

**Metformin reduces the risk of Long COVID or Death over 6 months in an  
Emulated Target Trial of  
Primarily Omicron-infected Adults  
without Diabetes or Prediabetes**

New-User, Active-Comparator Analysis  
using the  
National COVID Cohort Collaborative (N3C) Database

ID Week  
Los Angeles, CA  
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Assistant Professor, General Internal Medicine

# Funding, Disclosures

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- Intramural/Extramural research program of the National Center for Advancing Translational Sciences (NCATS), NIH
  - N3C Public Health Study Initiative, PHASTR Project: [RP-C06B65]
- Dr. Bramante funded by NIDDK, K23DK124654
- No financial disclosures
- Will be discussing off-label use of metformin, ivermectin, montelukast, fluticasone, and fluvoxamine

# Overview

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- **Scientific rationale for studying metformin**
- Methods
  - Trial Emulation Design
  - Target Trials
- Results
- Context within other literature
  - Other sources of data
  - COVID-OUT data

# Why metformin? COVID Observational, *in silico*, *in vitro* data

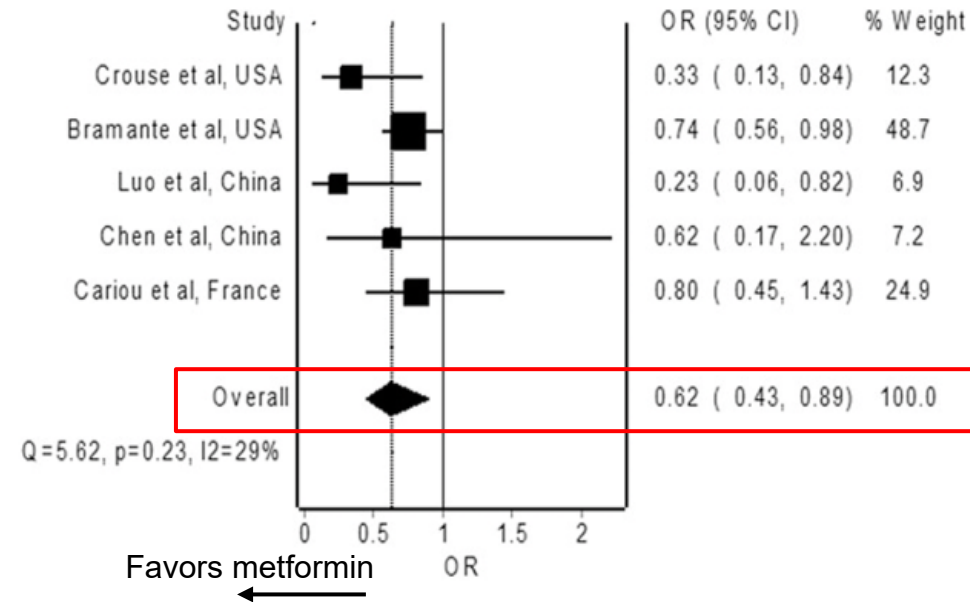
- Mechanistic data

Chen et al. *Diabetes Care*, 2020  
Retrospective cohort adults with Type 2 DM

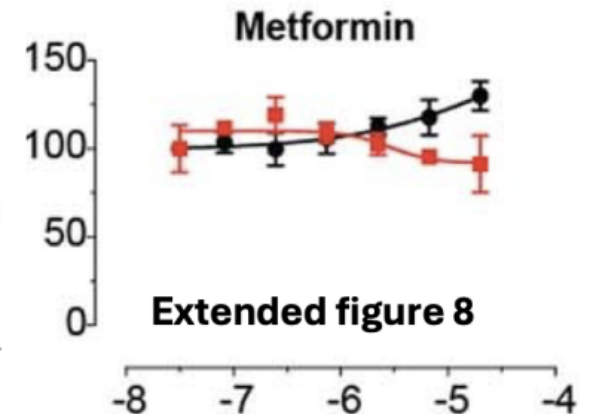
Metformin users had lower IL-6:  
4.07 vs 11.1,  $p=0.02$

- Observational data  
(as of summer 2020,  
there are more now)

*Journal of  
Virology*



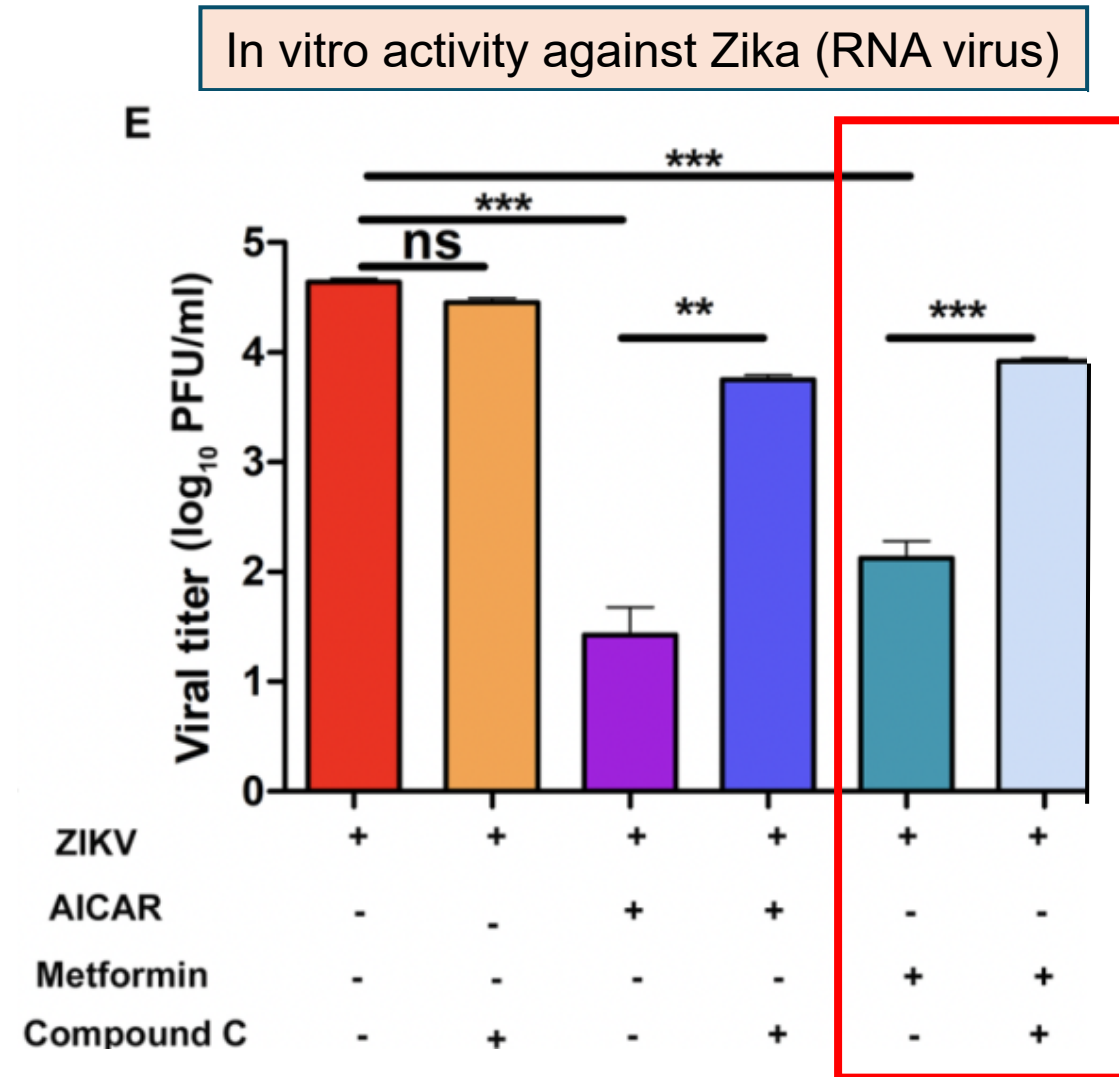
- In vitro data. The red line is viral growth, the black line is cell viability



Metformin is safe, well tolerated, widely available, inexpensive

# Why metformin? *Pre-COVID* anti-viral & anti-inflammatory

- 1950s, studied in influenza
  - incidence of H3N2 influenza (5.4 vs 24%,  $p < 0.001$ )
  - Other biguanides had safety issues
- 1990s FDA approved for diabetes
- Anti-inflammatory actions
  - IL-6, TNF-alpha, protects endothelium
  - mTOR respiratory complex 1
- 2010 anti-viral studies
  - Hep C, Zika
- RCT's: TB, dengue



# Why Metformin? 2 RCT showed compelling clinical outcomes

## COVID-OUT, Day 14, mITT (n=1,323)

Severe Covid Day 14  
 1x SpO2 < 94% / ED / Hosp / Death  
 ED / Hosp / Death  
 Hosp / Death

A priori subgroups for ED / Hosp / Death:  
 < 4 days of symptoms  
 Omicron  
 Pregnant

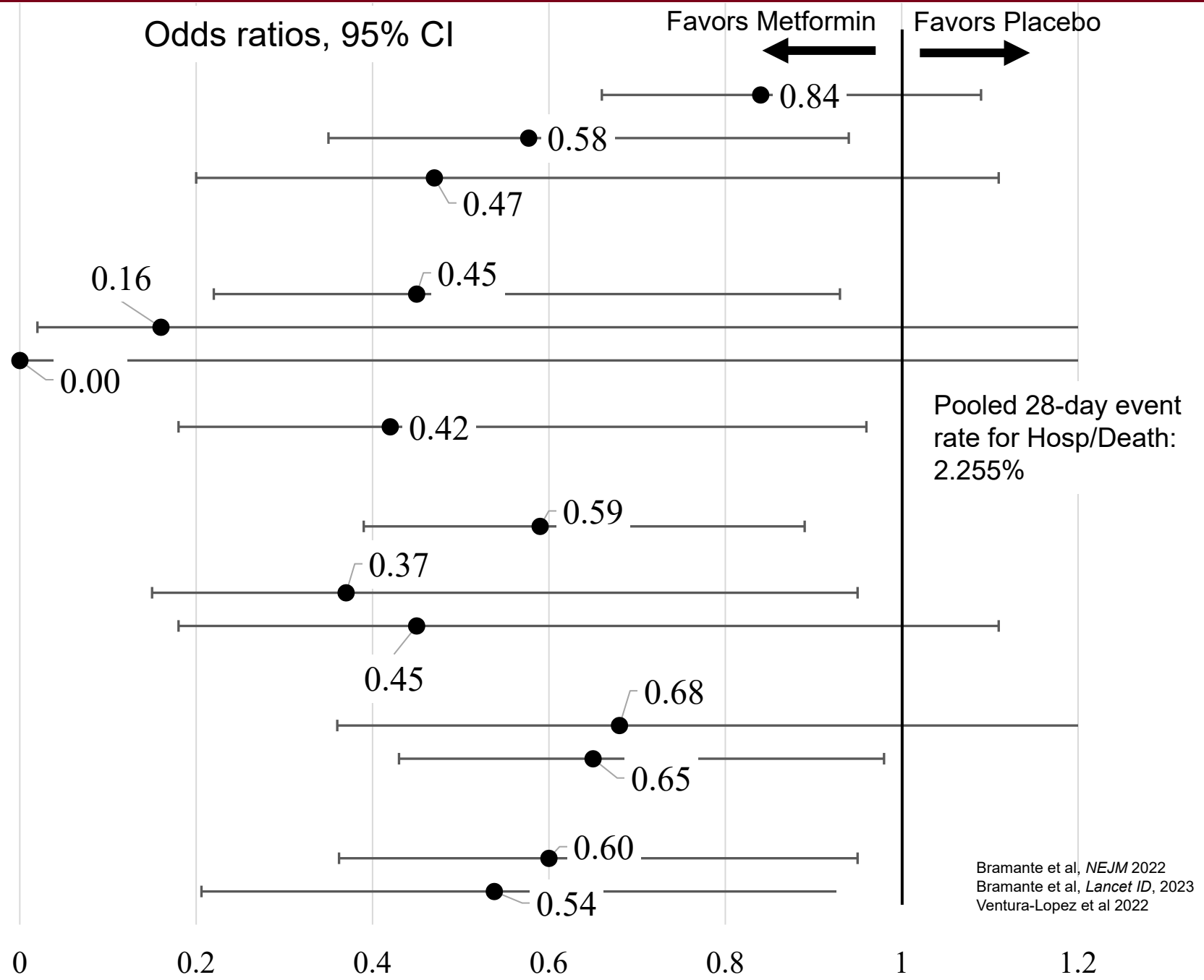
Day 300 outcomes  
 Long Covid

A priori subgroups for LC:  
 <4 days of symptoms  
 Omicron

Viral Load  
 Rebound viral load  
 Odds of detectable VL at Day 10

## Ventura-Lopez, n=20

Proportion with positive viral load after 3 days  
 Proportion with severe Covid



# Overview

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- Scientific rationale for studying metformin
- **Trial Emulation Methods**
  - Data Source
  - Trial Emulation Design
  - Target Trials
- Results
- Context within other literature
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# Data Source

## N3C: National COVID Cohort Collaborative

- Integrated and harmonized de-identified EHR data.

