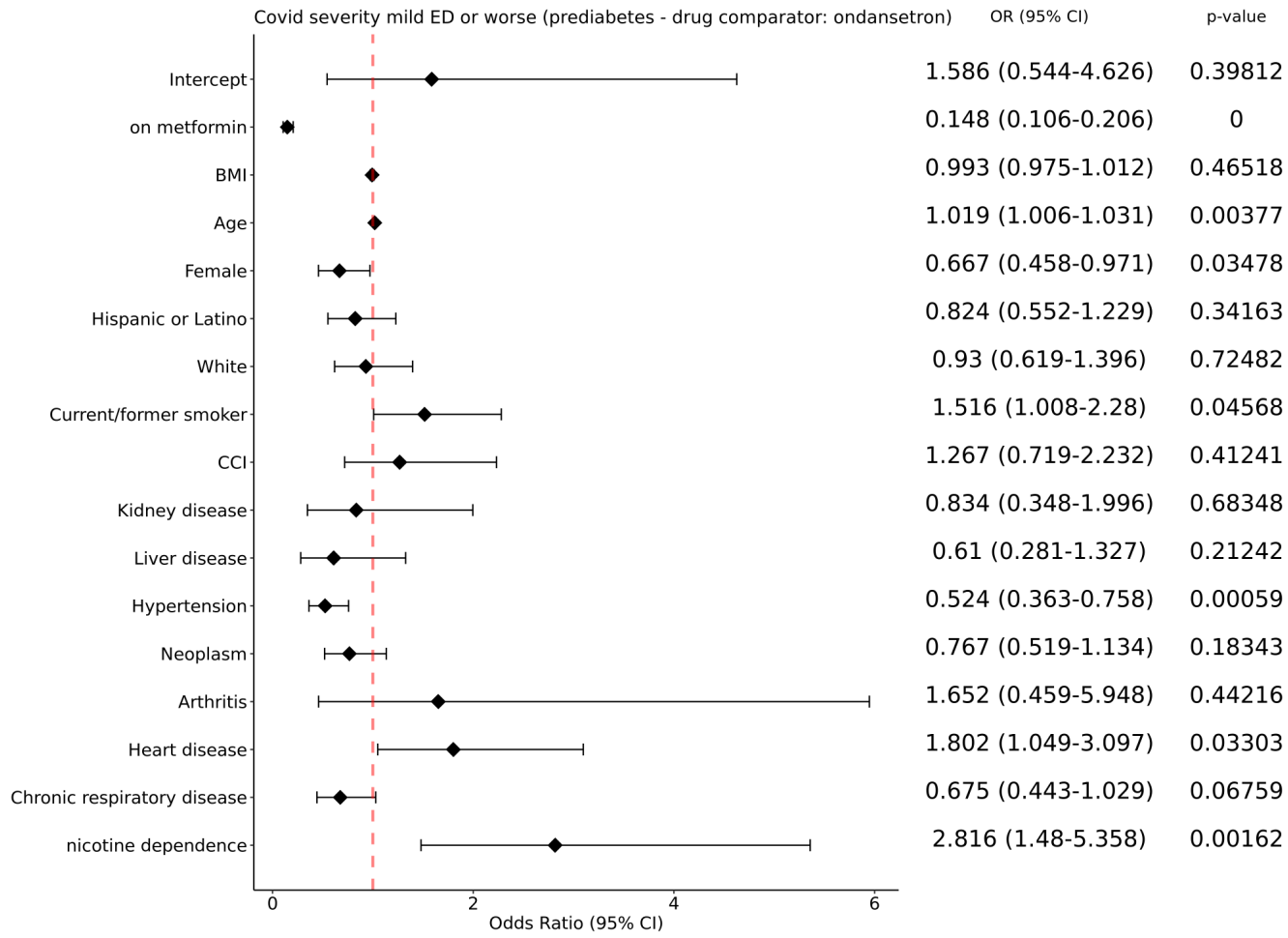
B. Ondansetron



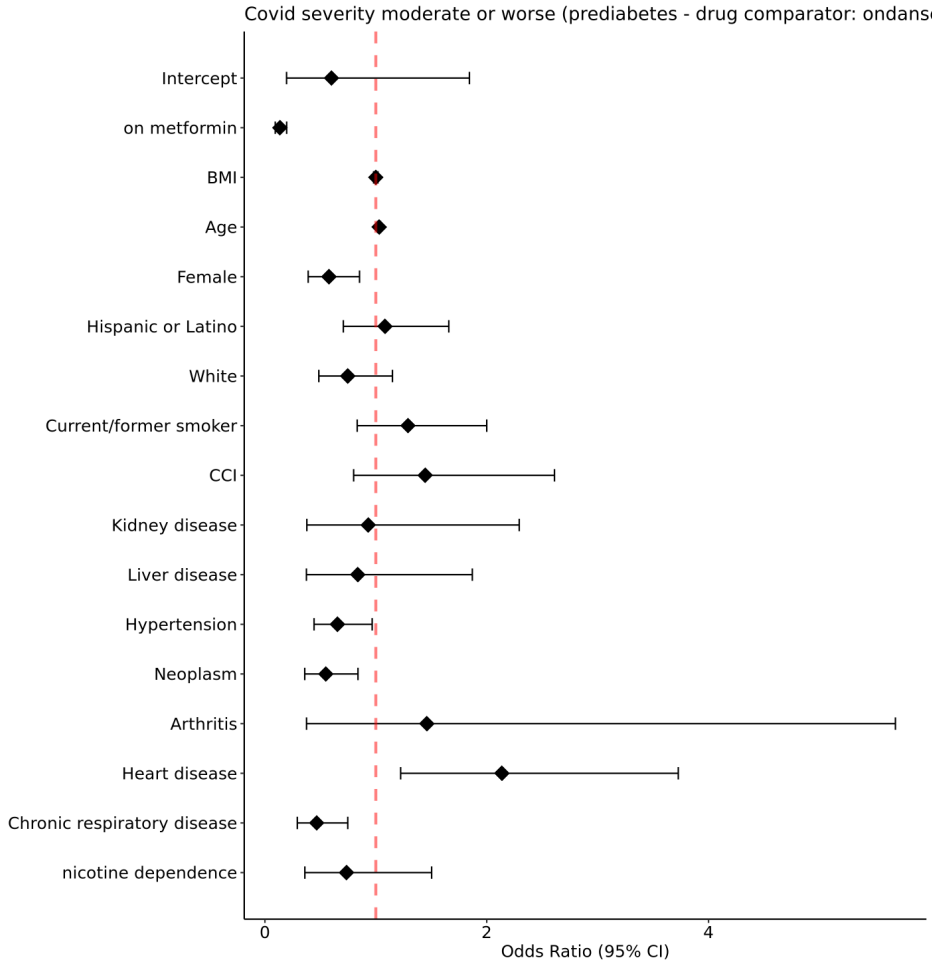
Supplementary Figure S6 A-B. Non-collapsibility tests for chronic respiratory disease, hypertension, and Hispanic or Latino ethnicity covariates. Forest plots for univariate odds ratios were computed to assess the non-collapsibility effect for chronic respiratory disease, hypertension disease, and ethnicity in the prediabetes cohort. Non-collapsibility effects on a covariate were estimated by comparing the odds ratio (OR) obtained by univariate logistic regression (LR) on the variable and the OR obtained in the multivariate analysis.[53] To check whether the OR, which in our prediabetes analysis indicated a significant protective effect for chronic-respiratory disease, is affected by the non-collapsibility effect we ran a univariate LR for each outcome. The Forest plot reports the results obtained when univariate LRs were applied to either drug usage ("on metformin") or chronic respiratory disease. The ORs for drug usage are comparable to those obtained by multivariate LR (Figure 2) showing the reliability of the estimate. On the other hand, the remarkable difference in the ORs estimated for chronic respiratory disease confirm the non-collapsibility effect for this variable.

