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Relationship Between SSRI Exposure During Later Life and Clinical and Neuropathological Correlates of Dementia

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ABSTRACT

Objectives: *While depression is a risk factor for dementia, few studies examining the association between selective serotonin reuptake inhibitors (SSRIs) and dementia risk have controlled for confounding major depression and none to our knowledge have examined neuropathological outcomes. We examined the association between continuation of SSRIs in older adults with a lifetime history of depression and progression of cognitive and functional impairment, depression, and neuropathologic correlates of dementia.* ***Design:*** *This retrospective cohort study analyzed data from the National Alzheimer's Coordinating Center.* ***Participants:*** *Participants aged 55 years or older were required to have clinician documented lifetime history of depression (n = 688). 463 (67.3%) reported continued SSRI use at every study visit prior to death.* ***Measurements:*** *Primary clinical outcomes included the Clinical Dementia Rating-Sum of Boxes (CDR-SB), Functional Activities Questionnaire (FAQ), and the 15-item Geriatric Depression Scale (GDS-15). Neuropathological outcomes included assessments of Alzheimer's Disease (AD) pathology and cerebrovascular changes relevant to Vascular dementia (VaD).* ***Results:*** *Continued SSRI use during later life was associated with a significantly slower increase on the CDR-SB compared to discontinuation of SSRIs. Rates of change on the FAQ and GDS-15 did not differ significantly between groups. While rates of AD pathology did not differ significantly between groups, continued SSRI use was associated with significantly lower rates of lacunes/infarcts on autopsy after controlling for smoking years and hypertension.* ***Conclusions:*** *Persistent use of SSRIs prior to death was associated with decreased progression of cognitive impairment and*

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a nearly 50% reduction of lacunes/infarcts on autopsy. Our study is the first of our knowledge to identify associations between SSRI exposure in later life and neuropathological changes relevant to VaD on autopsy, which is considered the gold standard of diagnosis. (Am J Geriatr Psychiatry 2026; 34:70–83)

Highlights

- **What is the primary question addressed by this study?**
  The primary question addressed by this study was to examine the association between continued SSRI use in older individuals with a history of depression and progression of cognitive and functional impairment, depression, and histologic markers of dementia obtained via brain autopsy.
- **What is the main finding of this study?**
  The main finding of this study was that persistent use of SSRIs prior to death was associated with decreased progression of cognitive impairment and a nearly 50% reduction of lacunes/infarcts on autopsy.
- **What is the meaning of the finding?**
  The significance of the finding is that our study is the first of our knowledge to identify associations between SSRI exposure in later life and cerebrovascular changes relevant to Vascular dementia on autopsy, which is considered the gold standard of diagnosis.

INTRODUCTION

Evidence from meta-analyses suggests that a history of depression is associated with an approximately twofold increase in dementia risk, including Alzheimer's Disease (AD).[1,2] One study observed a 14% increase in risk for all-cause dementia with each episode of depression in at-risk older adults.[3] Timing of depression within the life course may also influence dementia risk, with some studies suggesting higher dementia risk in early onset depression[4] and others finding higher risk in late-life depression.[5–7] Depression can also arise as an early feature of an impending dementia syndrome, often before the onset of significant cognitive decline.[8–10] Depression as a prodromal feature of dementia may open a window for early identification and/or intervention, especially given that the associated neurodegenerative changes are thought to precede clinical diagnosis.[11]

Antidepressants, including selective serotonin reuptake inhibitors (SSRIs), may improve cognition when used as a treatment for depression in mild cognitive impairment (MCI) and AD.[12–16] Long-term SSRI treatment in MCI may also decrease the rate of progression to AD by up to 3 years.[17] Conflicting with these results, a meta-analysis and several large cohort studies found that antidepressant use in older adults was associated with accelerated cognitive decline[18] and an increased risk of dementia.[19–21] However, most existing studies observing harmful effects of SSRIs did not account for differences in baseline depression severity between SSRI users and non-users, acknowledging that the observed associations could mimic the association between depression and dementia rather than an effect of antidepressants.[21] Moreover, a more precise understanding of timing and/or duration of SSRI use may clarify the role of SSRI use before and after dementia onset, with possible implications for clinical management.