The N3C is a partnership among:

- NCATS-supported Clinical and Translational Science Awards (CTSA) Program institutions
- National Center for Data to Health
- National Institute of General Medical Sciences–funded Institutional Development Award (IDeA) Program Networks for Clinical and Translational Research (IDeA-CTR) networks

overall stewardship by NCATS.

The N3C Data Enclave represents one of the largest secure collections of harmonized clinical health data in the United States.



Sites: 84



Persons: 22.8 million



COVID+ Cases: 8,914,402



# of Rows: 33.9 billion



Clinical Observations: 3.3 billion



Lab Results: 16.3 billion



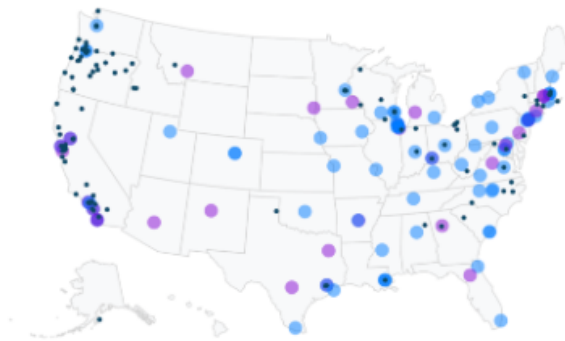
Medication Records: 5.3 billion



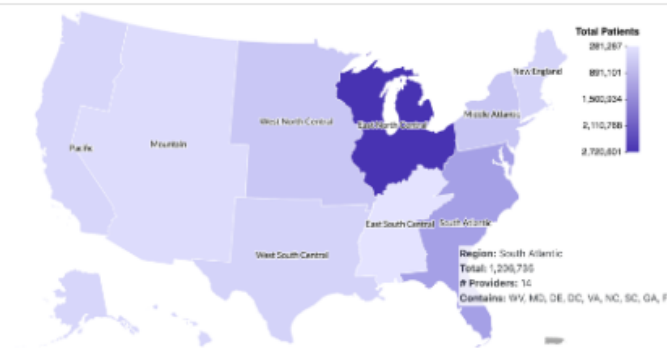
Procedures: 1.2 billion



Visits: 2.0 billion



Institutions Contributing Data



Regional Distribution of COVID+ Patients



# Target Trial Emulation

New-User, Active-Comparator Design:

- New Prescription of Metformin

versus

- New Prescription of an Active Comparator (aka Control)
  - fluvoxamine; fluticasone; ivermectin, or montelukast

At the time of infection (Days 0 to 6 relative to infection)

The comparator medications were chosen to mimic placebo

Having a comparator is important for having equalizing unmeasured confounders:

- the placebo effect
- engagement in healthcare

# Why Metformin? 2 RCT showed compelling clinical outcomes

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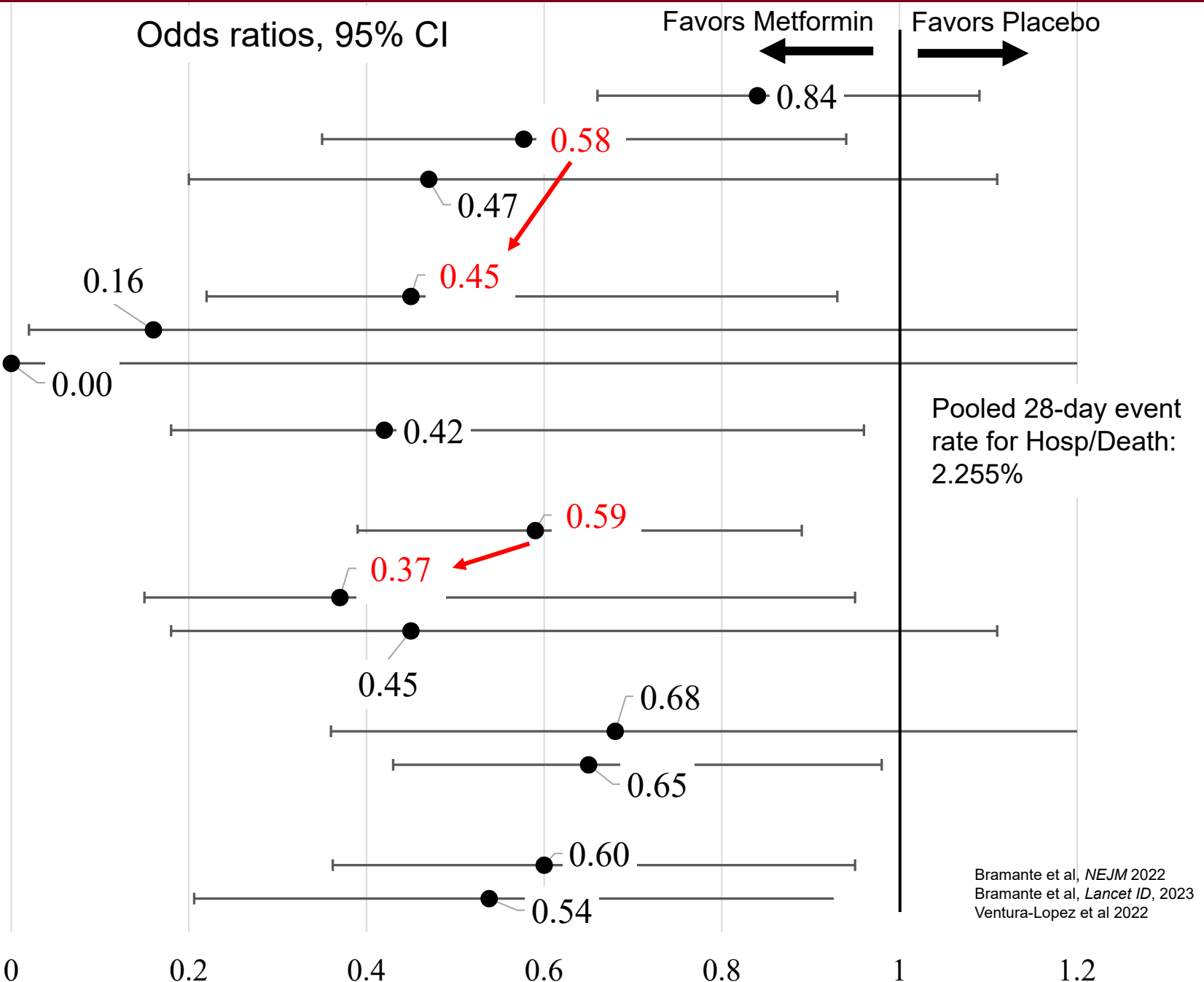
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Day 300 outcomes  
 Long Covid  
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Viral Load  
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## Ventura-Lopez, n=20

Proportion with positive viral load after 3 days  
 Proportion with severe Covid



Bramante et al, *NEJM* 2022  
 Bramante et al, *Lancet ID*, 2023  
 Ventura-Lopez et al 2022

# Target Trials

## Eligibility Criteria

ACTIV-6	COVID-OUT	Target Trial Emulation
<ul style="list-style-type: none"><li>• Documented SARS-CoV-2 within 10 days of enrollment</li><li>• Enrolled within 7 days of symptoms</li><li>• Age 30 – 85</li><li>• No current metformin use</li><li>• Does not exclude prior infection</li></ul>	<ul style="list-style-type: none"><li>• Documented SARS-CoV-2 within 3 days of enrollment</li><li>• Symptoms not required, but if present, &lt;7 days</li><li>• Age 30-85</li><li>• No current metformin use</li><li>• BMI <math>\geq 25\text{kg/m}^2</math></li><li>• Excluded prior infection</li></ul>	<ul style="list-style-type: none"><li>• Documented SARS-CoV-2</li><li>• Prescription within 6 days (primary analysis), secondary analyses with prescriptions within 1 day &amp; 14 days</li><li>• Age &gt; 18 years</li><li>• No metformin or control prescription <math>\leq 12</math> months</li><li>• No minimum body mass index</li><li>• First documented SARS-CoV-2 infection</li></ul>

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Intervention	<ul style="list-style-type: none"> <li>• Metformin immediate release or exact-matching placebo tablets</li> </ul>	<ul style="list-style-type: none"> <li>• Metformin immediate release or exact-matching placebo tablets</li> </ul>	<ul style="list-style-type: none"> <li>• Prescription: metformin or any control: fluvoxamine, ivermectin, fluticasone, montelukast</li> </ul>
Treatment assignment	<ul style="list-style-type: none"> <li>• Randomization</li> </ul>	<ul style="list-style-type: none"> <li>• Randomization</li> </ul>	<ul style="list-style-type: none"> <li>• Prescription for metformin or control; propensity scores to balance measured covariates across treatment cohorts</li> </ul>

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Considerations for medication acquisition	<ul style="list-style-type: none"> <li>Delivery of medication takes 2-3 days on average</li> </ul>	<ul style="list-style-type: none"> <li>Delivery of medication takes 1 day on average</li> </ul>	<ul style="list-style-type: none"> <li>Obtaining a medication prescription then filling it at a pharmacy likely takes 0 to 3 days on average</li> </ul>
Post - randomization exclusions	<ul style="list-style-type: none"> <li>Hospitalized at the time of medication delivery</li> <li>Delivery failure</li> <li>Death before day 1</li> </ul>	<ul style="list-style-type: none"> <li>Hospitalized at the time of medication delivery</li> <li>Delivery failure</li> <li>Death before day 1</li> </ul>	<ul style="list-style-type: none"> <li>Hospitalized between -3 days to +1 days of infection because this would preclude the ability to fill a prescription</li> <li>Death on or before day 1</li> </ul>
Day 1	<ul style="list-style-type: none"> <li>First day of study drug</li> </ul>	<ul style="list-style-type: none"> <li>First day of study drug</li> </ul>	<ul style="list-style-type: none"> <li>Day prescription placed</li> </ul>
Follow-up	<ul style="list-style-type: none"> <li>Day 1 to 180</li> </ul>	<ul style="list-style-type: none"> <li>Day 1 to 300</li> </ul>	<ul style="list-style-type: none"> <li>Day 1 to 180</li> </ul>

# Analysis plan

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Outcome: Long Covid or Death

