

Dementia risk with long-term vs. short-term selective serotonin reuptake inhibitor or selective serotonin and norepinephrine reuptake inhibitor use in patients with major depressive disorder

Lindsey Rush¹, David C Kaelber MD, PhD, MPH³, Pauline Terebuh, MD, MPH²

¹CWRU SOM University Program, ²CWRU, ³MetroHealth



Introduction/Significance

Major depressive disorder (MDD) at any age is a known risk factor for dementia with MDD in mid-life (45-64 years old) associated with the highest risk of dementia. Increased duration and frequency of depressive episodes are also associated with a higher risk of dementia.

Selective serotonin reuptake inhibitors (SSRIs) and selective serotonin and norepinephrine reuptake inhibitors (SNRIs) are the current first-line pharmacologic therapy for MDD but the evidence on their association with dementia is conflicting. This study's objective is to compare the dementia risk between long-term and short-term SSRI/SNRI treatment, as defined by the number of prescriptions, among adults with an encounter diagnosis of MDD and at least one SSRI or SNRI prescription between 2018-2020 with subsequent continuous healthcare coverage for 5 years with ≤ 45 -day gap. The short-term cohort had 1-4 SSRI or SNRI prescriptions while the long-term cohort had ≥ 10 between 2018-2020. The index event is the first healthcare encounter in 2021 of patients aged 50-70 years. Thus, the long-term and short-term cohorts differ in the number of SSRI/SNRI prescriptions in the three years prior to the index event.

Materials and Methods

We conducted a retrospective cohort study using de-identified electronic health record data from the Linked network of the TriNetX Analytics platform. Cohorts included patients with at least one International Classification of Diseases - Tenth Revision (ICD-10) encounter diagnosis of recurrent MDD and at least one SSRI or SNRI prescription between 2018-2020 with subsequent continuous healthcare coverage for 5 years with ≤ 45 -day gap. The short-term cohort had 1-4 SSRI or SNRI prescriptions while the long-term cohort had ≥ 10 between 2018-2020. The index event was the first 2021 visit and patients were required to be aged 50-70 at the index. Patients with a dementia or Alzheimer's disease (AD) ICD-10 encounter diagnosis before 2021 were excluded. There was 1:1 propensity score-matching on demographics, dementia and/or MDD risk factors, SSRI/SNRI indications, prior SSRI/SNRI prescriptions, prior psychotherapy, factors associated with MDD severity, and diagnoses associated with social determinants of health. The primary outcome was a new dementia or AD ICD-10 encounter diagnosis 1-3 years after the index event. Additional outcomes were an ICD-10 encounter diagnosis of contact dermatitis, which was used as a negative control outcome since it should not be associated with the exposure or the outcome, and subsequent SSRI or SNRI prescription in the same follow-up period after the index.

Sub-analyses were performed on different age groups, including those aged 50-60, 60-70, and 70+ at the index. Sensitivity analyses were run extending the follow-up period to 1-5 years, on adults with recurrent MDD, excluding a diagnosis of MDD, on long-term vs. short-term psychotherapy treatment, and changing the definition of number of prescriptions for long-term and short-term SSRI/SNRI treatment.

