

# Metformin is Associated with Reduced Risk for Sepsis: Analysis of a U.S. Cohort from 2009-2019

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## Background

- Metformin is a first-line agent for type 2 diabetes (T2DM)
- Metformin has also been shown to have immunomodulating properties in vaccine responses, chronic inflammation, and various infectious diseases<sup>1,2</sup>
- Global rates of sepsis has not significantly declined
- Few studies address metformin's role in risk for sepsis<sup>3</sup>

## Objective

- To determine whether metformin-use is associated with lower risk for all-cause sepsis in those with and without T2DM

## Methods

**Study Design:** retrospective, propensity matched U.S. cohort analysis of a third-party medical and pharmacy claims database from 2009 – 2019

### Inclusion Criteria:

- Adults ≥ 18 years
- Receipt of a pneumococcal vaccine (PNV) within the study period (index date)
- Continuously enrolled in benefits ≥ 1 year before and after a PNV

### Definitions/Outcome:

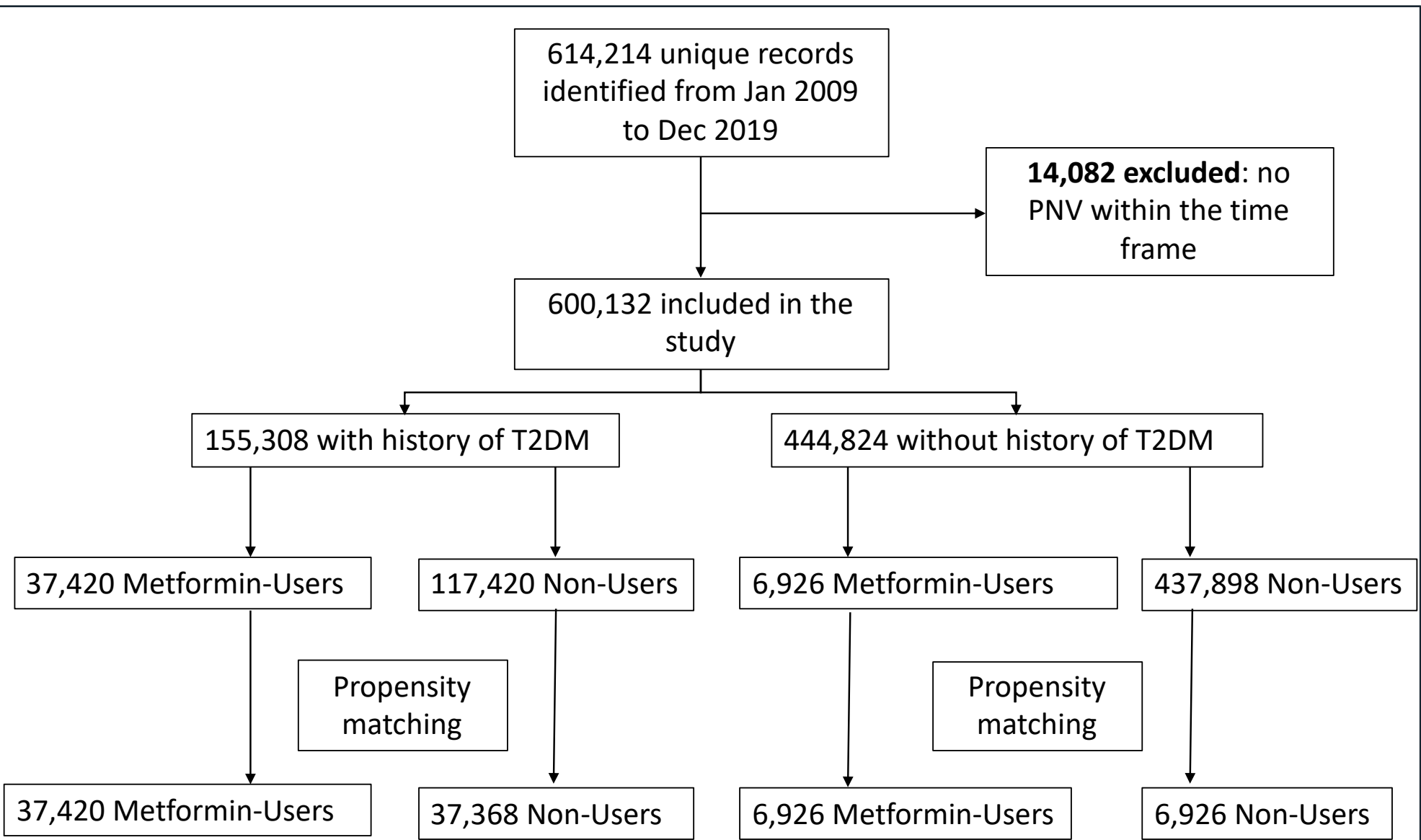
- Primary outcome: sepsis was evaluated from day 14 to day 366 post index date
- Sepsis was determined using ICD-9/10-CM codes: A40, A40.1, A40.3 A40.8, A40.9, A41.9, I40.0, R65.2, R65.20, R65.21,038.0, 038.2, 041.2, 422.92, 785.52, 995.92,and 995.91
- Metformin-use: ≥ 90-day supply filled prior to index date