- U09.9 or
- Computable phenotype based on symptoms and conditions

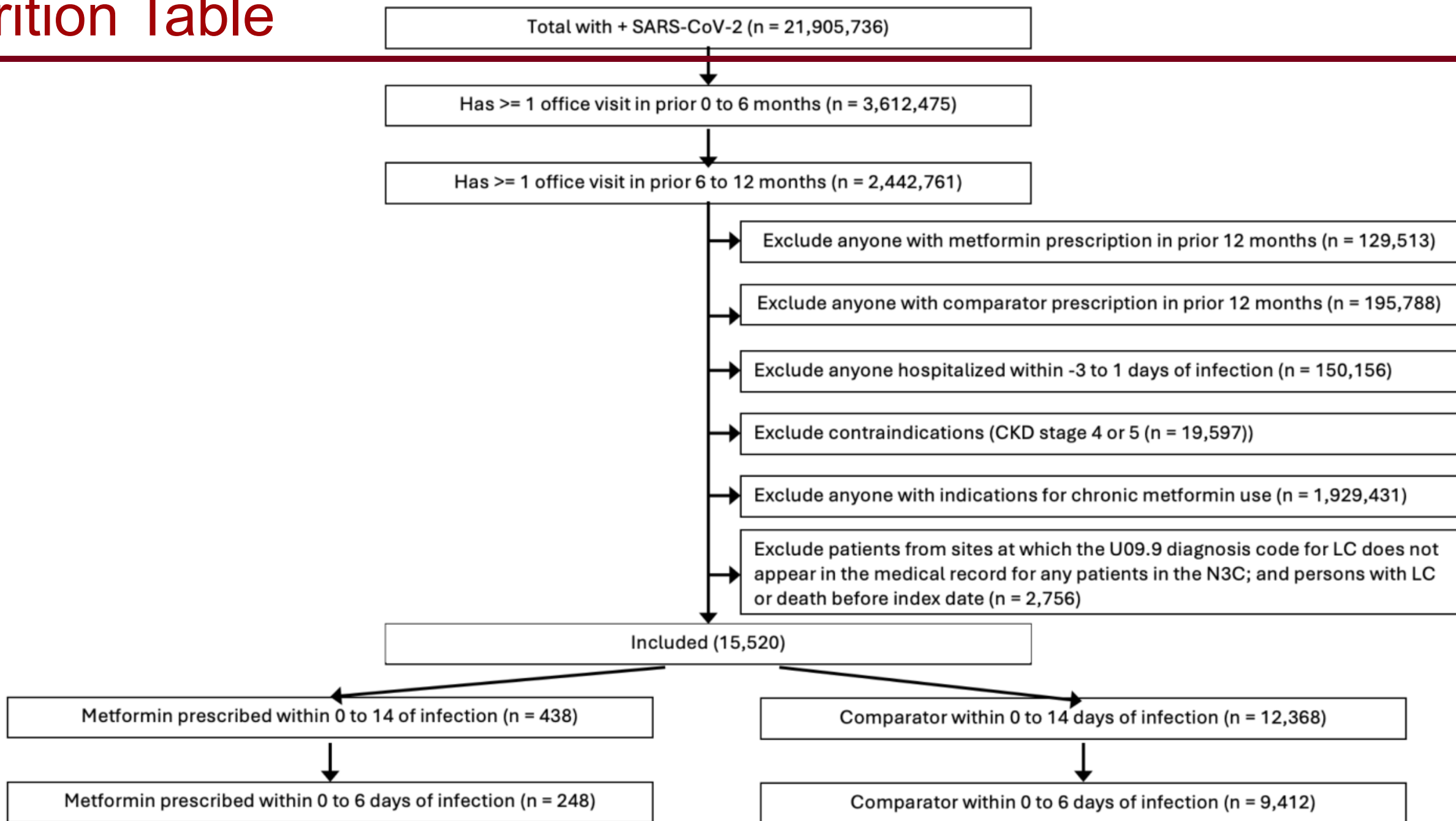
Follow-up: starting day 1

Intention to Treat

Entropy balancing of covariates

Estimation of average treatment effect with a weighted log linear model.

# Attrition Table



# Overview

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- Scientific rationale for studying metformin
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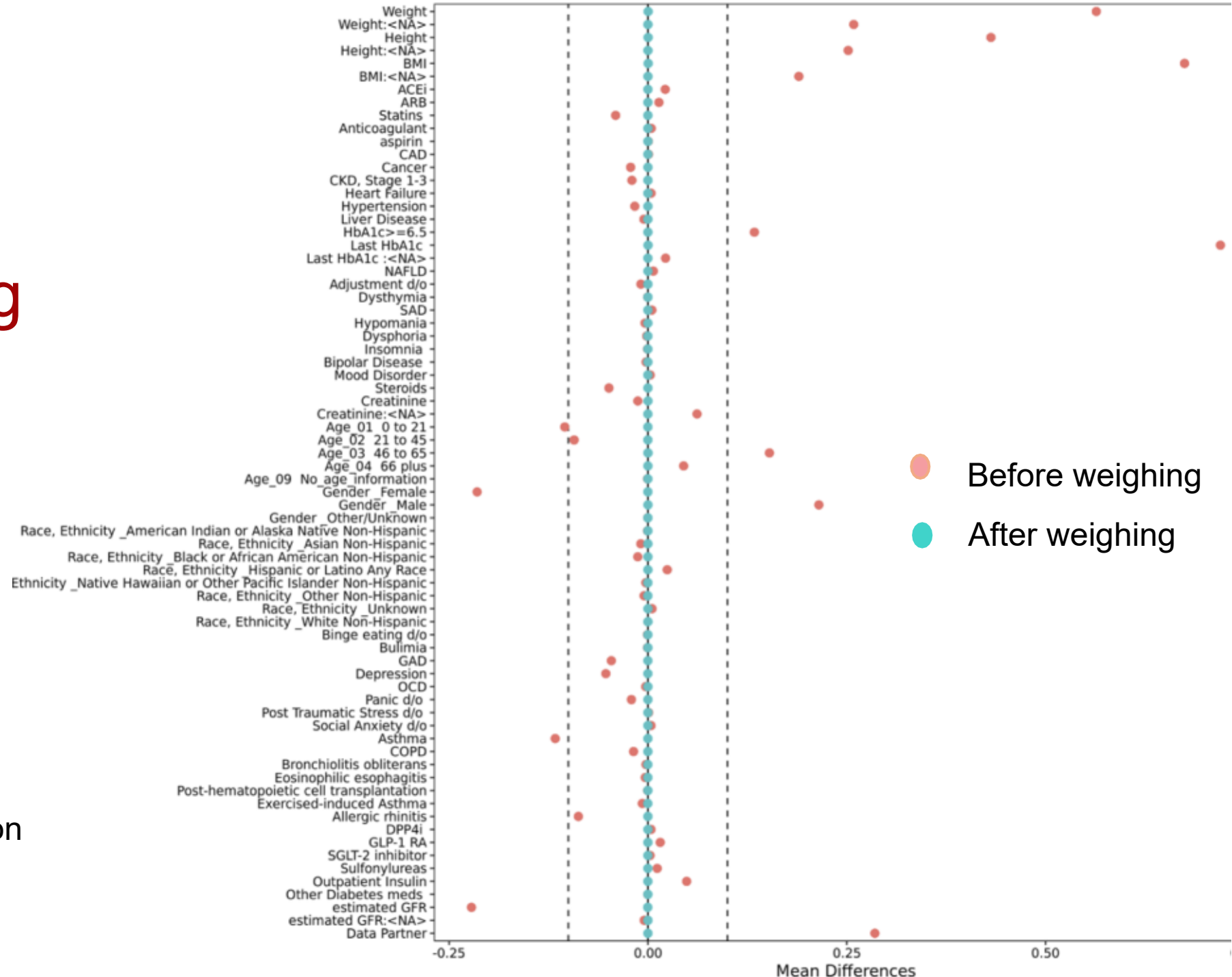


# Baseline Characteristics

	Before Weighting			After Weighting		
	Metformin (n=248)	Control (n=9,412)	SMD*	Metformin (n=248)	Control (n=248.1)	SMD
Age, mean (SD)	53.31(16.48)	45.28 (20.66)	0.430	53.31(16.45)	52.74 (17.25)	0.034
Female	113 (0.46)	6,310 (0.67)	0.444	113 (0.46)	113.1 (0.46)	0.000
American Indian or Alaska Native	< 10	42 (0.00)	0.007	< 10	< 10	0.000
Asian	< 10	236 (0.03)	0.063	< 10	< 10	0.000
Black or African American	40 (0.16)	1,638 (0.17)	0.034	40 (0.16)	40.0 (0.16)	0.000
Native Hawaiian, or Pacific Islander	0 (0.00)	24 (0.00)	0.072	0 (0.00)	< 10	0.009
Hispanic or Latino Any Race	39 (0.16)	1,251 (0.13)	0.069	39 (0.16)	39.0 (0.16)	0.000
White non-Hispanic	153 (0.62)	5,807 (0.62)	0	153 (0.62)	153.1 (0.62)	0.000
<b>Number of office visits before infection, mean (SD)</b>						
0-6 mo before	6.28 (9.56)	7.87 (9.89)	0.163	6.28 (9.54)	7.38 (10.94)	0.107
6-12 mo before	5.19 (7.95)	7.34 (9.17)	0.251	5.19 (7.94)	6.38 (8.52)	0.144
<b>Body Mass Index (BMI)</b>						
BMI, mean (SD)	35.91 (9.30)	29.64 (8.26)	0.712	35.91 (9.27)	35.90 (11.05)	0.000
18.5 to 24.9	< 10	1,651 (0.18)	0.483	< 10	14.1 (0.06)	0.120
25.0 to 29.9	< 29	1,849 (0.20)	0.233	< 29	28.5 (0.12)	0.007
>=30.0	94 (0.38)	2,907 (0.31)	0.148	94 (0.38)	87.5 (0.35)	0.055
Missing	117 (0.47)	2,654 (0.28)	0.399	117 (0.47)	117.0 (0.47)	0.000