Beyond clinical outcomes, the relationship between depression and serum or neuroimaging biomarkers of dementia, as well as the effect of antidepressant use on these biomarkers, requires further study.[22] One meta-analysis found that out of 31 animal studies, all but one demonstrated that antidepressant exposure was associated with decreased microglial activation.[23] Chronic increases in microglial activation has been implicated in the pathogenesis of AD,[24] Frontotemporal Lobar Dementia,[25] and Parkinson's.[26] In humans, associations between antidepressant use and decreased aggregation of AD biomarkers (i.e., amyloid-β in cerebrospinal fluid (CSF) and positron

emission tomography) have been observed in cognitively normal older adults,[27,28] while other studies have found no association.[29]

In addition to AD pathology, depression in late life may be precipitated and/or perpetuated by cerebrovascular disease,[30] which may independently impact AD progression.[31] Existing research on the relationship between antidepressant use and cerebrovascular markers of dementia relevant to Vascular dementia (VaD) during later life have also produced contrasting results, with some studies even demonstrating increased burden of white matter hyperintensities on MRI in antidepressant users.[32,33] However, those studies are confounded by combining SSRI and tricyclic antidepressant users into one group (the latter of which is associated with high anticholinergic burden) and using current mood symptoms, rather than lifetime diagnosis, as a proxy for depression.

The relationship between SSRI use in older adults and histologic markers of dementia at autopsy ("neuropathological correlates of dementia") has yet to be studied. Given that current clinical AD diagnostic methods are subject to significant variability between clinicians, with sensitivity estimates ranging between 41% and 100%, examination of tissue samples obtained via autopsy is considered the gold standard method of diagnosis for AD and VaD.[34-36] Thus, associations between SSRI use and histologic markers of AD and VaD obtained via autopsy would provide more definitive evidence regarding the relationship between SSRI use and pathologic processes underlying dementia.

Using the rich clinical and neuropathological data of the National Alzheimer's Coordinating Center (NACC), the primary aims of this study were to: 1) examine the association between continuation of SSRIs and progression of cognitive and functional impairment and depression in older individuals with a lifetime history of depression, and 2) evaluate the relationship between continuation of SSRIs and neuropathologic correlates of dementia in these individuals. We hypothesized that continued SSRI use during later life would be associated with decreased progression of cognitive and functional impairment and depression symptoms compared to discontinuation of SSRIs. We also hypothesized that continuation of SSRIs would be associated with decreased neuropathological evidence of AD and VaD.

METHODS

Participants

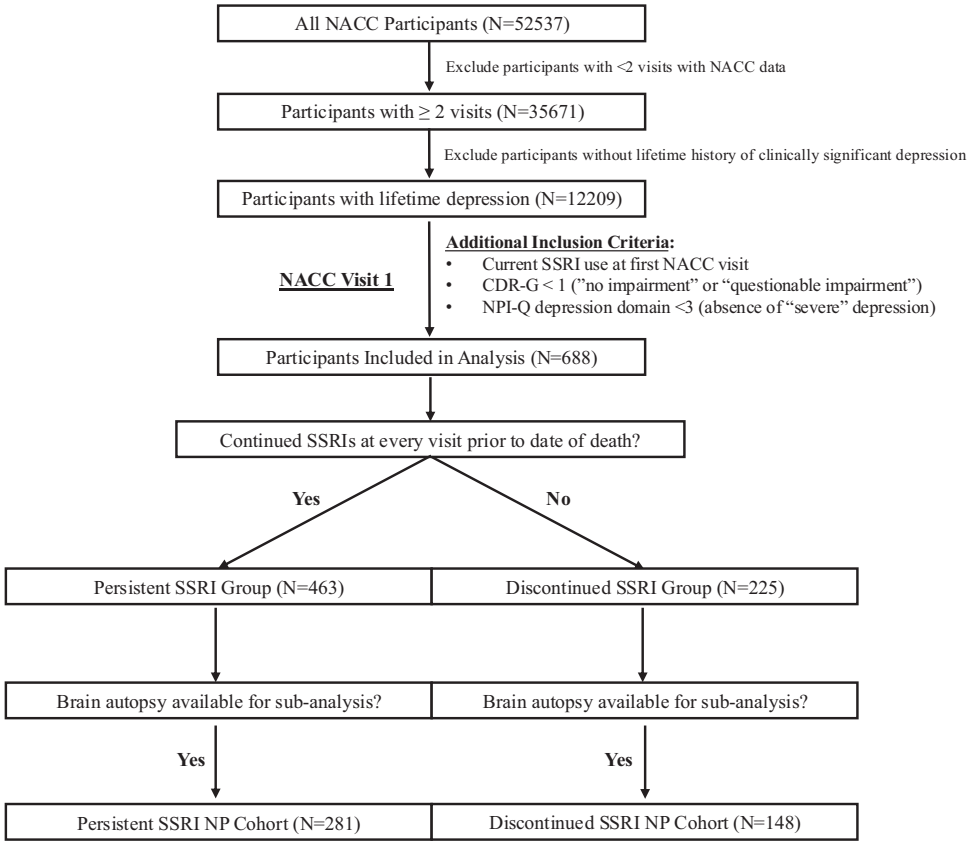
This retrospective longitudinal cohort study analyzed clinical and neuropathological data from the National Alzheimer's Coordinating Center (NACC) Uniform Data Set (UDS).[37] Data were collected between September 2005 and June 2024 from 36 NIA-funded Alzheimer's Disease Research Centers (ADRCs) at academic medical centers throughout the United States. ADRCs obtained data and samples after securing written informed consent from participants or authorized proxies, under the oversight of local institutional review boards, before submitting data to the NACC.