Sensitivity Analysis

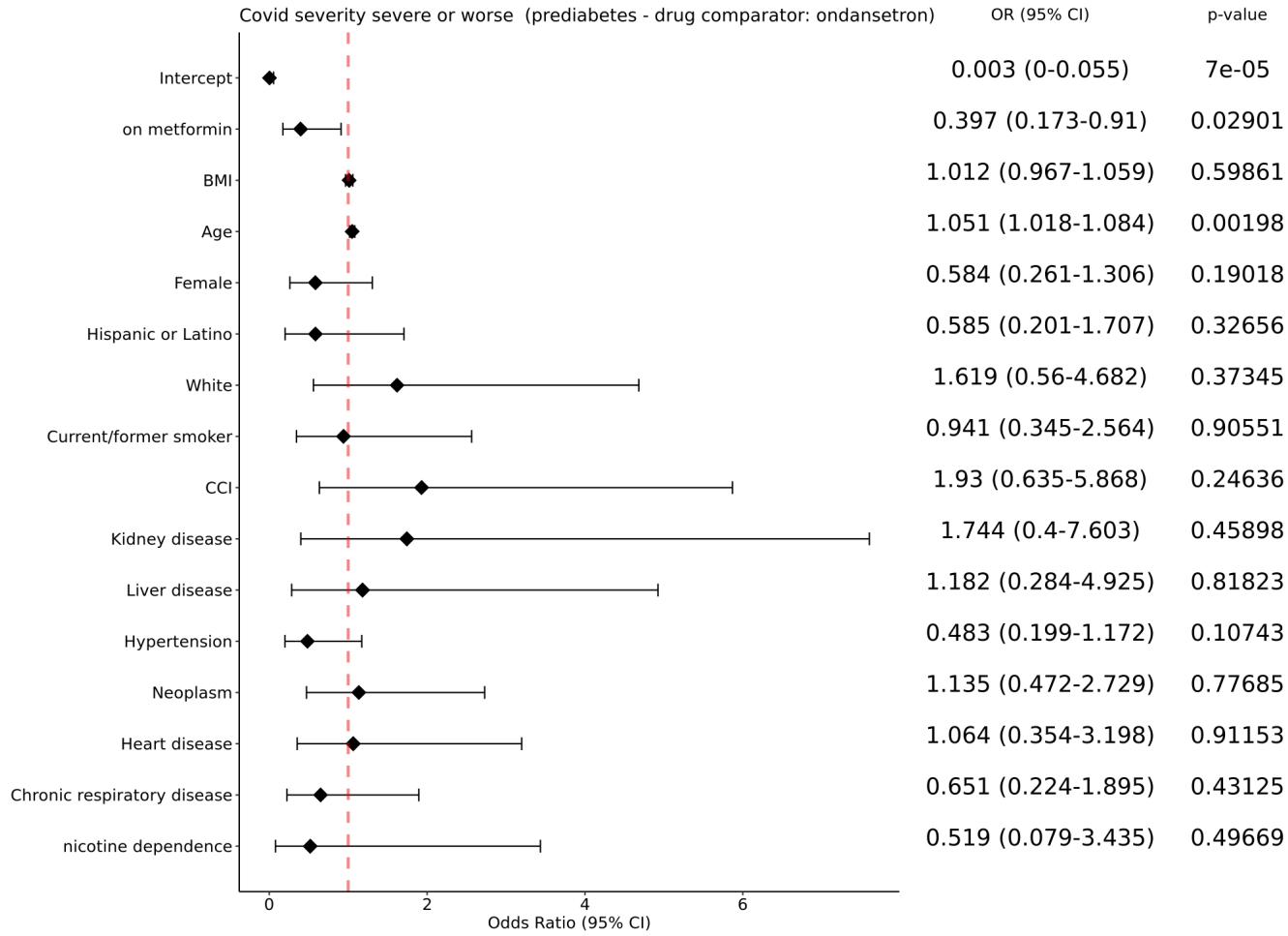
A.