\*Standardized mean difference

# Potential confounders: well-balanced after weighting



Limitation: did not balance on vaccination

# Baseline Characteristics

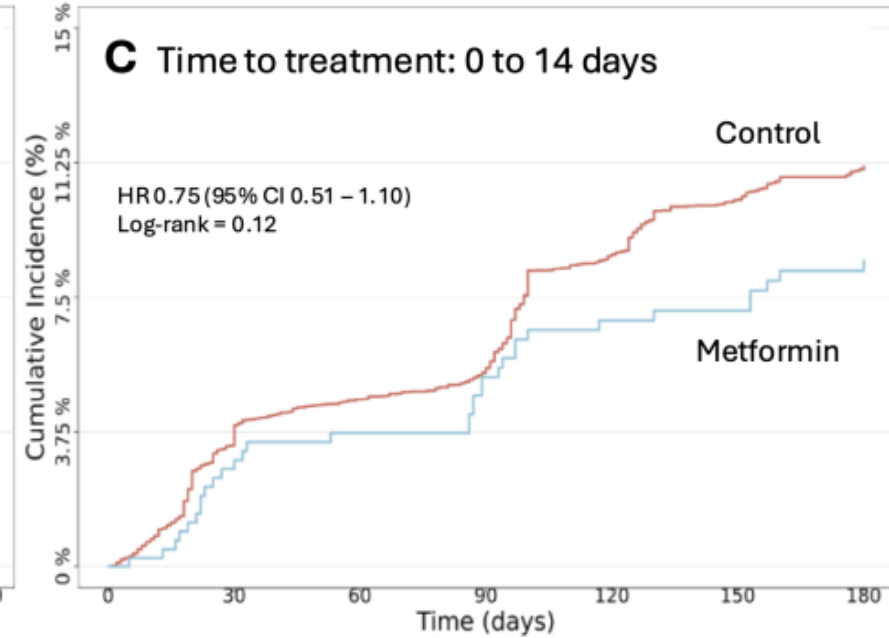
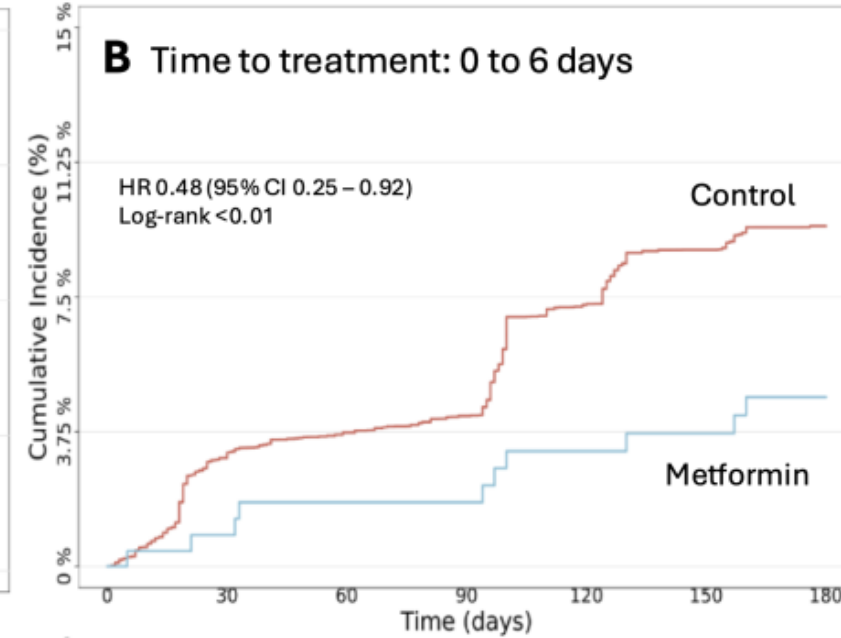
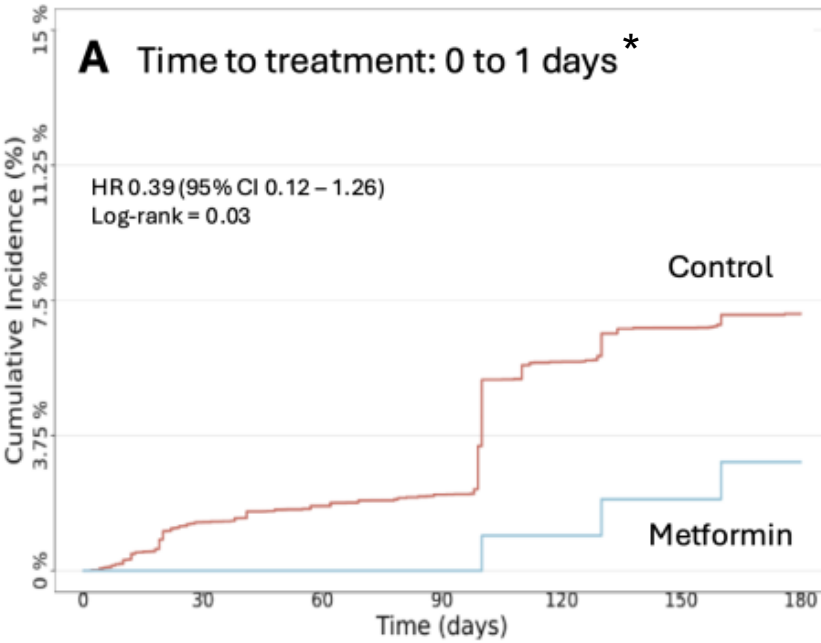
	Before Weighting			After Weighting		
	Metformin	Control	SMD	Metformin	Control	SMD
<b>COVID Variant Epoch (not used for weighting)</b>						
<b>Ancestral</b>	21 (0.08)	391 (0.04)	0.178	21 (0.08)	20.9 (0.08)	0.001
<b>Alpha</b>	70 (0.28)	1,651 (0.18)	0.256	70 (0.28)	48.7 (0.20)	0.203
<b>Delta</b>	34 (0.14)	1,691 (0.18)	0.117	34 (0.14)	48.9 (0.20)	0.162
<b>Omicron</b>	123 (0.50)	5,664 (0.60)	0.214	123 (0.50)	129.4 (0.52)	0.051

## Days from infection to treatment (not used for weighting; >5 days not shown)

<b>Control</b>	0	< 10	5,751 (0.61)	1.557	< 10	126.7 (0.51)	1.257
	1 to 3	< 10	2,165 (0.23)	0.613	< 10	66.9 (0.27)	0.703
	3 to 5	< 10	1,018 (0.11)	0.438	< 10	34.8 (0.14)	0.521
<b>Metformin</b>	0	94 (0.38)	0 (0.00)	1.105	94 (0.38)	0.0 (0.00)	1.105
	1 to 3	85 (0.34)	0 (0.00)	1.021	85 (0.34)	0.0 (0.00)	1.021
	3 to 5	43 (0.17)	< 10	0.647	43 (0.17)	< 10	0.625

# Results

## Primary analysis:



**Number  
at risk:**

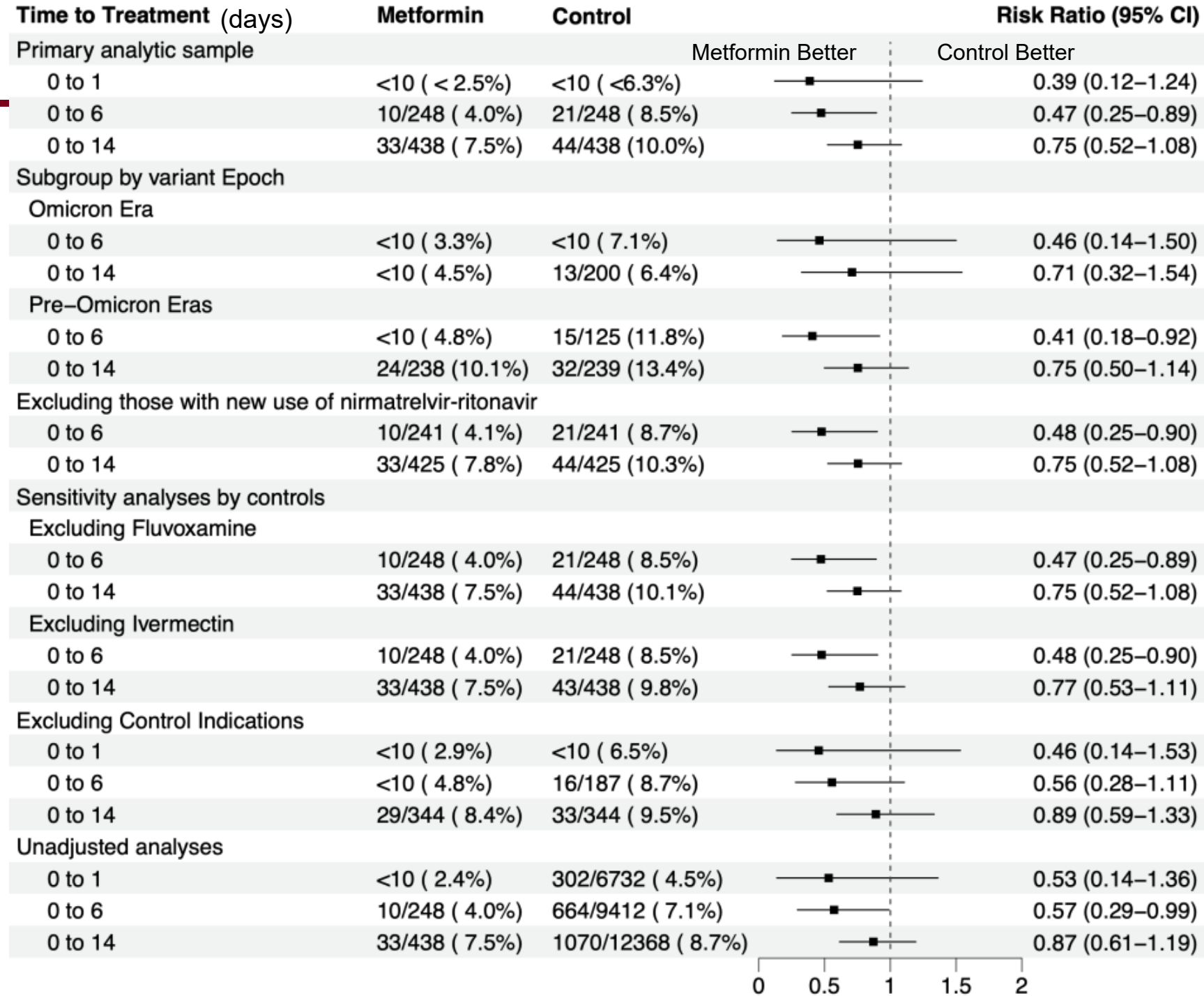
Metformin	218	213	208	195	191	187
Control	223	217	211	198	189	180

Metformin	390	380	363	346	336	325
Control	395	380	366	344	328	312

\*Number at risk omitted due to small numbers and data use agreements

# Results

Consistent across  
*a priori* subgroups  
and sensitivity analyses



0 0.5 1 1.5 2

# Cumulative incidence of the outcome components

	Days 0 - 1			Days 0 - 6			Days 0 - 14		
	Overall (n= 6,858)	Metformin	Control	Overall (n= 9,660)	Metformin (n=248)	Control (n=9,412)	Overall (n=12,806)	Metformin (n=438)	Control (n=12,368)
<b>Unweighted frequencies</b>									
<b>Long Covid/Death</b>	305 (4.4%)	< 2.5%	< 4.6%	674 (7.0%)	10 (4.0%)	664 (7.1%)	1103 (8.6%)	33 (7.5%)	1070 (8.7%)
<b>Death</b>	61 (0.9%)	0	<1%	160 (1.7%)	< 1.7%	< 1.8%	245 (1.9%)	12 (2.7%)	233 (1.9%)
<b>LC (U09.9 + Computable phenotype)</b>	251 (3.7%)	< 2.5%	< 3.8%	529 (5.5%)	< 2.9%	< 5.6%	883 (6.9%)	22 (5%)	861 (7%)
<b>Weighted frequencies</b>									
<b>Long Covid/Death</b>	4.3%	< 2.5%	< 6.3%	6.3%	4%	8.5%	8.8%	7.5%	10%
<b>Death</b>	0.8%	0	1.6%	2.2%	< 1.7%	< 2.8%	2.7%	2.7%	2.6%
<b>LC (U09.9 + Computable phenotype)</b>	3.5%	< 2.5%	< 4.7%	4.4%	< 2.9%	< 6%	6.3%	5%	7.5%

Abbreviations: LC=Long Covid

# Overview

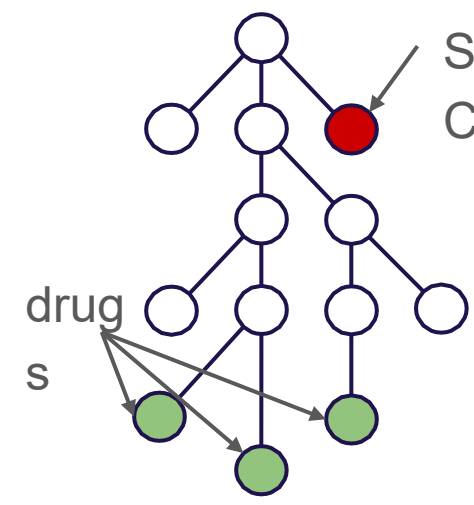
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- Results
- **Context within other literature**
  - Observational
  - *In vitro, In vivo*

# Other modeling predicted metformin

Using graph machine learning on KG-COVID-19 to prioritize drug repurposing candidates

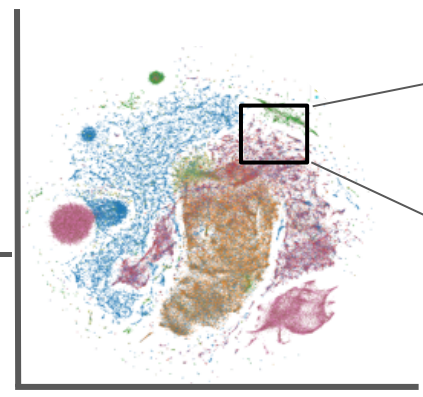
KG-COVID-19



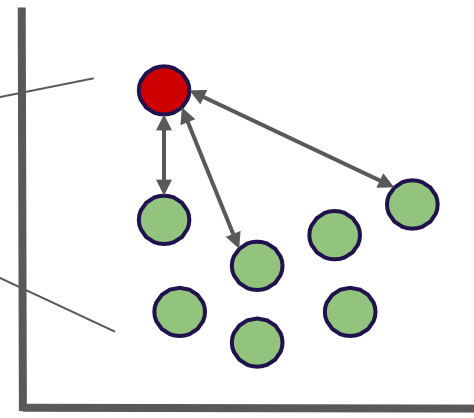
SARS-CoV-2

Node2Vec - Embed in low-dimensional space

Generate "Embeddings"