Inclusion Criteria

Inclusion criteria for this analysis are presented in Fig. 1. We aimed to control for the known impact of depression on cognitive and neuropathological outcomes by evaluating two groups with approximately comparable burden of major depression, severe enough to require SSRIs, at baseline assessment. Thus, inclusion criteria at the initial NACC visit were as follows: 1) current use of citalopram, escitalopram, fluoxetine, paroxetine, or sertraline, 2) clinician-documented history of depression, and 3) Neuropsychiatric Inventory Questionnaire (NPI-Q) depression domain score <3 (absence of "severe" depression by caregiver rating) at the initial NACC visit. A history of depression was recorded as a participant- or caregiver-report positive response to one or both of the following prompts: 1) "Active depression in the last 2 years" and 2) "Depression episodes more than 2 years ago." NACC clinicians or ADRC staff were instructed to confirm with the participants that positive responses were based on a diagnosis and/or treatment by a physician. Patients were excluded if they had "severe" depression at the initial NACC visit to further limit the risk of confounding bias by initial depression symptomatology, as patients with uncontrolled, severe depression at study initiation may be more likely to discontinue SSRIs shortly thereafter. Data on fluvoxamine use was not systematically collected.

After restricting to a cohort with approximately comparable burden of major depression at the first

FIGURE 1. Inclusion criteria for participants (*n* = 688) included in this analysis. SSRI use included use of citalopram, escitalopram, fluoxetine, paroxetine, and sertraline. NACC: National Alzheimer's Coordinating Center; SSRI: selective serotonin reuptake inhibitor; CDR-G: Clinical Dementia Rating-Global; NP: neuropathological; NPI-Q: Neuropsychiatric Inventory Questionnaire.



NACC visit, participants were then divided into two groups based on whether they continued SSRIs at every NACC visit prior to the date of death ("Persistent SSRI Group") or discontinued SSRIs at any time prior to the date of death ("Discontinued SSRI Group"). Individuals who discontinued SSRIs and then restarted SSRIs were excluded. To maximize power, group designations were made irrespective of number of SSRIs being used or concurrent use of other antidepressant classes (i.e., selective norepinephrine reuptake inhibitors, atypical antidepressants).

Additional inclusion criteria at the initial NACC visit included age ≥55 years old and Clinical Dementia Rating-Global (CDR-G) score <1. The age cutoff of 55 years or older at the initial clinical visit was chosen to maximize statistical power and ensure inclusion of older individuals who may be in the preclinical stage of their dementia prior to the onset of clinical decline (clinical dementia incidence has been shown to sharply increase at 60 years old).[38] Finally, participants were required to be known to be deceased during the study period (irrespective of whether they consented for brain autopsy evaluation) to allow for more complete characterization of their pattern of SSRI use during later life.

Clinical and Neuropathological Outcome Variables

Clinical variables were collected by trained clinicians and clinical personnel using a standardized protocol for all participants enrolled in ADRCs.[39] The

CDR Sum of Boxes (CDR-SB) is an ordinal measure of cognition and function obtained by patient and caregiver interview, examining six domains of functioning − memory, orientation, judgement/problem-solving, community affairs, home/hobbies, and personal care − that are summed to equal an 18-point total score.[40] It is useful for tracking changes within and between stages of dementia severity and provides more information than the CDR-G score in the early stages of dementia. NACC clinicians completed the CDR-SB form based on participant and/or caregiver report and behavioral and neurological exam of the subject. Total score on the Functional Activities Questionnaire (FAQ) was used to further assess functional impairment, which was completed by NACC clinicians per participant and/or caregiver interview and intended to measure activities of daily living (ADLs) in older adults.[41] Depression severity was operationalized by the 15-item Geriatric Depression Scale (GDS-15), a well-validated screening measure for depression in older adults, completed by NACC clinicians as a direct participant interview.[42] A recent meta-analysis found the pooled sensitivity and specificity of the GDS-15 to be 80% and 79%, respectively, for indicating clinically significant depression (with a cutoff score of ≥5 in most studies).[43] The GDS-15 was included to assess the association between continuation of SSRI and depression symptomatology, clarifying the mechanism by which SSRI use might be associated with cognition and functioning.

