

Sodium-glucose cotransporter-2 inhibitors and dementia risk in patients with psychiatric disorders

Tianshe He,^{1,3*} David T. Liebers,^{1,2*} Rebecca A. Betensky,⁴ Chunlei Zheng,^{3,5} Kaitlin Swinnerton,³ Paola Gilsanz,⁶ Mary Brophy,³ Nhan V. Do,³ Ricardo S. Osorio,^{1,2} Nunzio Pomara,^{1,2} Antonio Convit,^{1,2} Donald C. Goff,^{1,2} Dan Iosifescu,^{1,2} Nathanael R. Fillmore,^{3,7} and Jaime Ramos-Cejudo^{1,3,8}

Authors affiliations:

1 Department of Psychiatry, New York University (NYU) Grossman School of Medicine, New York, NY.

2 Nathan Kline Institute, Orangeburg, New York, USA

3 VA Boston Cooperative Studies Program, MAVERIC, VA Boston Healthcare System, Boston, MA

4 Department of Biostatistics, NYU School of Global Public Health, New York, NY.

5 Department of Medicine, Boston University School of Medicine, Boston, MA

6 Division of Research, Kaiser Permanente Northern California, Pleasanton, California, USA

7 Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA

8 Department of Neurology, NYU Grossman School of Medicine, New York, NY.

NYU Grossman
School of Medicine



Contact email

Tianshe.He@nyulangone.org

David.liebers@nyulangone.org

Jaime.ramoscejudo@nyulangone.org

BACKGROUND

- SGLT2 inhibitors are diabetes drugs linked to a lower risk of dementia in large population studies.¹
- They produce ketones (unlike other diabetes drugs) and have also been linked to a lower risk of depression.²
- Lab studies show they improve mitochondrial function and reduce oxidative stress in neurons. People with psychiatric illness face higher dementia risk—2–3× higher in mood disorders, and up to 10× higher in schizophrenia.³

OBJECTIVE

We tested whether SGLT2 inhibitors are associated with lower rates of dementia and markers of psychiatric severity in people with psychiatric disorders, using a target trial emulation design.⁴

SAMPLE

Veterans Health Administration (VA) patients with

- Major depressive disorder (MDD),
 - Bipolar disorder (BIP)
 - Schizophrenia spectrum disorders (SCZ),
- eligibility conditions in
- Figure 1**
- .

METHODS

Exposure: SGLT2-inhibitor use, either initiation (Intention to treat: ITT) or adherence (per-protocol: PP)

Outcomes: I. All-cause dementia: Alzheimer's Disease (AD), AD-related dementias (RD), or non-specific dementias (NSD)

II. Psychiatric Emergency Department visit (PED), with primary psychiatric symptoms as the cause of admission

III. Psychiatric-related hospitalization (PHS), either admission or transfer.

Statistical Analysis: Marginal structural models for person-period level data. Each patient is represented as a sequence of 3-month periods. Time-varying covariates (Table 1) were adjusted per period. Inverse probability weights for treatment (IPTW) and censoring (IPCW) were used towards a pooled logistic regression towards outcome.

PP analysis focused on participants who continuously adhered to their initial treatment assignment throughout the follow-up period. ITT analyzed patients according to their initial treatment assignment regardless of subsequent changes.

Figure 1 – Schematic diagram of trial emulation design.