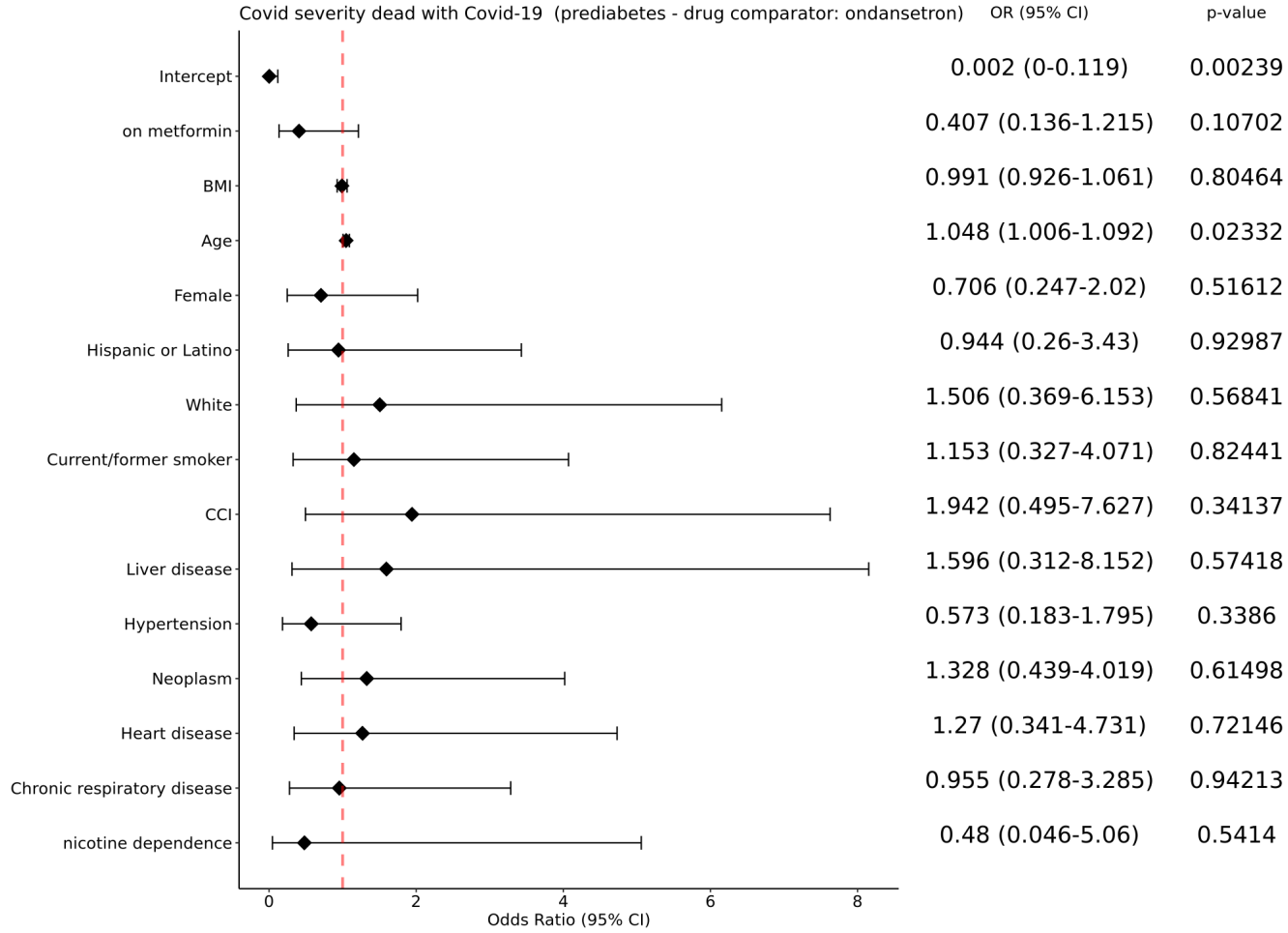
B.


Covid severity moderate or worse (prediabetes - drug comparator: ondansetron)
OR (95% CI)
p-value
Intercept
on metformin
BMI
Age
Female
Hispanic or Latino
White
Current/former smoker
CCI
Kidney disease
Liver disease
Hypertension
Neoplasm
Arthritis
Heart disease
Chronic respiratory disease
nicotine dependence
0.6 (0.195-1.844)
0.3725
0.135 (0.093-0.196)
0
0.999 (0.98-1.019)
0.95106
1.03 (1.016-1.043)
2e-05
0.577 (0.39-0.853)
0.00586
1.083 (0.707-1.658)
0.71512
0.747 (0.486-1.15)
0.18518
1.29 (0.832-2)
0.25464
1.445 (0.8-2.611)
0.22266
0.931 (0.378-2.293)
0.8758
0.837 (0.374-1.87)
0.66369
0.654 (0.443-0.967)
0.03345
0.549 (0.359-0.839)
0.00559
1.46 (0.375-5.685)
0.5855
2.136 (1.224-3.727)
0.00757
0.467 (0.292-0.747)
0.00149
0.736 (0.36-1.503)
0.40016
0
2
4
Odds Ratio (95% CI)