Although neuropathological data was not required for inclusion in analysis of clinical outcome variables (Aim 1), a subset of individuals within the NACC cohort consented for postmortem brain evaluation and had available neuropathological data on outcomes of interest, which was collected using a standardized neuropathological evaluation across ADRCs. To quantify AD pathology, the National Institute on Aging and Alzheimer's Association Neuropathologic Change score (ABC score) was used, a composite of three components of AD pathology: amyloid-β deposits ("A" for Amyloid), neurofibrillary degeneration ("B" for Braak stage), and neuritic plaques ("C" for CERAD rating of plaque distribution).[44] The ABC score and other AD measures from the NACC neuropathologic dataset demonstrate good agreement across centers (average weighted κ =0.88).[45] To quantify cerebrovascular changes relevant to VaD, two dichotomous NACC variables were used assessing for: 1) the presence of infarcts and lacunes and 2) the presence of hemorrhages and microbleeds. These variables were chosen given that they represent defining pathological features of VaD.[46,47]

Analyses

To assess differences in demographic characteristics between the Persistent SSRI Group and Discontinued SSRI Group, chi-squared tests and two-sample t-tests were used for categorical (i.e., sex) and continuous (i.e., age at initial NACC visit) variables, respectively. Demographic characteristics between participants with and without neuropathological data were also compared using the tests outlined above.

To assess the association between continuation of SSRIs and progression of cognitive impairment, a linear mixed-effects model was estimated using the *lmerTest* package in RStudio with CDR-SB total score as the dependent variable, time since initial NACC visit as the independent variable, and individual specific random effects. Age,[48] education,[49] CDR-G at initial visit (baseline cognition), and number of Apolipoprotein E-ε4 (APOE-ε4) alleles[50] were included as covariates given their associations with trajectories of cognitive decline in later life (i.e., APOE-ε4 homozygotes have a faster memory decline between ages 43-69 compared to noncarriers).[50] The fitted model was used to estimate mean differences in CDR-SB between groups (Persistent SSRI Group versus Discontinued SSRI Group). An interaction term was included to determine the interactions between visit time and group and its relationship with the CDR-SB total score, to evaluate between-group differences in the rate of change on the CDR-SB over the study period. Additional linear mixed-effects models were repeated for the FAQ and GDS-15 as dependent variables, as well as for exploratory subgroup analyses (i.e., based on CDR-G at initial visit or number of NACC visits with a cutoff of >4 visits), with predominantly the same independent variables, covariates and interaction terms as above. Participants with missing values for the dependent variable at a given visit were excluded from that specific observation but could contribute data from other visits. Participants with missing data on relevant covariates were excluded.

To identify associations between continuation of SSRIs and neuropathological correlates of dementia

(AD, VaD), we applied propensity score matching using the *MatchIt* package in RStudio. Propensity score matching was applied to create balanced comparison groups, reducing selection bias and accounting for inherent differences between groups that might impact the outcome variables, thereby strengthening the validity of our findings. Participants were matched based on their CDR-G score at initial visit, age of death, sex, and years of education. A nearest-neighbor matching algorithm with a 2:1 ratio and caliper adjustment were used to ensure balance between groups. Standardized mean differences were assessed to confirm adequate matching between groups. Following propensity score matching, we applied linear regression models for continuous outcomes (hippocampal atrophy, ABC Score) and logistic regression models for binary outcomes (presence of lacunes/infarcts, presence of hemorrhages/microbleeds) adjusting for the covariates listed above. One model was fit per outcome.

All analyses were restricted to participants with available data for the relevant outcome. The threshold for statistical significance was $a = 0.05$ and the tests were 2-tailed. To correct for multiple hypothesis testing, we applied the Benjamini−Hochberg procedure to control the false discovery rate at 5% (FDR = 0.05) for non-subgroup analyses.[51] Analyses were performed using R, version 4.4.1 (2024-06-14),[52] and RStudio version 2023.12.0.[53]

RESULTS

Demographics

Demographic characteristics for all participants are presented in Table 1. Of the 688 participants who met criteria for inclusion in this analysis, 85.2% had "no" or "mild" depression per caregiver rating at study onset. Years (mean ± SD) of participant study follow-up time was 6.6 ± 3.4. In addition, 463 (67.3 %) endorsed current SSRI use at every NACC visit prior to death ("Persistent SSRI group"), while 225 discontinued SSRIs prior to death ("Discontinued SSRI group"). No differences were observed between groups in age at initial NACC visit, years of education, proportion of white participants, proportion of male participants, number of APOE-ε4 alleles, or

TABLE 1. Demographic Characteristics for Participants (n = 688) Included in This Analysis