### Statistics:

- Comparisons of all-cause sepsis between groups were analyzed using Wilcoxon Rank Sum and Chi-squared tests
- Multivariable logistic and linear regression models were conducted as appropriate
- Propensity score-matched analyses was compared for adults with T2DM and without T2DM, who were metformin-users to non-users
- Statistics were run using SPSS version 28.0 (IBP Corp, Armonk, NY)

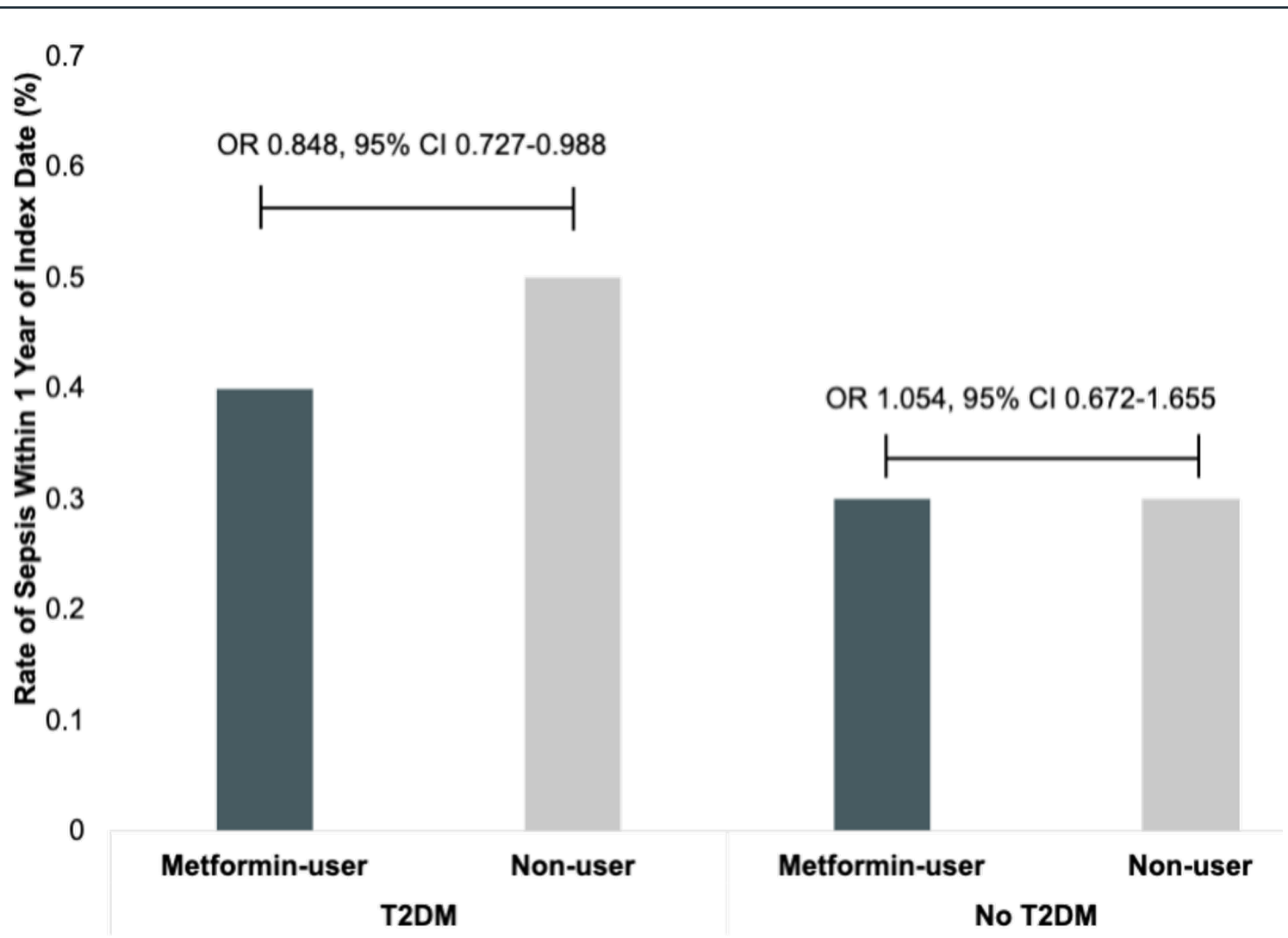
## Results

### Cohort Flow Diagram



**Figure 1:** Cohort flow diagram. PNV = pneumococcal vaccine; T2DM = type 2 diabetes mellitus

### Propensity Score Matched Results



**Figure 2:** Among the matched cohort with T2DM, **metformin-use was associated with reduced risk of sepsis** compared to matched controls (non-users). T2DM = type 2 diabetes mellitus

**Table 1: Logistic regression model of metformin's association with reduced risk hospitalization due to sepsis among those with T2DM**

	aOR	95% CI	P-value
Age (yr)	1.016	1.011-1.021	<b>&lt;0.001</b>
Female	1.002	0.905-1.108	<b>0.975</b>
Vaccine Year	1.000	1.000-1.000	<b>&lt;0.001</b>
T2DM w/ kidney complications	1.524	0.990-2.346	0.056
T2DM w/ neurologic complications	1.422	0.992-2.040	0.056
T2DM w/ ophthalmic complications	0.474	0.195-1.154	0.100
T2DM w/out complications	0.837	0.746-0.939	<b>0.002</b>
CKD	2.038	1.178-3.525	<b>0.011</b>
COPD	3.469	3.023-3.981	<b>&lt;0.001</b>
Heart Disease	1.783	1.109-2.866	<b>0.017</b>
PPSV23	1.088	0.975-1.215	0.132
<b>Metformin</b>	<b>0.776</b>	<b>0.684-0.882</b>	<b>&lt; 0.001</b>

T2DM = type 2 diabetes mellitus; aOR = adjusted odds ratio; CI = confidence interval; CKD = chronic kidney disease; COPD; chronic obstructive pulmonary disease

**Table 2: Propensity score matched cohort baseline characteristics for metformin-users and non-users among those with and without T2DM**

Variables*	T2DM			No T2DM		