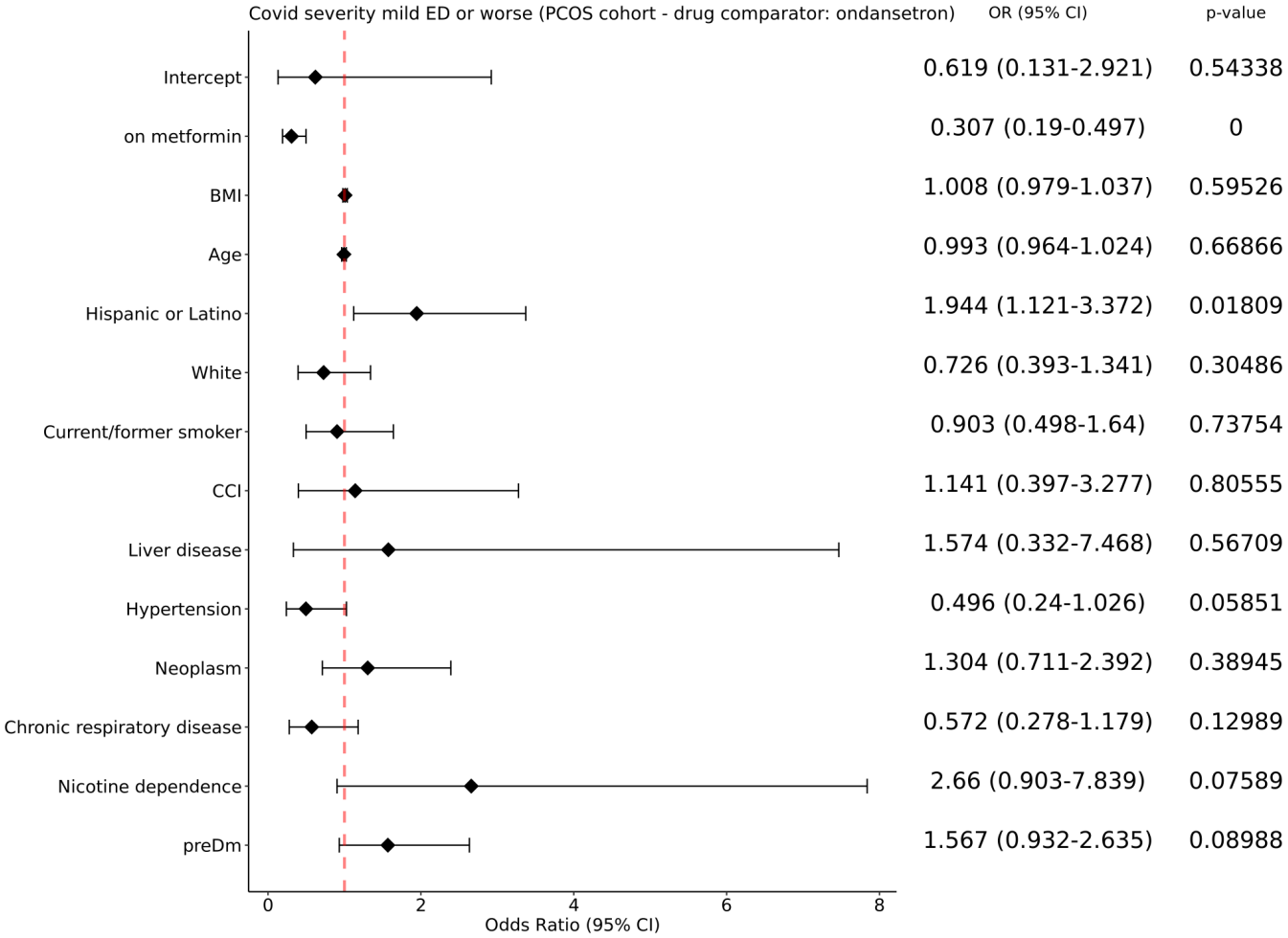
C.