	Persistent SSRI Group (n = 463)	Discontinued SSRI Group (n = 225)	t-Value (df) or X^2 (df)	p-Value
Initial visit age (Mean ± SD, years)	73.5 ± 8.5	73.6 ± 8.6	−0.03 (438)	0.97
Education (Mean ± SD, years)	15.3 ± 3.0	15.3 ± 3.1	0.17 (437)	0.87
Sex				
Females, N (%)	249 (53.8)	124 (55.1)	0.11 (1)	0.74
Race				
White, N (%)	436 (94.2)	209 (92.9)	0.42 (1)	0.52
Black or African American, N (%)	22 (4.8)	8 (3.6)		
Asian, N (%)	1 (0.2)	3 (1.3)		
Other, N (%)	4 (0.9)	5 (2.2)		
Number of APOE-ε4 alleles				
0 Alleles, N (%)	220 (47.5)	118 (52.4)	1.57 (2)	0.46
1 Allele, N (%)	164 (35.4)	70 (31.1)		
2 Alleles, N (%)	39 (8.4)	19 (8.4)		
NPI-Q depression severity at baseline				
None, N (%)	265 (57.2)	114 (50.7)	3.01 (2)	0.22
Mild, N (%)	135 (29.2)	72 (32.0)		
Moderate, N (%)	63 (13.6)	39 (17.3)		
Type of SSRI				
Citalopram, N (%)	121 (26.2)	38 (17.0)	-	
Escitalopram, N (%)	110 (23.8)	71 (31.7)	-	
Fluoxetine, N (%)	63 (13.6)	35 (15.6)	-	
Paroxetine, N (%)	32 (6.9)	26 (11.6)	-	
Sertraline, N (%)	136 (29.4)	54 (24.1)	-	

The persistent SSRI group comprised individuals who continued SSRIs at every visit prior to death. Chi-squared and two-sample T-tests were used for categorical (i.e., sex) and continuous (i.e., age at initial NACC visit) variables, respectively, to assess between-group differences. APOE-ε4: apolipoprotein E-ε4; NPI-Q: neuropsychiatric inventory-questionnaire; SSRI: selective serotonin reuptake inhibitor.

depression severity. 429 (62.4%) participants had neuropathological data on at least one outcome of interest. Demographic characteristics of eligible participants with and without neuropathological data are presented in Supplemental Table 1, with differences observed between groups in age at initial NACC visit, years of education, proportion of male participants, and proportion of white participants.

SSRI Exposure and Progression of Impairments in Cognition, Functioning, and Depression

Linear mixed-effects models adjusted for age, CDR-G score at initial visit, years of education, and number of APOE-ε4 alleles were estimated to examine the relationship between continuation/discontinuation of SSRIs and progression of cognition, functioning, and depression, see Table 2 and Figure 2. The Discontinued SSRI group had a significantly greater increase on the CDR-SB per year compared to the Persistent SSRI group (β [95% CI] = 0.14 [0.06-0.23], adjusted p = 0.007, Hedges's g effect size = 0.28), although the rate of increase on the FAQ per year did not differ significantly between groups. Change in GDS-15 total score per year, adjusted for the same covariates above except CDR-G score at initial visit, did not differ significantly between groups.

Sensitivity analyses with linear mixed effects models for participants with CDR-G scores of 0 (n = 140, "no impairment") and 0.5 (n = 548, "questionable impairment") at the initial NACC visit were conducted for all outcomes, see Supplemental Table 2. In addition, to maximize the amount of follow-up time available, an additional sensitivity analysis was conducted requiring participants to have available data from > 4 NACC visits (n = 297), for which the linear-mixed effects model results for all outcomes are presented in Supplemental Table 3.

SSRI Exposure and Alzheimer's Disease or Vascular Dementia Neuropathology

For participants with available neuropathological data (n = 429), propensity score matching was applied to create balanced Persistent SSRI and Discontinued SSRI groups by age at death, CDR-G score at initial visit, education, and sex. Linear and logistic regressions were estimated postmatching to assess for associations with neuropathological outcomes (Table 3). While rates of AD pathology (ABC Score) as well as severity of hippocampal atrophy did not differ significantly between groups, patients who continued SSRIs prior to death had significantly lower rates of lacunes/infarcts on autopsy. This finding was not significant after correcting for multiple comparisons. Presence of hemorrhages and microbleeds on autopsy did not differ between groups.

Additional posthoc linear regressions were estimated for A Score, B Score, and C score, to decipher whether associations between SSRI exposure may be restricted to one component of AD pathology. No differences were observed between groups in any of these scores. To minimize confounding by baseline risk factors relevant to cerebrovascular disease, comparisons of rates of lacunes/infarcts on autopsy between groups were repeated after matching for smoking years and hypertension at the last study visit prior to death. In this adjusted logistic regression, the