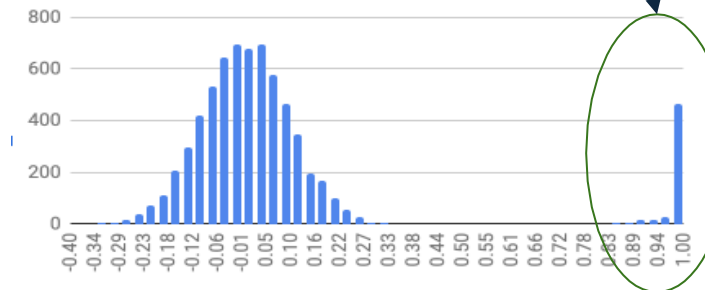


Rank drugs by "proximity" to SARS-CoV-2



Close to SARS-CoV-2 == Good drug candidates

Cosine similarity to SARS-CoV-2



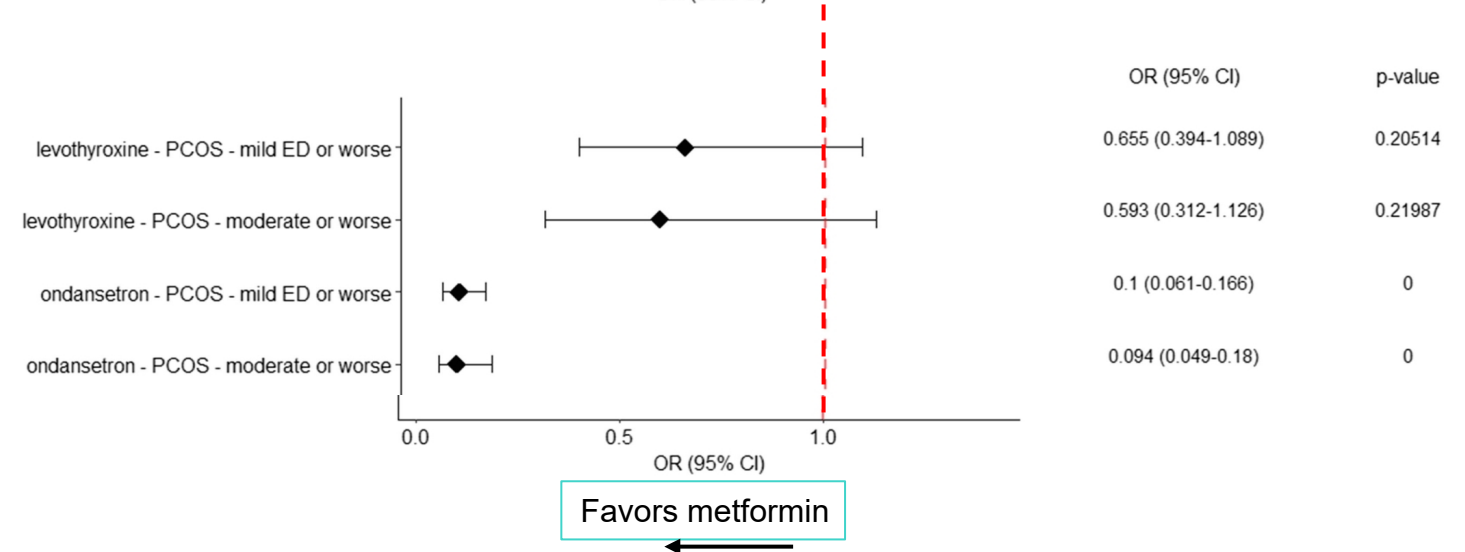
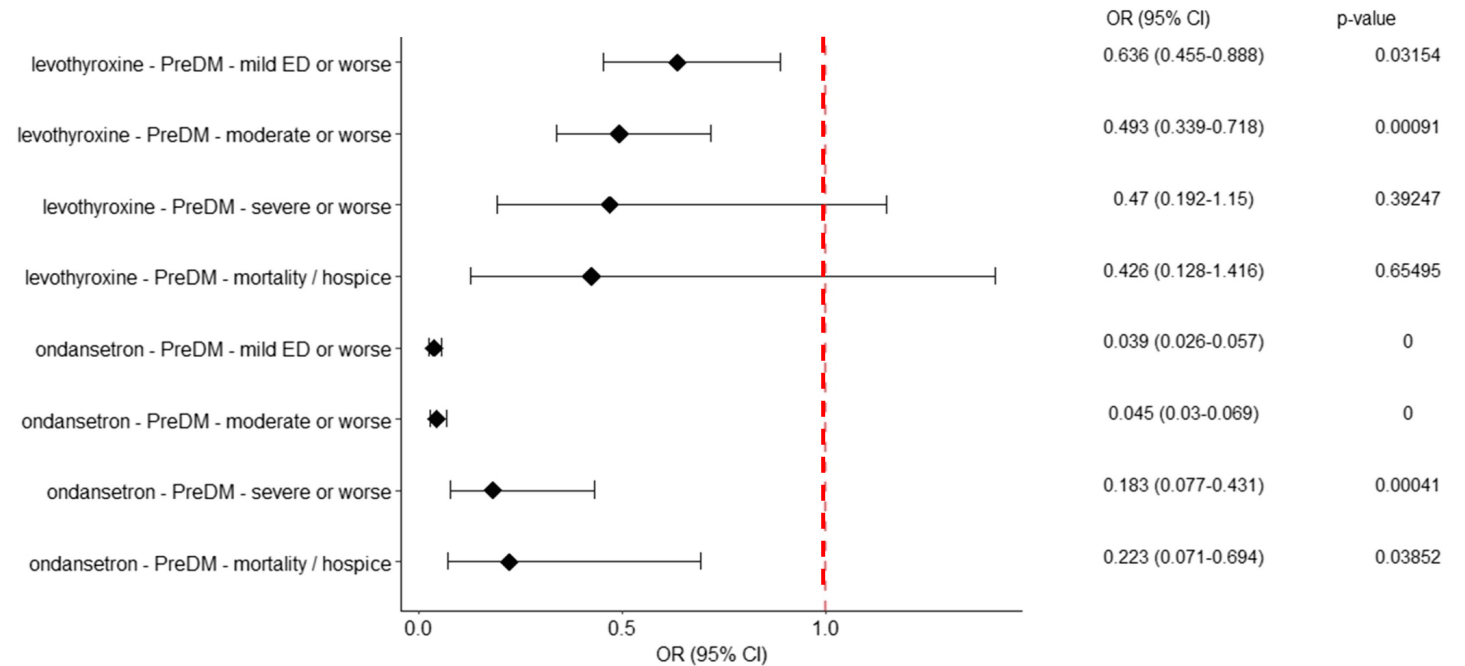
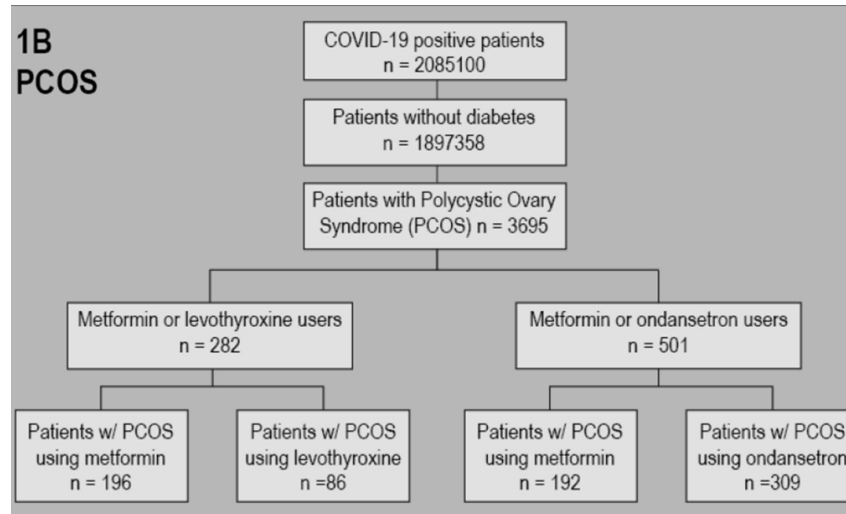
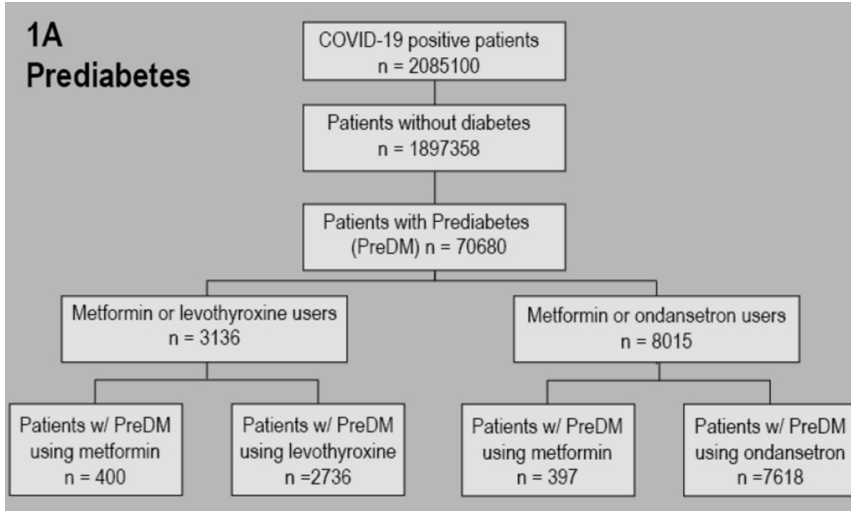
Themes in top ranked drugs:

- steroids
- antivirals
- NSAIDs
- SSRI antidepressants
- **metformin - rank 505 (of 6901 high priority ChEMBL drugs)**