Covid severity severe or worse (prediabetes - drug comparator: ondansetron)
OR (95% CI)
p-value
Intercept
0.003 (0-0.055)
7e-05
on metformin
0.397 (0.173-0.91)
0.02901
BMI
1.012 (0.967-1.059)
0.59861
Age
1.051 (1.018-1.084)
0.00198
Female
0.584 (0.261-1.306)
0.19018
Hispanic or Latino
0.585 (0.201-1.707)
0.32656
White
1.619 (0.56-4.682)
0.37345
Current/former smoker
0.941 (0.345-2.564)
0.90551
CCI
1.93 (0.635-5.868)
0.24636
Kidney disease
1.744 (0.4-7.603)
0.45898
Liver disease
1.182 (0.284-4.925)
0.81823
Hypertension
0.483 (0.199-1.172)
0.10743
Neoplasm
1.135 (0.472-2.729)
0.77685
Heart disease
1.064 (0.354-3.198)
0.91153
Chronic respiratory disease
0.651 (0.224-1.895)
0.43125
nicotine dependence
0.519 (0.079-3.435)
0.49669
0
2
4
6
Odds Ratio (95% CI)

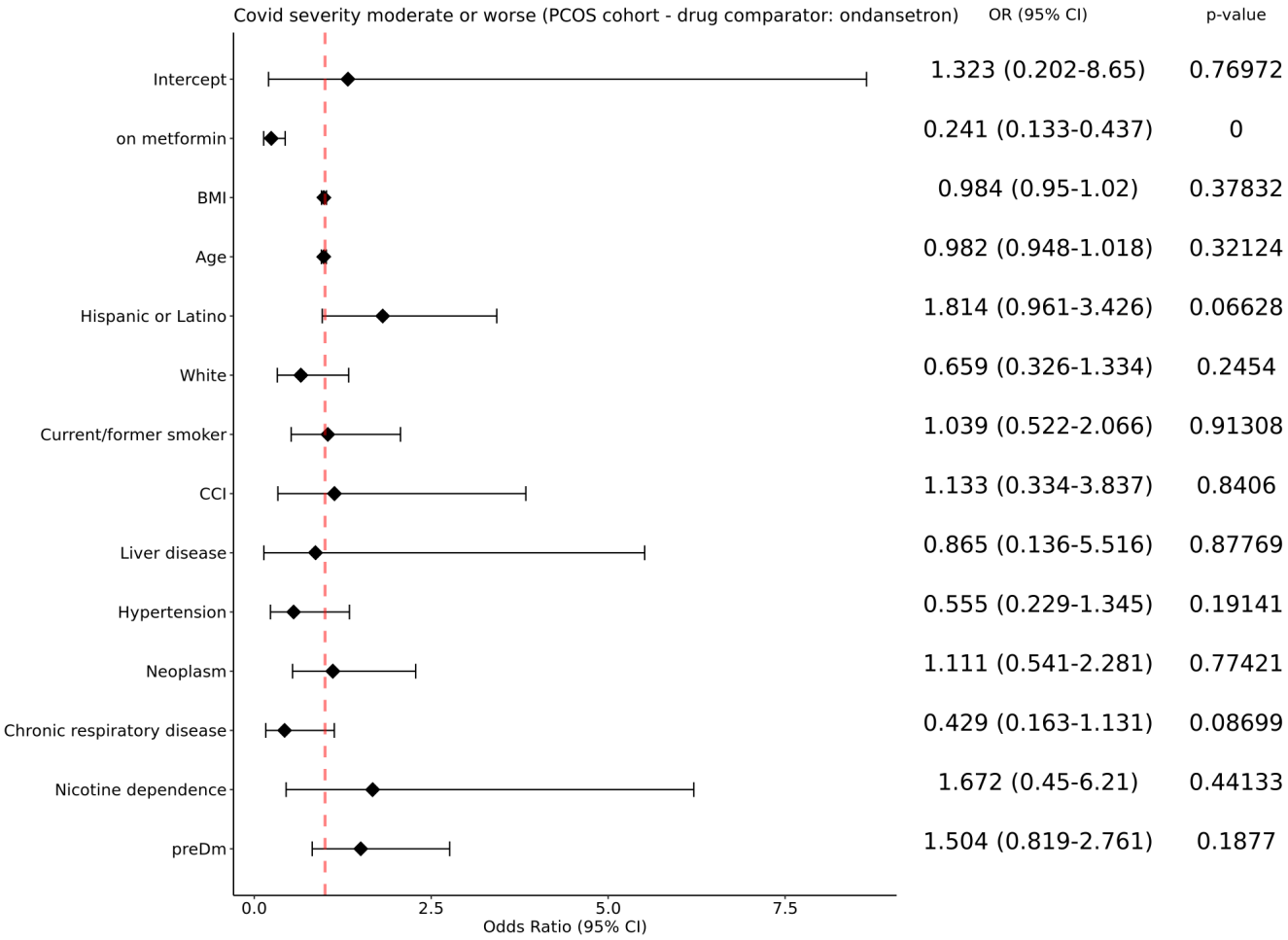
D.