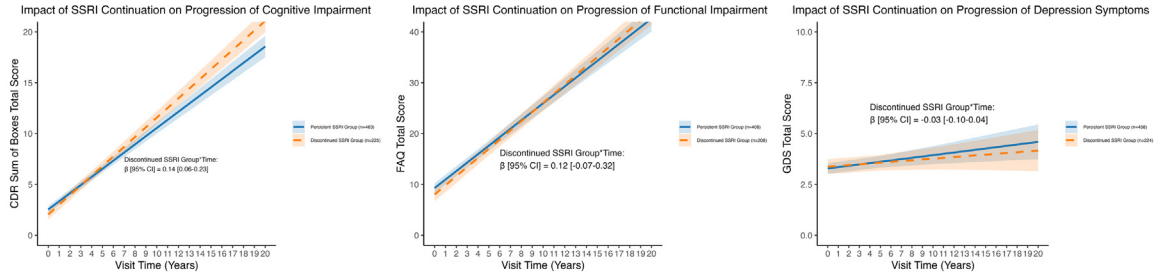
TABLE 2. Linear Mixed-Effects Models Examining the Interaction Between Visit Time and Group on Progression of Cognition, Functioning, and Depression

	Variable	β [95% CI]	t-Value, Degrees of Freedom	p-Value, q-Value
Progression of cognitive Impairment (Clinical Dementia Rating-Sum of Boxes)	Group (Discontinued SSRI group)	−0.30 [−0.85-0.25]	−1.08, 893.5	0.28
	Visit time*group	0.14 [0.06-0.23]	3.40, 2,802.5	0.0007, 0.007[a]
Progression of functional impairment (Functional Activities Questionnaire)	Group (Discontinued SSRI group)	−0.77 [−2.23-0.69]	−1.03, 706.5	0.30
	Visit time*group	0.12 [−0.07-0.32]	1.25, 1,785.7	0.21, 0.28
Progression of depression symptoms (Geriatric Depression Scale-15)	Group (Discontinued SSRI group)	0.061 [−0.41-0.53]	0.26, 734.5	0.80
	Visit time*group	−0.033 [−0.10-0.04]	−0.91, 2,105.8	0.36, 0.44

Models adjusted for age at NACC visit, education, number of APOE-ε4 Alleles, and Clinical Dementia Rating-Global (CDR-G) score at baseline (for cognition and functioning only). The Persistent SSRI group was used as the reference group. Satterthwaite's method was used to estimate degrees of freedom and p-values. P-values represent the probability of observing the data under the null hypothesis, while Q-values are Benjamini-Hochberg (BH) adjusted P-values that control for the false discovery rate across multiple comparisons for the primary outcomes.

[a] $p < 0.05$ after adjustment. SSRI: selective serotonin reuptake inhibitor.

FIGURE 2. Linear mixed-effects model examining the impact of group (Persistent SSRI Group versus Discontinued SSRI Group) on progression of (A) cognition, (B) functioning, and (C) depression over time. CDR: Clinical Dementia Rating; SSRI: selective serotonin reuptake inhibitor; FAQ: Functional Activities Questionnaire; GDS: Geriatric Depression Scale.



Persistent SSRI group had significantly lower rates of lacunes/infarcts after adjusting for multiple comparisons (β [95% CI] = 0.97 [0.28−1.66], adjusted p = 0.03).

DISCUSSION

We report that continued SSRI use prior to death in older adults with a lifetime history of depression is associated with a small but statistically significant decrease in progression of cognitive impairment compared to discontinuation of SSRIs. Moreover, individuals with persistent SSRI use had significantly fewer cerebrovascular findings relevant to VaD on autopsy after adjustment for hypertension and smoking years, with a nearly 50% reduction of lacunes or infarcts. While causality cannot be inferred in this observational study, our findings suggest that persistent SSRI use in later life is not associated with an increased risk of dementia progression, in contrast to recent literature not controlling for baseline depression

TABLE 3. Propensity Score Matching Was Used to Compare Neuropathology Relevant to Alzheimer's Disease and Vascular Dementia Between the Persistent SSRI Group (n = 169-281) and the Discontinued SSRI Group (n = 109-148).

	Neuropathological Outcome	Persistent SSRI Group	Discontinued SSRI Group	Propensity-Matched Groups (β [95% CI])	Propensity Matched Groups (p-Value, q-Value)
Alzheimer's disease pathology	ABC score (N, mean ± SD)	181, 2.00 ± 1.09	113, 2.02 ± 1.09	0.04 [−0.21-0.29]	0.75, 0.75
	Hippocampal atrophy (N, mean ± SD)	169, 1.28 ± 1.03	109, 1.49 ± 1.11	0.22, [−0.03-0.47]	0.09, 0.17
	A score (N, mean ± SD)	181, 3.38 ± 1.81	114, 3.40 ± 1.83	0.06 [−0.36-0.48]	0.79, 0.79
	B score (N, mean ± SD)	280, 3.80 ± 2.02	147, 4.04 ± 1.99	0.22 [−0.18-0.62]	0.28, 0.31
	C score (N, mean ± SD)	281, 1.82 ± 1.25	148, 1.89 ± 1.22	0.10 [−0.15-0.34]	0.44, 0.44
Vascular dementia neuropathology	Lacunes/Infarcts (N, % of sample)	36, 13.0%	33, 22.6%	a) 0.59 [0.05-1.12] **(not matched for vascular risk factors)** b) 0.97 [0.28-1.66] **(matched for vascular risk factors)**	a) 0.03, 0.06 **(not matched for vascular risk factors)** b) 0.006, 0.03* **(matched for vascular risk factors)**
	Hemorrhages/Microbleeds (N, % of sample)	17, 6.3%	7, 4.9%	−0.71 [−2.34-0.93]	0.40, 0.44