How does metformin rank? Very high



# Observational data: associated with less severe acute Covid



# Observational data: associated with less severe acute Covid

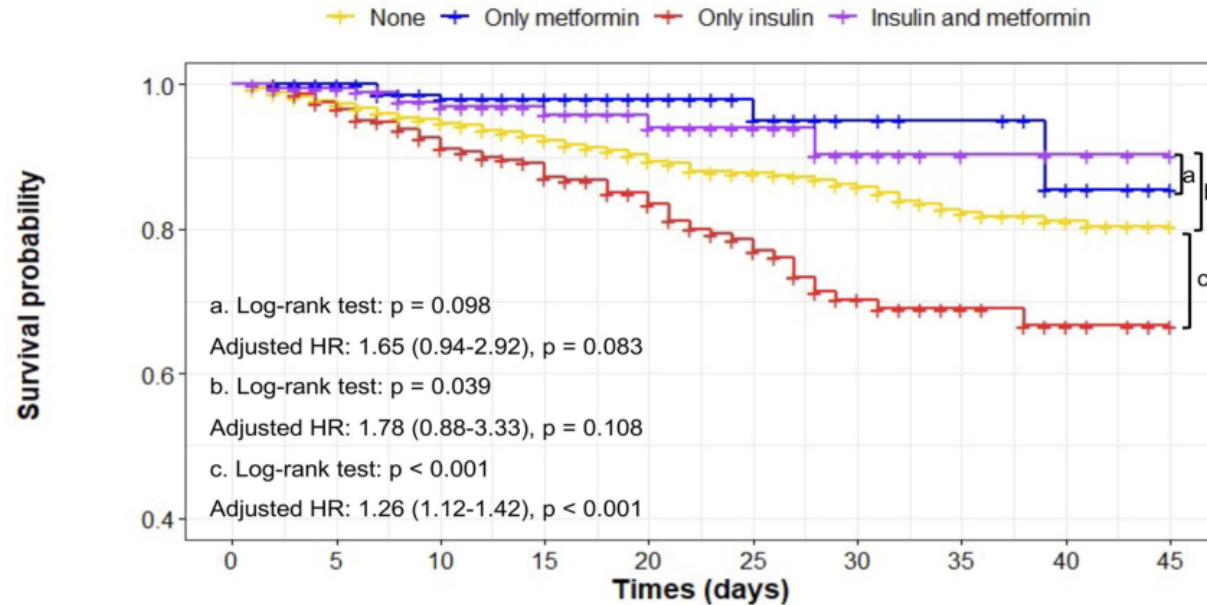
RESEARCH

Open Access



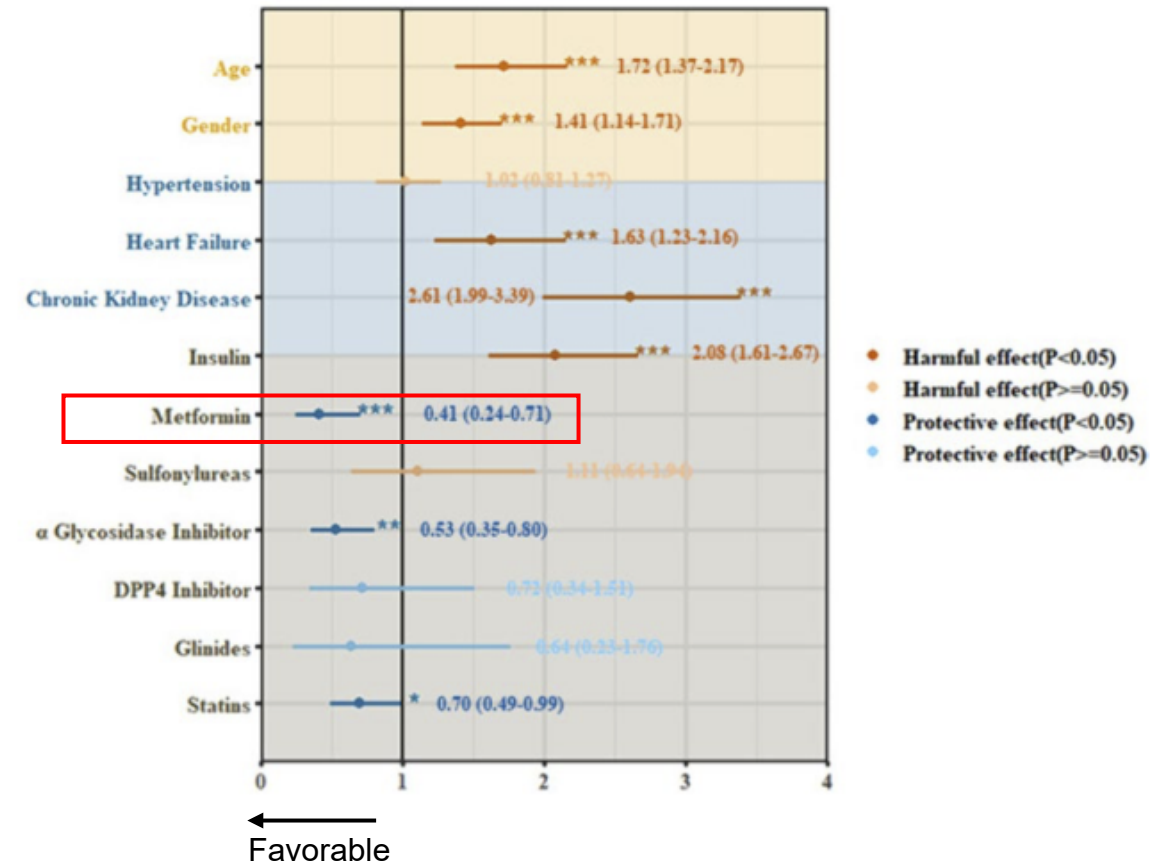
## Effects of different treatments for type 2 diabetes mellitus on mortality of coronavirus disease from 2019 to 2021 in China: a multi-institutional retrospective study

Ke Xu<sup>1</sup>, Wu He<sup>1</sup>, Bo Yu<sup>1</sup>, Kaineng Zhong<sup>2</sup>, Da Zhou<sup>2</sup> and Dao Wen Wang<sup>1\*</sup>



Number at risk

	0	5	10	15	20	25	30	35	40	45
None	3838	3375	2208	1390	830	554	343	181	118	91
Only metformin	267	245	160	106	59	33	17	12	8	2
Only insulin	618	559	380	258	166	101	64	39	22	10
Insulin and metformin	199	186	128	90	54	33	19	9	7	4



# Observational data: associated with less severe acute Covid

[Home](#) > [Therapeutic Innovation & Regulatory Science](#) > [Article](#)

## The Effect of Antihyperglycemic Medications on COVID-19: A Meta-analysis and Systematic Review from Observational Studies

Original Research | Published: 29 April 2024

Volume 58, pages 773–787, (2024) [Cite this article](#)

### Metformin

Al Hayek et al., 2020

Dave et al., 2021

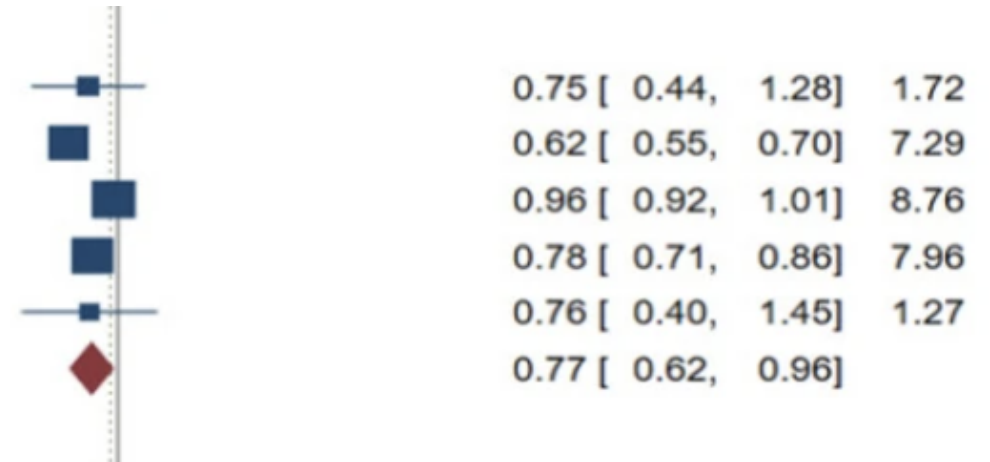
Wander et al., 2021

Boye et al., 2021

Cernigliaro et al., 2020

Heterogeneity:  $\tau^2 = 0.04$ ,  $I^2 = 91.80\%$ ,  $H^2 = 12.19$

Test of  $\theta = 0$ :  $z = -2.33$ ,  $p = 0.02$



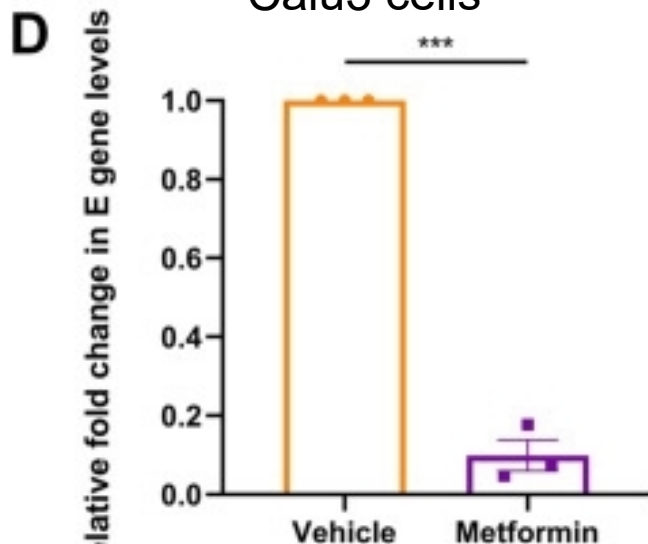
← Favours metformin

Forest plot of the relationship between antihyperglycemic medications and hospitalization risk. a Forest plot of the relationship between non-insulin antihyperglycemic medications and hospitalization risk: proof by contradiction. b Forest plot of the relationship between insulin and hospitalization risk: subgroups with region.

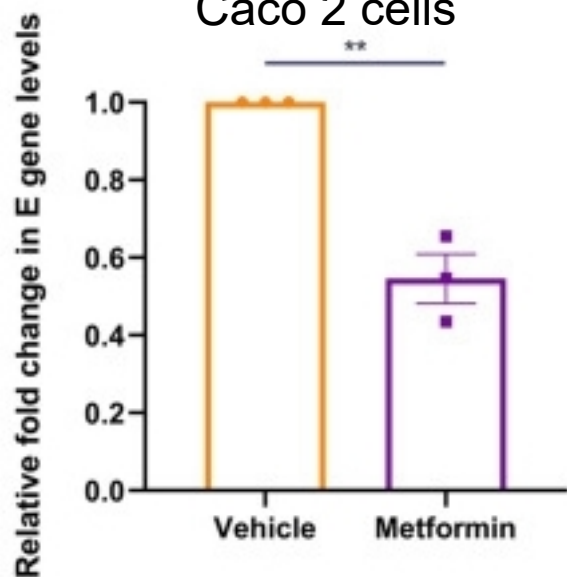
# Anti-viral actions: *in vitro* studies and *in vivo* studies

Parthasarathy et al, 2022

Calu3 cells

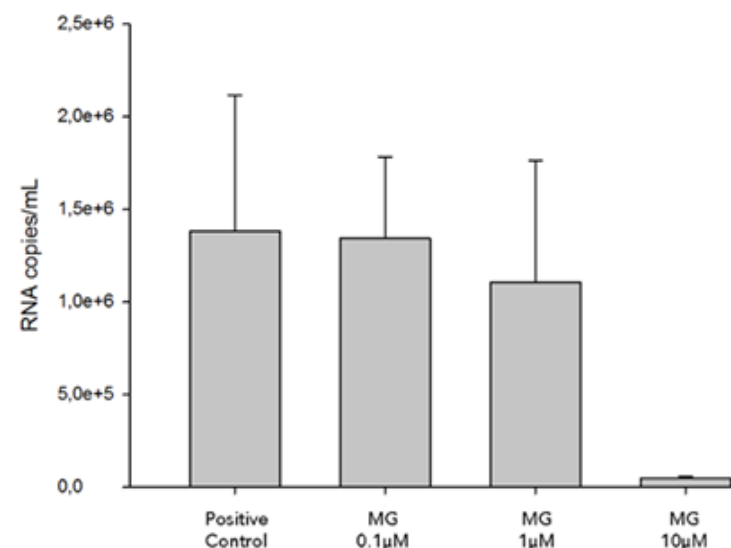


Caco 2 cells

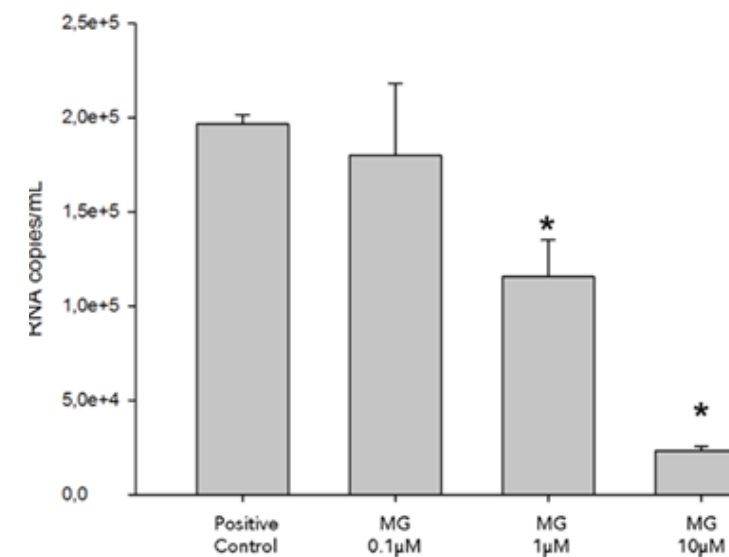


Ventura-Lopez et al, 2022.