Covid severity dead with Covid-19 (prediabetes - drug comparator: ondansetron)
OR (95% CI)
p-value
Intercept
on metformin
BMI
Age
Female
Hispanic or Latino
White
Current/former smoker
CCI
Liver disease
Hypertension
Neoplasm
Heart disease
Chronic respiratory disease
nicotine dependence
0.002 (0-0.119)
0.00239
0.407 (0.136-1.215)
0.10702
0.991 (0.926-1.061)
0.80464
1.048 (1.006-1.092)
0.02332
0.706 (0.247-2.02)
0.51612
0.944 (0.26-3.43)
0.92987
1.506 (0.369-6.153)
0.56841
1.153 (0.327-4.071)
0.82441
1.942 (0.495-7.627)
0.34137
1.596 (0.312-8.152)
0.57418
0.573 (0.183-1.795)
0.3386
1.328 (0.439-4.019)
0.61498
1.27 (0.341-4.731)
0.72146
0.955 (0.278-3.285)
0.94213
0.48 (0.046-5.06)
0.5414
0
2
4
6
8
Odds Ratio (95% CI)

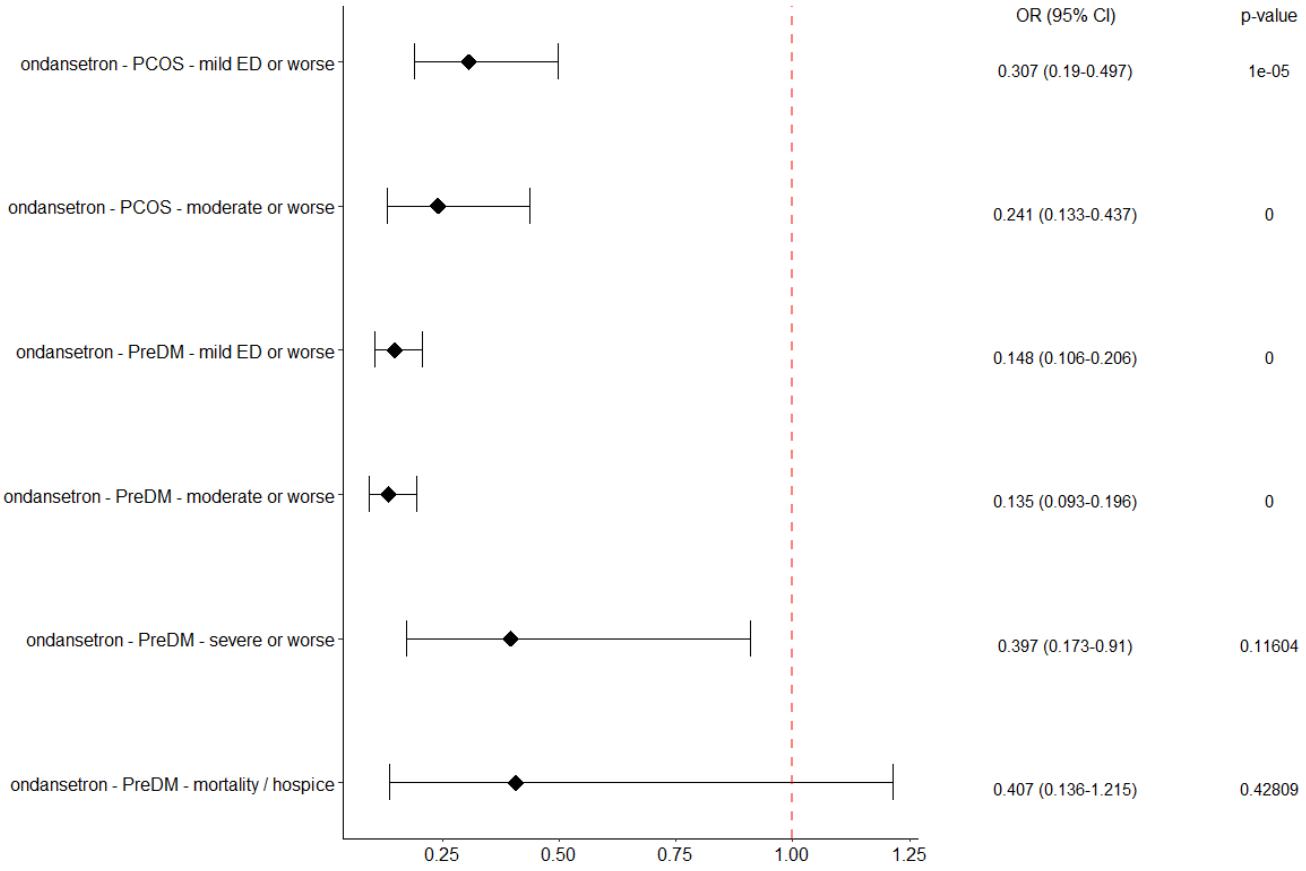
E.