Groups were matched by age at death, Clinical Dementia Rating-Global score at the initial NACC visit, years of education, and sex. Linear and logistic regressions were conducted postmatching for continuous and dichotomous variables, respectively. The Persistent SSRI group was used as the reference group. P-values represent the probability of observing the data under the null hypothesis, while Q-values are Benjamini-Hochberg (BH) adjusted P-values that control for the false discovery rate across multiple comparisons.

* $p < 0.05$ after adjustment. Vascular risk factors included hypertension and years of smoking at the last visit prior to death. SSRI: selective serotonin reuptake inhibitor.

severity, and may even be associated with improved cognitive outcomes.

SSRI Use and Dementia Progression (Aim 1)

These data refute recent studies reporting harmful effects of SSRI use on risk of clinical dementia progression, which did not adequately control for key factors such as depression presence and severity.[18,54] For example, Mo et al.[18] reported that SSRI use was associated with more rapid cognitive decline in individuals with dementia, although the authors did not account for baseline depression severity and found that the effect was driven largely by individuals with severe dementia. Our analysis required all participants to have a lifetime history of depression and excluded participants with severe depression at the initial NACC visit, in efforts to isolate the association between continuation of SSRIs and outcome variables independent of its association with baseline depression symptomatology (and thus, risk of dementia). We also controlled for other variables known to impact dementia risk such as age at initial visit, years of education, and number of APOE-ε4 high risk alleles.

To interpret the clinical significance of our findings, we examined a retrospective NACC analysis by Andrews et al.[55] who found that a 1-point difference on the CDR-SB represented the threshold for a clinically meaningful decline. By this metric, the observed difference in rate of progression between groups in our analysis (0.14 point difference on the CDR-SB per year per β estimate) would reach clinical significance after approximately 7 years. Given the frequency by which clinicians treat older adults with depression and the extended length of time that some patients remain on SSRIs,[9,56,57] this difference holds clinical relevance when aggregated over time (and approaches a clinically significant difference during the study period itself, with mean participant study follow-up of 6.6 years). In addition, it is worth noting that the observed Hedges's g effect size of change in CDR-SB per year (effect size = 0.28) is larger than that observed in a recent meta-analysis comparing changes in CDR-SB at 18 months between individuals with AD receiving anti-amyloid-β monoclonal antibodies and placebo (effect size = 0.06).[58]

Alternative hypotheses explaining the association between continuation of SSRIs and progression of cognitive impairment must also be considered, such as that participants may have discontinued SSRIs due to lack of efficacy, prompting switch to another antidepressant agent in the setting of relapsed depression. However, lack of differences between groups in progression of depression symptoms over the study period decreases this likelihood, suggesting that the association between SSRI exposure and cognitive decline is less likely to be explained by impacts of SSRI treatment on depression symptomatology. In addition, given that depression is both a risk factor and potential prodrome of dementia, it is possible that dementia may have been misclassified as depression in some portion of individuals in the Discontinued SSRI group, prompting initiation of SSRIs prior to the study period and discontinuation once the dementia diagnosis was clearer. Similarly, participants may have experienced worsening cognitive function *prior* to SSRI discontinuation, prompting subsequent discontinuation of SSRI use by clinicians in efforts to avoid polypharmacy.[59] Finally, it is possible that individuals in the Discontinued SSRI group had "vascular depression", which is known to impact cognition and is more likely to be resistant to SSRI treatment.[60]

SSRI Use and Neuropathological Changes (Aim 2)

In addition to associations between continuation of SSRIs and clinical outcomes of dementia, we also observed an association with cerebrovascular changes relevant to VaD on autopsy after controlling for relevant vascular risk factors including hypertension and years of smoking, in contrast to existing research suggesting a relationship between SSRI use and increased white matter hyperintensities on MRI.[32,33] The observed association between persistent SSRI use and lacunes/infarcts may be mediated by decreased expression of neuroinflammatory markers and/or enhanced negative feedback of the HPA axis.[11,61,62] One meta-analysis of 22 studies concluded that SSRI use contributed to a reduction in IL-1β expression in depressed patients.[63] Escitalopram[64,65] and sertraline[64] are among the SSRIs associated with the largest reduction in inflammatory cytokine release, which were among the most frequently used SSRIs in the Persistent SSRI Group.