Cell 48h



supernatant 48h



<i>Nasal swabs</i>	Metformin	Placebo	P	OR (95 %CI)
	n = 10	n = 10		
Negative viral load (days)	3.3 ± 2.16	5.6 ± 0.89	0.029	
Negative viral load < 3.3 days (n, %)	4.0 (40.0)	0.0 (0.0)	0.043	6.67 (0.60–74.0)
Negative viral load > 4.0 days (n, %)	6.0 (60.0)	10.0 (100.0)		

# Overview

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- Scientific rationale for studying metformin
- Methods
  - Data Source
  - Trial Emulation Design
  - Target Trials
- Results
- Context within other literature
- **Summary**

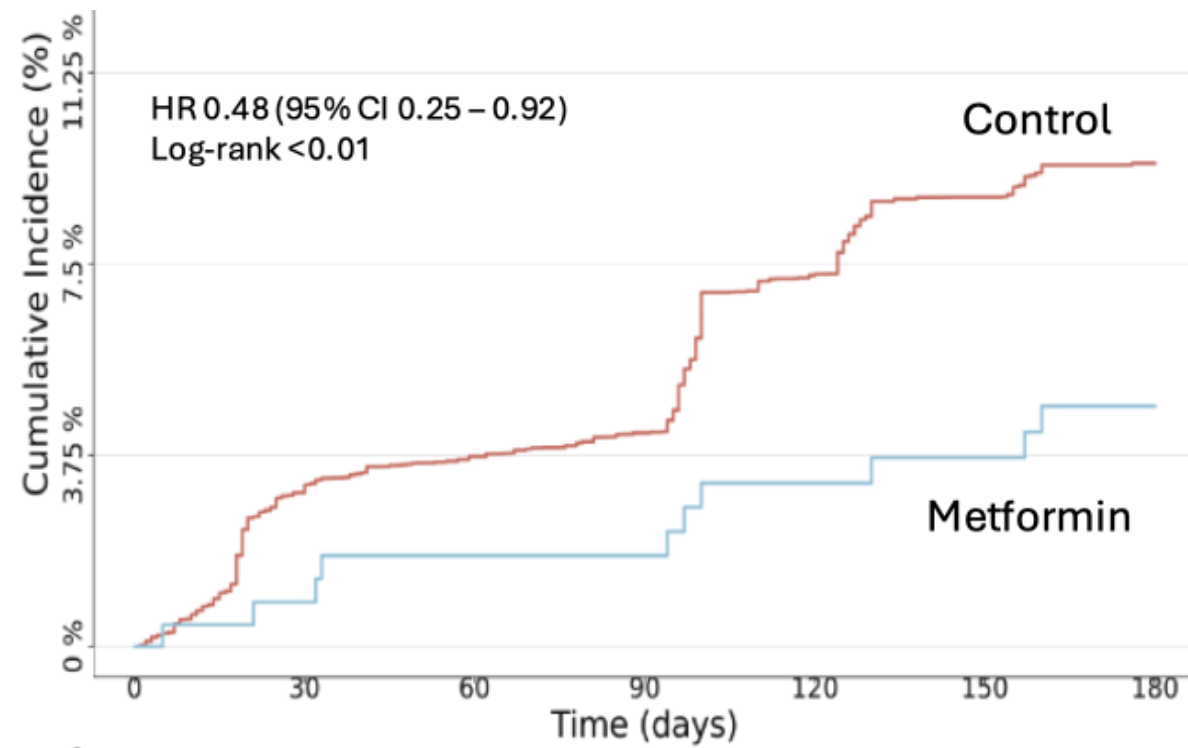
# Summary

## Target Trial Emulation:

Metformin within a week of SARS-CoV-2 infection was associated with a 53% lower risk of LC or death over 6 months

## These results are Consistent with other data

With emerging observational analyses of clinical outcomes  
With emerging data on anti-viral actions



# Summary

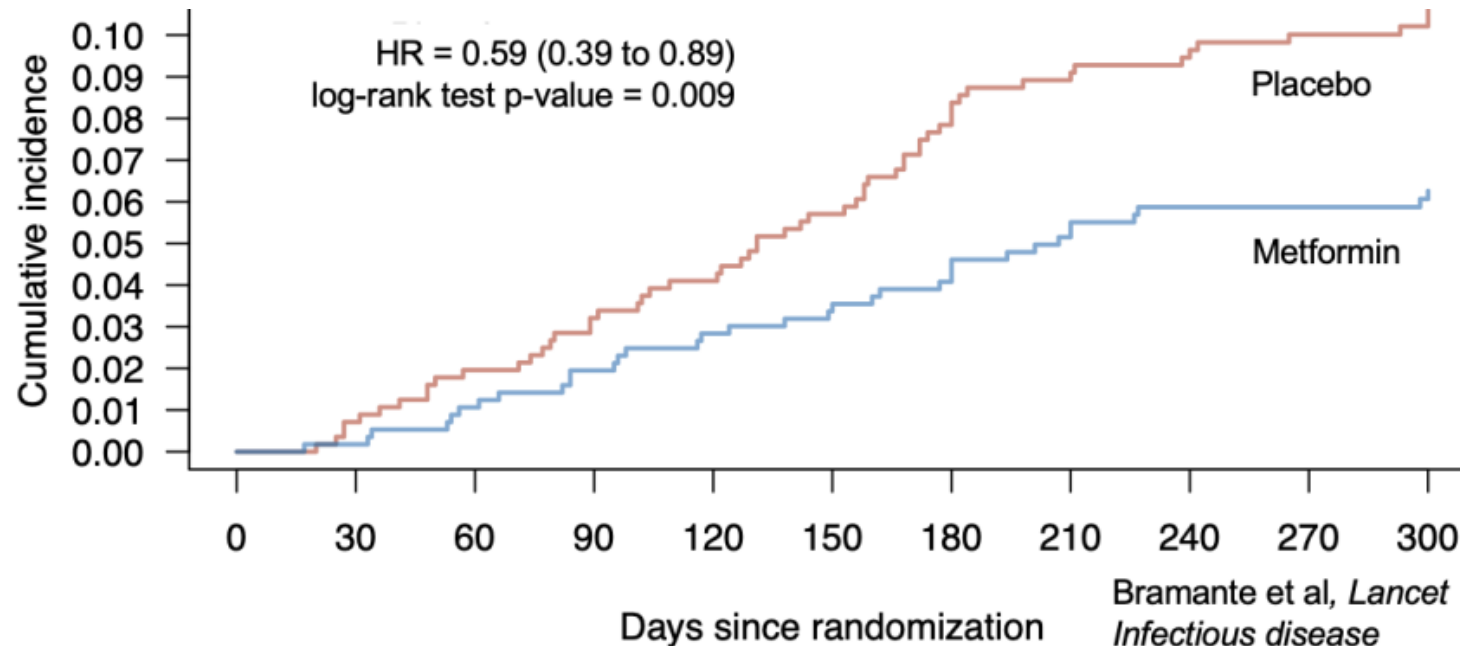
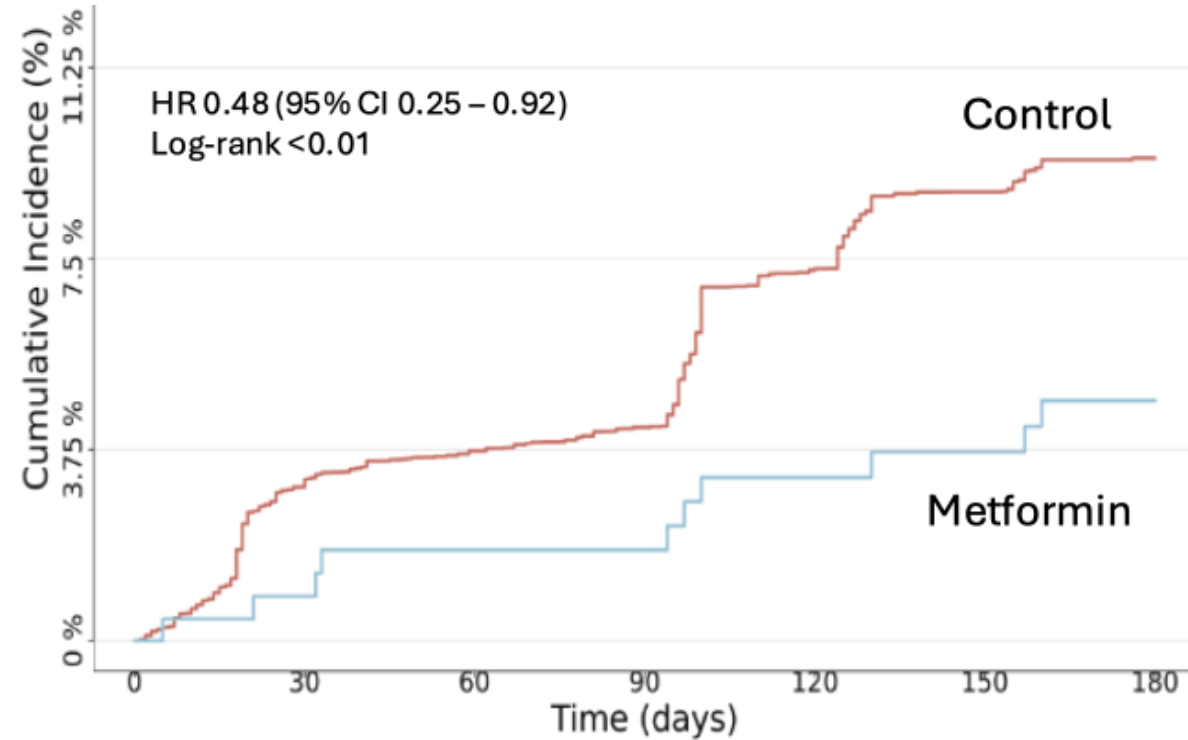
## Target Trial Emulation:

Metformin within a week of SARS-CoV-2 infection was associated with a 53% lower risk of LC or death over 6 months

## These results are Consistent with other data

With emerging observational analyses of clinical outcomes  
With emerging data on anti-viral actions

With a randomized trial of >1,000 adults,  
> 50% vaccinated, enrolled during omicron  
(COVID-OUT Trial)



# Thank you

## Thank you to Collaborators:

Til Stürmer, MD, PhD<sup>1</sup>; Jared D. Huling, PhD<sup>2</sup>; John B Buse, MD, PhD<sup>3</sup>; Christopher Lindsell, PhD<sup>4</sup>; Thomas Stewart, PhD<sup>5</sup>; Russell L. Rothman, MD, MPP<sup>6</sup>; David Sahner, MD<sup>7,10</sup>; Sarah E. Dunsmore, PhD<sup>7</sup>; Eric Topol, MD<sup>8</sup>; Talia D. Wigger, MPH<sup>9</sup>; Steve Makkar, PhD<sup>7,10</sup>; Andrew Toler, MS<sup>7,10</sup>; Taylor Estep, PhD<sup>7,10</sup>, and Steven G. Johnson, PhD<sup>10</sup> on behalf of the N3C Consortium.