Covid severity mild ED or worse (PCOS cohort - drug comparator: ondansetron)
OR (95% CI)
p-value
Intercept
on metformin
BMI
Age
Hispanic or Latino
White
Current/former smoker
CCI
Liver disease
Hypertension
Neoplasm
Chronic respiratory disease
Nicotine dependence
preDm
0.619 (0.131-2.921)
0.54338
0.307 (0.19-0.497)
0
1.008 (0.979-1.037)
0.59526
0.993 (0.964-1.024)
0.66866
1.944 (1.121-3.372)
0.01809
0.726 (0.393-1.341)
0.30486
0.903 (0.498-1.64)
0.73754
1.141 (0.397-3.277)
0.80555
1.574 (0.332-7.468)
0.56709
0.496 (0.24-1.026)
0.05851
1.304 (0.711-2.392)
0.38945
0.572 (0.278-1.179)
0.12989
2.66 (0.903-7.839)
0.07589
1.567 (0.932-2.635)
0.08988
0
2
4
6
8
Odds Ratio (95% CI)

F.



Supplementary Figure S7. Sensitivity analysis for ondansetron use initiated prior to COVID-19 diagnosis. We conducted an analysis to confirm that removal of patients starting ondansetron treatment on the day of COVID-19 diagnosis did not impact our analysis. Results on both prediabetic patients (Fig S6 A-D) and PCOS patients (Fig S6 E-F) confirmed the main results of the original analysis. Forest plots are shown for A: Prediabetes, Mild vs Mild ED and worse, B: Prediabetes, Mild and mild ED vs moderate and worse, C: Mild, mild ED, and moderate vs severe and worse, D: Mild, mild ED, moderate, and severe vs death with COVID-19, E: PCOS, Mild vs Mild ED and worse, F: PCOS, Mild and mild ED vs moderate and worse.



Supplementary Figure S8. Sensitivity analysis for ondansetron use initiated prior to COVID-19 diagnosis. Summary of Forest plots in Supplementary Figure S7 showing the association of metformin with COVID-19 outcome using ondansetron initiated prior to COVID-19 diagnosis (p-values are Bonferroni adjusted).

Cohort	Drug comparator	Age	BMI	Race	Ethnicity	Cases with any missing value
PCOS	Levothyroxine	-	14%	17%	10%	30%
	Ondansetron	-	23%	14%	12%	35%
Prediabetes	Levothyroxine	-	24%	15%	7%	38%
	Ondansetron	3%	42%	14%	8%	53%

Supplemental Table 1. Proportion of missing values per predictor variable and proportion of cases with any missing value.