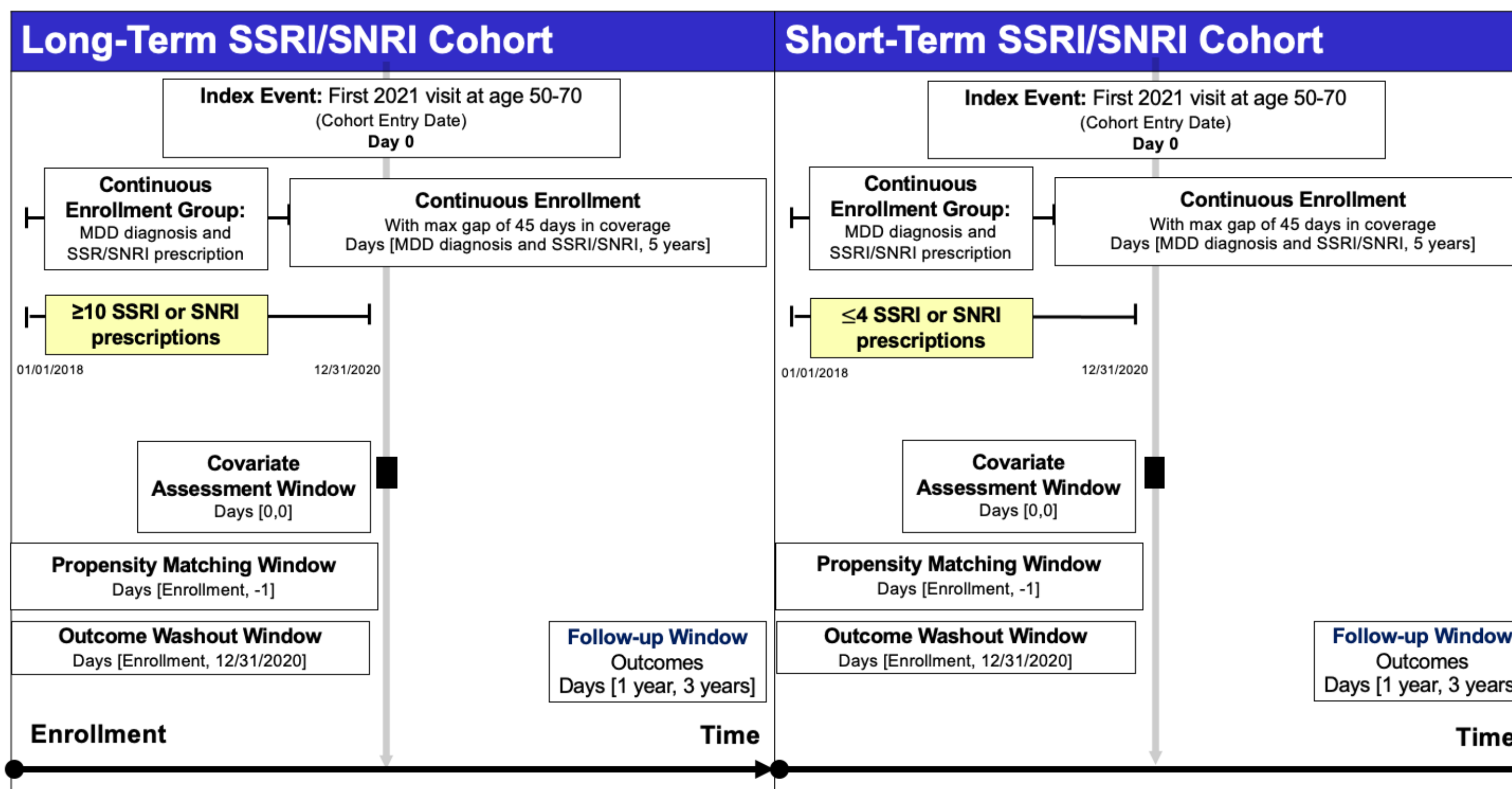


Figure 1: Visualization tool of primary study design comparing dementia risk in recurrent MDD patients receiving short-term SSRI/SNRI prescription to those receiving long-term SSRI/SNRI prescription as defined by number of prescriptions in 2018-2020

Analyses of Dementia Risk with Long-Term vs. Short-Term Antidepressant Treatment in Patients Diagnosed with MDD