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5. Division of Biostatistics, University of Virginia School of Data Science
6. Vanderbilt Institute for Medicine and Public Health, Nashville, TN
7. National Center for Advancing Translational Science (NCATS)
8. Institute for Health Informatics, University of Minnesota, Minneapolis, MN
9. Scripps Research Translational Institute, La Jolla, CA
10. NCATS contractor Axle Informatics



National COVID Cohort Collaborative



National Center  
for Advancing  
Translational Sciences

## Questions

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# Extra Slides

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# Rapid dose escalation is tolerated

1,500mg over 6 days

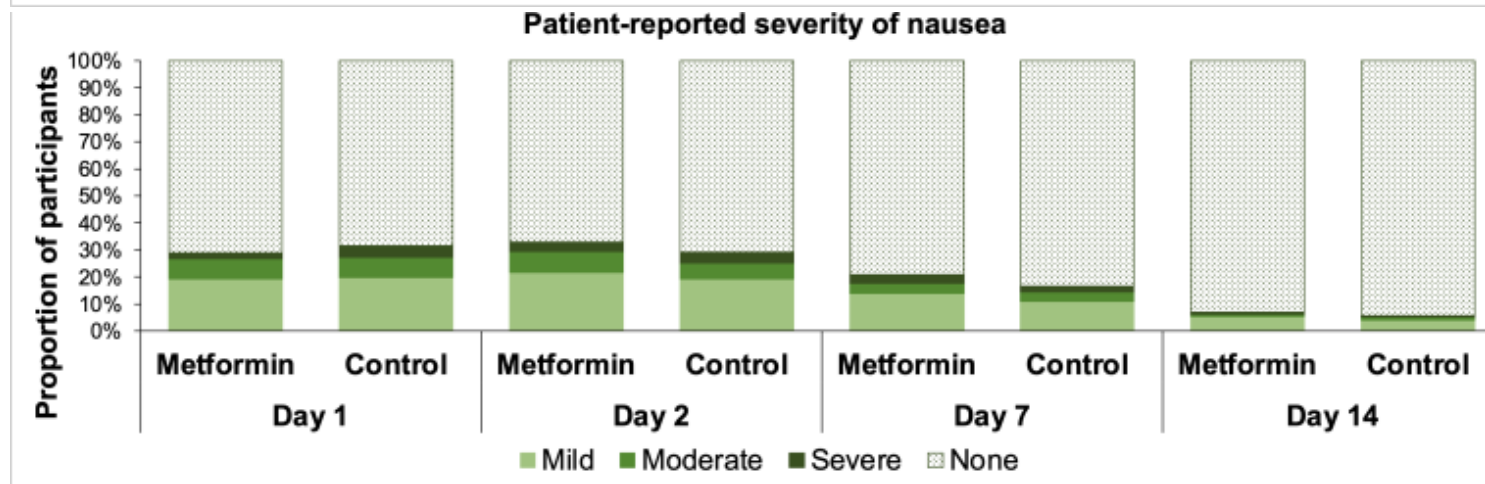
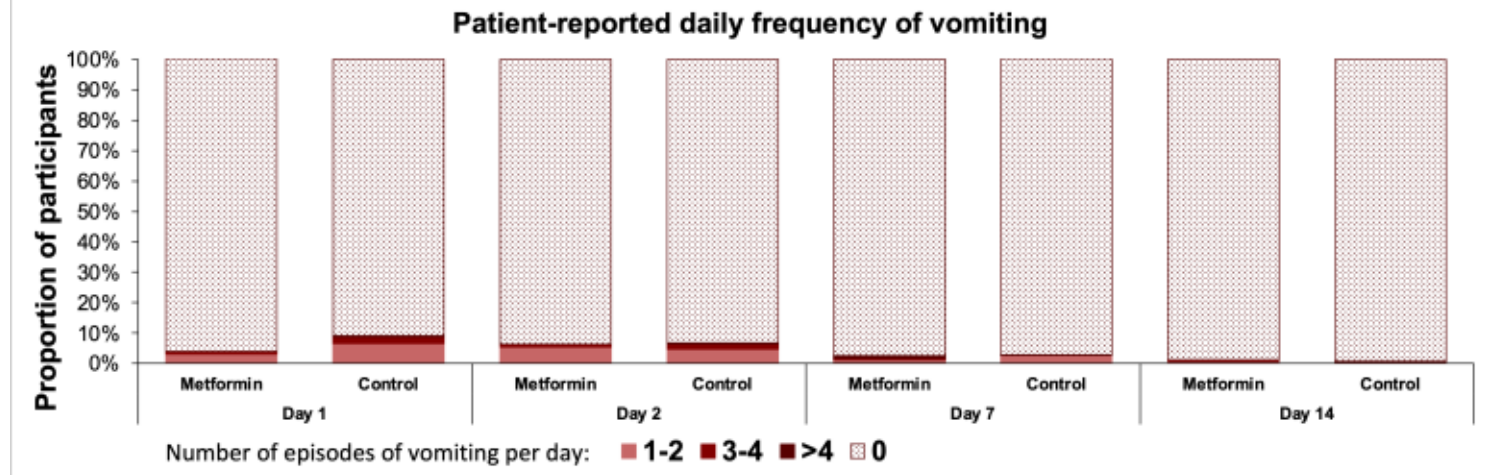
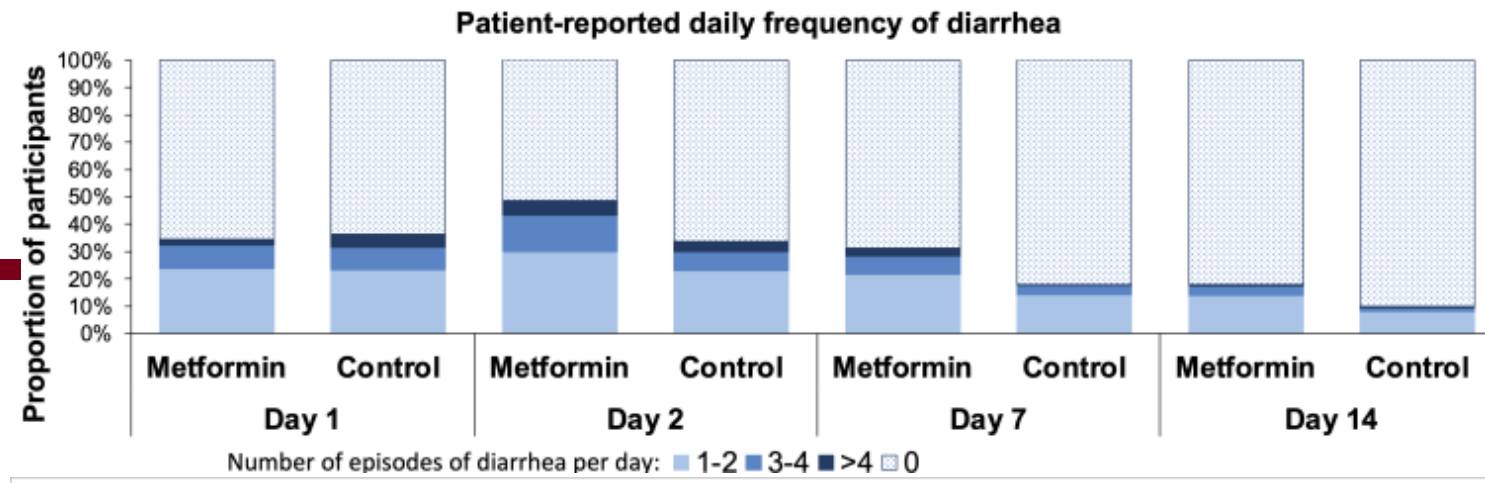
## PROMIS GI Diarrhea

- 3.92 points greater than placebo (p<0.001)
- a difference >= 5 points is clinically meaningful

## Side effects were minimal in trial:

- 0.45 episodes/day of diarrhea more than placebo
- 0.9 episodes/day total

Bramante et al, NEJM 2022  
Avula et al, in preparation



# Why metformin? Safe well-tolerated, widely available, \$1

## Metformin: no longer stopped at all admissions or perioperatively.

Chang LL, Umpierrez GE, Inzucchi SE. Management of Hyperglycemia in Hospitalized, Non-Critically Ill Adults. Case Reports. *The New England journal of medicine*. Sep 15 2022;387(11):1040-1042.

## Fewer cases of lactic acidosis, in persons on metformin.

Inzucchi SE, Lipska KJ, Mayo H, Bailey CJ, McGuire DK. Metformin in patients with type 2 diabetes and kidney disease: a systematic review. *^*. Dec 24-31 2014;312(24):2668-75. doi:10.1001/jama.2014.15298

Salpeter SR, Greyber E, Pasternak GA, Salpeter EE. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. Systematic Review. *^*. Apr 14 2010;2010(4):CD002967.

Zhang X, Harmsen WS, Mettler TA, et al. Continuation of metformin use after a diagnosis of cirrhosis significantly improves survival of patients with diabetes. *Hepatology*. 2014/12/01 2014;60(6):2008-2016. doi:<https://doi.org/10.1002/hep.27199>

Clegg LE, Jing Y, Penland RC, et al. Cardiovascular and renal safety of metformin in patients with diabetes and moderate or severe chronic kidney disease: Observations from the EXSCEL and SAVOR-TIMI 53 cardiovascular outcomes trials. *Diabetes, obesity & metabolism*. May 2021;23(5):1101-1110. doi:10.1111/dom.14313

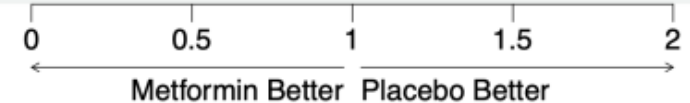
## Metformin safe in pregnancy, lactation, children

## Participants could not distinguish metformin from placebo; no higher rates of GI side effects on metformin.

Orloff, JN, Touhamy, SH, Truong, W, et al. Trial of restarting and tolerating metformin (TreatMet). *Diabetes Obes Metab*. 2020; 22: 2189–2192.

# COVID-OUT target trial

Outcome	Metformin [n/N (%)]	Placebo [n/N (%)]	Hazard/Odds Ratio for Outcome (95% CI)
<b>1) PMC9945922: Acute Outcomes (Day 14 and 28)</b>			
1x SpO2<94% / ED / Hosp / Death	154/652 (23.62%)	179/653 (27.41%)	0.84 (0.66;1.09)
ED / Hosp / Death	27/652 ( 4.14%)	48/655 ( 7.33%)	0.58 (0.35;0.94)
Hosp / Death	8/652 ( 1.23%)	18/655 ( 2.75%)	0.47 (0.20;1.11)
A priori subgroups for ED / Hosp / Death by Day 14 (Figure S2A of PMC9945922)			
Started study drug in <4 days of symptom onset	11/290 ( 3.79%)	26/299 ( 8.70%)	0.45 (0.22;0.93)
Vaccinated (>= primary series by enrollment)	5/358 ( 1.40%)	14/330 ( 4.24%)	0.31 (0.11;0.88)
Enrolled during Omicron	1/140 ( 0.71%)	7/148 ( 4.73%)	0.16 (0.02;1.32)
Pregnant individuals	0/22 ( 0.00%)	3/23 (13.04%)	0.00 (0.00; Inf)
Disease progression by Day 28 (Figure S8 of PMC9945922)			
ED / Hosp / Death	28/596 ( 4.70%)	54/601 ( 8.99%)	0.52 (0.34;0.81)
Hospitalization / Death	8/596 ( 1.34%)	19/601 ( 3.16%)	0.42 (0.19;0.96)
<b>2) PMC11259948: Day 300 outcomes</b>			
Long Covid, HR	35/564 ( 6.21%)	58/562 (10.32%)	0.59 (0.39;0.89)
A priori subgroups for Long Covid by Day 300 (Figures 2 and 3 of PMC11259948)			
Started study drug in <4 days of symptom onset	6/130 ( 4.62%)	17/144 (11.81%)	0.37 (0.15;0.95)
Enrolled during Omicron	7/131 ( 5.34%)	15/132 (11.36%)	0.45 (0.18;1.11)
Vaccinated (at least primary series by enrollment)	20/326 ( 6.13%)	21/293 ( 7.17%)	0.85 (0.46;1.57)
Vaccinated within 6 months of enrollment (post-hoc)*	9/138 ( 6.52%)	12/128 ( 9.38%)	0.69 (0.29;1.64)
<b>3) PMID 38690892: Viral Load Outcomes (Figure 1)</b>			
Rebound of viral load, OR**	12/366 ( 3.28%)	22/370 ( 5.95%)	0.68 (0.36;1.29)
Odds of detectable viral load on Day 10**	55/385 (14.29%)	88/390 (22.56%)	0.65 (0.43;0.98)
Viral load Results without Imputation (Figure S3 of PMID 38690892)			
Rebound of viral load, OR**	22/370 ( 5.95%)	12/366 ( 3.28%)	0.44 (0.20;0.94)
Odds of detectable viral load on Day 10**	55/385 (14.29%)	88/390 (22.56%)	0.39 (0.25;0.62)



Subgroups and sensitivity analyses in all three outcome papers showed point estimates that were all in the same direction of effect. Subgroups of interested (stage of pandemic, timing of starting medication, pregnant ) are pulled from each paper and presented here.

\*Those vaccinated >6 months prior to baseline acted like unvaccinated in baseline viral load analyses we had done. We did not explore boosted or vaccinated after the trial started, which may matter for Long Covid.

\*\*We imputed missing data (per the SAP), the viral load was an optional part of study. The complete case OR was smaller.