	Metformin-user (n=37,420)	Control (n=37,368)	P-Value	Metformin-user (n=6,926)	Control (n=6,926)	P-Value
Age, median (IQR)	62 (55-69)	63 (55-69)	0.307	63 (56-69)	64 (56-69)	0.067
Sex, n (%)			0.801			0.202
Male	18,423 (49.2)	18,363 (49.1)	-	3,337 (48.2)	3,412 (49.3)	-
Female	18,997 (50.8)	19,005 (50.9)	-	3,589 (51.8)	3,514 (50.7)	-
CKD, n (%)	58 (0.2)	50 (0.1)	0.445	4 (0.1)	4 (0.1)	1.000
T2DM without complications, n (%)	29,025 (77.6)	29,008 (77.6)	0.838	-	-	-
T2DM with kidney complications, n (%)	230 (0.6)	216 (0.6)	0.516	-	-	-
T2DM with ophthalmologic complications, n (%)	246 (0.7)	224 (0.6)	0.316	-	-	-
T2DM with neurologic complications, n (%)	483 (1.3)	429 (1.1)	0.075	-	-	-
Modified Charlson Comorbidity Index, median (IQR)	1 (1-1)	1 (1-1)	0.178	0 (0-0)	0 (0-0)	0.119

\*Select variables used in propensity score.  
IQR = interquartile range; CKD = chronic kidney disease; T2DM = type 2 diabetes mellitus

## Conclusions

**Among persons with T2DM, chronic metformin-use was associated with a 15% lower risk of sepsis within 1 year of the index date compared to matched non-users. These results add to the sparse data highlighting the immunomodulatory effects of metformin and its potential role in vaccine-care, aging, and preventative medicine.**

## Discussion

### Strengths:

- Large study > 600,000
- Propensity matched cohort study
- Novel data evaluating metformin and risk of diagnosis of all-cause sepsis

### Limitations:

- Unable to assess medication adherence, vaccination history, disease severity, or mortality
- Unable to assess long term outcomes, long-term metformin use, and other demographics and conditions other than T2DM

### References:

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- Frasca D, Diaz A, Romero M, Blomberg BB. Frontiers in Aging. 2021;30.
- Liang H, Ding X, Wang T, et al., Critical Care. 2019;23 (50)