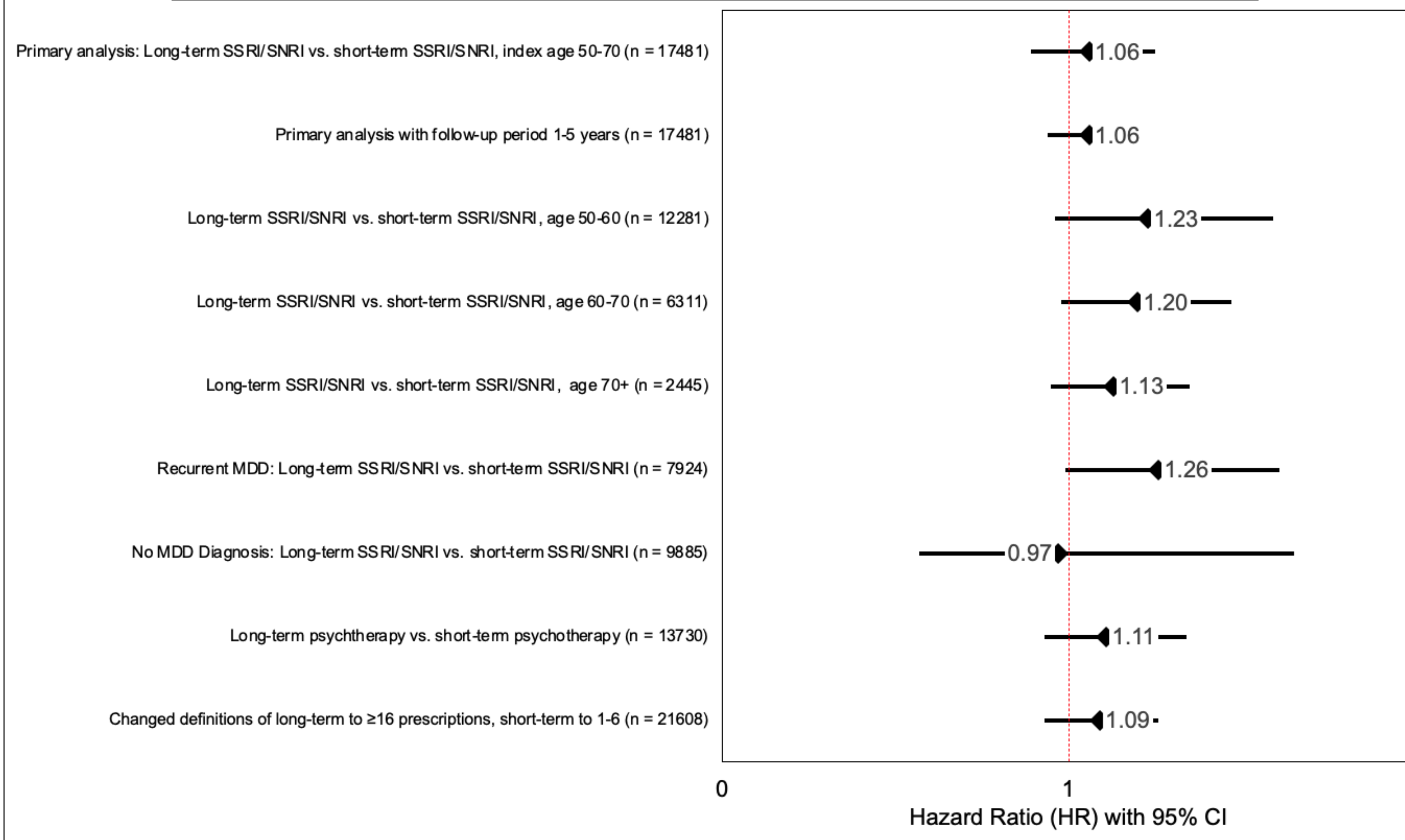


Figure 2: TriNetX analyses with hazard ratio (HR) of ICD-10 encounter diagnosis of dementia or Alzheimer's disease and 95% confidence intervals (CIs) after the index event of the first visit in 2021 in the primary analysis and other analyses