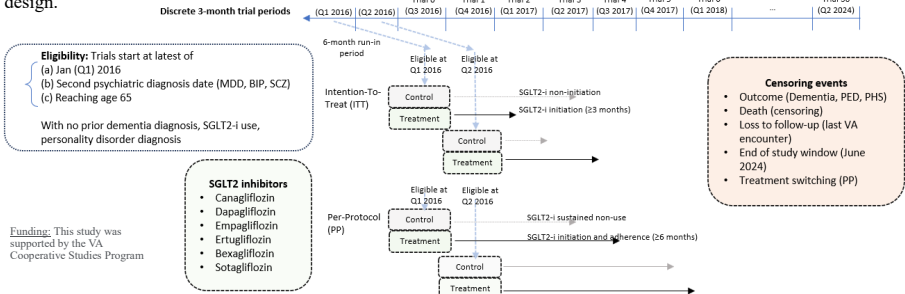


Table 1 – Cohort Characteristics at Baseline

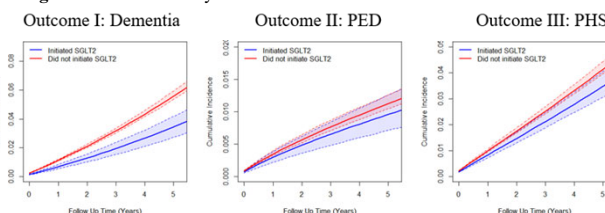
Variable	Type	Temporality	Did not use SGLT2-i (N = 105,094)	Used SGLT2-i (N = 7,631)
Sex (female), n (%)	Demographics	Static	7907 (7.5%)	273 (3.6%)
Age, median [IQR]		Dynamic	73.9 [69.4, 77.5]	74.6 [71.1, 77.2]
Race (Black), n (%)		Static	20557 (19.6%)	1422 (18.6%)
Ethn. (Hispanic), n (%)		Static	6974 (6.6%)	652 (8.5%)
Obese, n (%)	Vital	Dynamic	50204 (47.8%)	5313 (69.6%)
Hgb. A1C, median [IQR]		Dynamic	5.8 [5.6, 5.9]	6.5 [5.8, 6.9]
Tobacco use, n (%)	Lifestyle	Dynamic	33209 (31.6%)	2235 (29.3%)
Alcohol use, n (%)		Dynamic	3817 (3.6%)	139 (1.8%)
Benzo. use, n (%)	Other Drugs	Dynamic	34188 (32.5%)	3195 (41.9%)
Antidep. use, n (%)		Dynamic	83408 (79.4%)	6647 (87.1%)
DPP4-I use, n (%)		Dynamic	4230 (4.0%)	2043 (26.8%)
GLP1-a use, n (%)		Dynamic	2693 (2.6%)	2074 (27.2%)
SCZ, n (%)	Psychiatric diagnosis at baseline*	Both	5801 (5.5%)	272 (3.5%)
BIP, n (%)		Both	8089 (7.7%)	646 (8.5%)
MDD, n (%)	MDD subtype	Both	91204 (86.8%)	6713 (88.0%)
Psychotic MDD, n (%)		Both	2243 (2.1%)	169 (2.2%)
Diabetes, n (%)	Comorbidities	Dynamic	41859 (39.8%)	7038 (92.2%)
Hypertension, n (%)		Dynamic	86594 (82.4%)	7380 (96.7%)
PVD, n (%)		Dynamic	13254 (12.6%)	1662 (21.8%)
CAD, n (%)		Dynamic	47416 (45.1%)	5261 (68.9%)
KD, n (%)		Dynamic	24724 (23.5%)	3429 (44.9%)
TBI, n (%)		Dynamic	4321 (4.1%)	367 (4.8%)
PTSD, n (%)		Dynamic	43144 (41.1%)	3516 (46.1%)
Neurodege., n (%)		Dynamic	7050 (6.7%)	539 (7.1%)
Follow-up time (years), median [IQR]	Follow-up		3.0 [1.3, 5.3]	4.8 [3.2, 6.4]
All-Cause Dementia, n (%)	Outcome		4485 (4.3%)	131 (1.7%)
Death, n (%)			17387 (16.5%)	504 (6.6%)

Table 2 – Main Effects

Effect / Outcome	I: DEM	II: PED	III: PHS
ITT Treatment Coefficient (- log odds ratio) [95% CI]	-0.49 ** [-0.66, -0.31]	-0.22 ** [-0.42, -0.03]	-0.38 [-0.81, 0.04]
PP Treatment Coefficient [95% CI]	-0.61 ** [-0.92, -0.31]	-0.30* [-0.64, 0.05]	-0.58** [-1.16, 0.00]

** Indicates significance at 95%

Figure 2 – Estimated 5-year CIF curves for ITT effect



RESULTS

- Cohort:** 112,725 patients (median age 74.1; 93.6% male; median follow-up 3.3 yrs); 7,631 initiated SGLT2i and 4,616 (4.1%) developed dementia.
- DEM (Outcome I):** SGLT2i initiation significantly lowered dementia risk (ITT OR 0.61 [0.52–0.73]; PP OR 0.54 [0.40–0.73]); 1.3% absolute 5-yr risk reduction (1.6% vs. 2.9%).
- PED (Outcome II):** Significant reduction in psychiatric ED visits (ITT OR 0.80 [0.66–0.97]; PP OR 0.74 [0.53–1.05]); 0.7% absolute 5-yr risk reduction.
- PHS (Outcome III):** Non-significant trend in ITT (OR 0.68 [0.44–1.04]); significant in PP (OR 0.56 [0.31–1.00]); 0.2% absolute 5-yr risk reduction.

CONCLUSIONS AND FUTURE WORK

- In a target trial emulation using VA data, starting an SGLT2 inhibitor was linked to a significantly lower risk of dementia in people with major depression, bipolar disorder, or schizophrenia.
- The risk of psychiatric emergency visits and hospitalization rates (among adherent users) also reduced. Future studies should confirm these findings in other psychiatric populations.
- This work will be published in *JAMA Network Open* as of July 1, 2026

REFERENCES

- Wium-Andersen IK, Osler M, Jørgensen MB, Rungby J, Wium-Andersen MK. Antidiabetic medication and risk of dementia in patients with type 2 diabetes: a nested case-control study. *Eur J Endocrinol*. 2019 Nov;181(5):499-507. doi: 10.1530/EJE-19-0259.
- Liebers DT, Ebina W, Iosifescu DV. Sodium-Glucose Cotransporter-2 Inhibitors in Depression. *Harv Rev Psychiatry*. 2023 Jul-Aug 01;31(4):214-221.
- Stroup TS, Olsson M, Huang C, Wall MM, Goldberg T, Devanand DP, Gerhard T. Age-Specific Prevalence and Incidence of Dementia Diagnoses Among Older US Adults With Schizophrenia. *JAMA Psychiatry*. 2021 Jun 1;78(6):632-641.
- Hernán MA, Robins JM. Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available. *Am J Epidemiol*. 2016;183:758-764.