Much of the effect of SSRI use on cerebrovascular disease burden has been postulated to stem from its impact on depression symptomatology, which is

associated with chronic endothelial and HPA axis dysfunction.[66,67] However, in this cohort, we found a significant association between continuation of SSRIs and cerebrovascular disease neuropathology relevant to VaD without observing an association between continuation of SSRIs and depression severity. It is possible that differences in prevalence of lacunes/infarcts observed on autopsy between groups may be confounded by baseline differences in risk factors for atherosclerotic burden. However, the association between continuation of SSRIs and prevalence of lacunes/infarcts was significant after matching groups for prevalence of hypertension and years of smoking recorded at the last visit prior to death, which are both independent risk factors for VaD.[68,69]

In contrast to existing literature suggesting an increased bleeding risk with SSRI use,[70] we did not find a difference between groups in the prevalence of hemorrhages and microbleeds on autopsy. We did not control for comorbid use of antiplatelets and anticoagulants, which could confound associations.[71] Other characteristics that could not be controlled for include the location of hemorrhage or microbleed, with some evidence suggesting differential impact of SSRI use on risk of intracranial versus subarachnoid hemorrhage.[72] Given the low prevalence of hemorrhages and microbleeds in our sample (6.1%), larger sample sizes are needed in future studies.

We also did not find an association between continuation of SSRIs and rates of AD pathology, including amyloid-β deposits, neurofibrillary tangles, and neuritic plaques. While this may reflect no effect, an association may have been missed due to small sample sizes, inadequate difference in estimated duration of SSRI use between groups, or an association between SSRIs and cognitive function mediated through non-AD related mechanisms. In addition, given that neurodegenerative changes in AD pathology precede clinical diagnosis, it is possible that SSRI use may be associated with a decreased rate of transition from neuropathological change to clinical decline rather than with the development of AD neuropathology itself. Our findings support those observed by Brendel et al.[73] in a population of AD patients with depressive symptoms demonstrating that SSRI use was not associated with PET amyloid burden but was associated with improvements in cognition.

LIMITATIONS

The observational nature of this analysis prevents ascertainment of causality between continuation/discontinuation of SSRI use and clinical and neuropathological outcomes. The NACC database does not include information on history of SSRI use prior to the study period; thus, the number of years of SSRI use prior to study initiation could not be assessed. We did not include a control group, such as individuals with a lifetime history of depression not on SSRIs at the study onset, due to inherent baseline differences in depression severity, dementia risk, and other psychiatric comorbidities between SSRI users and non-users in the NACC cohort that would increase the risk of confounding bias.[54] Duration of SSRI use as a continuous variable (i.e., number of years) could not be reliably assessed to determine a dose-response relationship between SSRI use and clinical and neuropathological outcomes due to large variations in study enrollment time between participants. Use of other antidepressants such as SNRIs or atypical antidepressants were not controlled for in order to maximize statistical power, and reasons for SSRI discontinuation were not available. Similarly, dosage information on SSRI use was not reported, limiting understanding of potential dosage effects. Sample sizes were smaller with respect to neuropathological outcomes, limiting statistical power. Finally, the high number of white, highly educated individuals, particularly in the neuropathological data cohort, limits the generalizability of these findings.

CONCLUSIONS AND FUTURE DIRECTIONS

Existing research has produced mixed results with regards to the association between SSRI use and risk of dementia onset and progression in older adults, largely due to inadequate control of depression severity between SSRI users and non-users. In our study of older adults with depression that was predominantly mild or below in severity at baseline assessment, we observed significant associations between continuation of SSRIs and decreased (1) progression of cognitive impairment and (2) prevalence of lacunes/infarcts on autopsy. Our study is the first of our knowledge to identify associations between SSRI

exposure in later life and cerebrovascular changes relevant to VaD (i.e., lacunes/infarcts) on autopsy, which is the gold standard of diagnosis. Our findings may aid clinicians treating older adults with a lifetime history of depression and worsening clinical decline, prompting reconsideration of the risk-benefit profile of these medications. More specifically, our findings are highly relevant given the frequency by which clinicians treat patients with cognitive decline and depression in later life, suggesting that SSRIs can be safely prescribed by clinicians without increasing the risk of dementia progression and may even be associated with measurable improvements in cognition over extended periods of time. Future well-designed studies (i.e., randomized-controlled trials) are needed to replicate the observed association between SSRI use and neuropathological markers relevant to VaD.

AUTHOR CONTRIBUTIONS

JSS, MB, and MP contributed to the conception, design, and data analysis of the study. All authors were involved in interpretation of the data. All authors were involved in drafting and revising the manuscript and approved the final version for submission.

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DATA STATEMENT

The data has not been previously presented orally or by poster at scientific meetings.

CONSENT STATEMENT

All Alzheimer's Disease Research Centers obtained written informed consent from their participants and were approved by their local institutional review board before submitting data to the NACC.

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SUPPLEMENTARY MATERIALS

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