Results Summary

Compared to patients who received short-term SSRI/SNRI prescription, patients who received long-term SSRI/SNRI prescription during the previous 3 years did not have a significantly different risk in subsequent dementia/AD diagnosis in 1-3 years with an associated hazard ratio of 1.06 (95% CI: 0.89, 1.25). Similar results were seen with the negative control outcome (HR = 1.10 (0.94, 1.29)). The long-term cohort was significantly more likely to receive an SSRI or SNRI prescription (HR = 3.68 (3.58, 3.78)) and received more prescriptions on average with a mean of 15.31 (SD = 12.76) as compared to a mean of 8.70 (SD = 9.16) in the short-term cohort; this shows that prior long-term SSRI/SNRI prescription was highly associated with subsequent and ongoing SSRI/SNRI prescription and that this method of characterization of “long-term” did capture patients who had more exposure to these medications during mid-life. Similar results were seen in the sub-analyses and sensitivity analyses. There was no significant difference in dementia/AD diagnosis between the long-term and short-term cohorts in any analysis.

Conclusion

Long-term SSRI/SNRI prescription during the preceding 3 years did not have a significantly different risk of dementia in 1-3 years than short-term prescription in patients with MDD aged 50-70. A major limitation of this study is confounding bias, as patients prescribed more SSRIs/SNRIs may have more severe depression. Diagnoses associated with depression severity including anhedonia, self-harm, and suicidal ideation were controlled through propensity-scored matching in an attempt to limit this bias. Although residual confounding remains possible, patients with greater SSRI/SNRI prescription exposure did not demonstrate a higher risk of dementia than those with shorter-term exposure. This study also looked at a relatively short follow-up period. Additionally, TriNetX also does not accurately report prescription dosage and has no method to measure adherence. However, these results may show that further investigation is warranted to help inform antidepressant prescription guidelines in older adults with MDD. Further studies with longer follow-up that are able to control for MDD severity and prescription dosages and adherence may more fully discern the dementia risk associated with antidepressants.

References

- Barbieri C, Bhatt M, Vogelstein J, et al. To Be Continued? Long-Term Treatment Effects of Antidepressant Drug Classes and Individual Antidepressants on the Risk of Developing Dementia: A German Case-Control Study. *J Clin Psychiatry*. 2020;81(11):15m1200. doi:10.4088/JCP.19m12000
- Barnes AL, Yaffe K. Depression and Risk of Developing Dementia. *Nat Rev Neurosci*. 2011;12(3):233-242. doi:10.1038/nrn2935
- Eller H, Horvath-Puhle E, Gassner J, et al. Association of Early-, Middle-, and Late-Life Depression With Incident Dementia in a Danish Cohort. *JAMA Neurology*. 2022;80(9):949-958. doi:10.1001/jamaneuro.2022.0775
- Kessing LV, Fennell J, Andersen PK. Do continued antidepressants protect against dementia in patients with severe depressive disorder? *International Clinical Psychopharmacology*. 2011;26(6):316-324. doi:10.1093/icp/ich018
- Koster K, Sullivan J, Jacobs L. Analysis of the Effects of Selective Serotonin (and Norepinephrine) Reuptake Inhibitors on the Risk of Dementia in Patients with Depression. *Journal of Alzheimer's Disease*. 2019;69(2):577-585. doi:10.1007/s12072-019-0999-9
- Lee J, Kim J, Kim C, Sung H, Lee C, Han C. Antidepressant treatment and risk of dementia: a population-based, retrospective case-control study. *J Clin Psychiatry*. 2016;77(1):117-122. doi:10.4088/JCP.15m10000
- Livingston G, Huntley J, Liu KY, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *The Lancet*. 2020;396(10263):927-953. doi:10.1016/S0140-6736(20)30268-8
- Quake VR, Fry B, Terebuh P, et al. With big data comes big responsibility: Strategies for utilizing aggregated, standardized, de-identified electronic health record data for research. *Clin Transl Sci*. 2022;18(1):e70093. doi:10.1002/ctsc.12009