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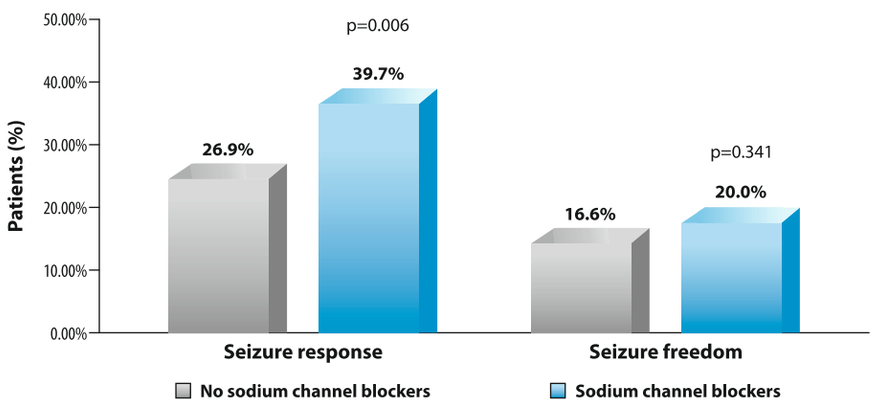

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JAMA Neurology

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VIEWPOINT

Advancing the Neuropalliative Care Approach—A Call to Action

Robert G. Holloway, MD, MPH
Department of Neurology, University of Rochester School of Medicine and Dentistry, Rochester, New York.

Neha M. Kramer, MD
Department of Internal Medicine, Rush University Medical Center, Chicago, Illinois; and Department of Neurological Sciences, Rush University Medical Center, Chicago, Illinois.

Neuropalliative care has become mainstream with more neurologists entering the field, a new specialty society to promote its growth, clinical guidelines and curricula to standardize education, condition-specific triggers to guide referrals, and a growing number of reviews to apply its principles to specific neurological diseases.[1] While we need the continued growth of neuropalliative care as a specialty, we more urgently need a widespread adoption of the neuropalliative care approach, given the enormity of unmet neuropalliative care needs across populations. Compassionate health care systems of the future will provide the leadership to innovate and organize themselves to best support these needs, which are expected to increase in the years ahead. Here we provide an overview of this challenge and the rationale to reimagine our approach and propose a coordinated call to action to address one of the greatest quality-of-care challenges and opportunities of our time.

A Silent Endemic of Unmet Patient and Family Care Needs

A growing body of research shows the basic medical care needs of patients and families with neurological disease are not being met. In the short- and long-term care settings and across multiple countries, we are often falling short in terms of coordinated communication about prognosis, guidance with advance care planning, attention to nonmotor symptoms, emotional support to manage psychological distress, spiritual support for existential pain, and social support to alleviate high caregiver burden.[2] Much of this research is from the direct reports of the patients and families themselves.

Viewed with a person-centered quality lens, this underuse of medical services (eg, consistent communication; effective goals of care discussions; and psychological, spiritual, and social services) leaves populations and patients in any setting vulnerable to unrelieved symptoms and avoidable suffering. In addition, there is evidence of overuse of aggressive care for dying patients leading to possible physical, psychological, and financial harm to both patients and health care systems, including high rates of hospital and facility deaths. As the prevalence of neurological disease continues to rise, so too will the global, serious health-related suffering of patients and families before they die, possibly doubling by the year 2060.[3] The neuropalliative care approach is well suited to address both domains of quality (underuse and overuse) and better align our efforts with the needs of patients and their families.[4]

The Neuropalliative Care Approach to Narrow the Quality Gap

The neuropalliative care approach applies palliative care principles to improve the lives of all persons living with neurologic illness. It is a person- and family-centered approach that provides expert management of the physical, functional, psychological, and spiritual aspects of neurological illness. The approach also optimizes communication from diagnosis to death, aligns treatments with a patient's goals, and helps patients and families plan for the future. Studies demonstrate that palliative care improves symptom control, reduces costs, and, in some cases, increases survival.[5] Consequently, integrating the neuropalliative care approach into health systems is an ethical and economic imperative we cannot ignore.

Only a minority of patients who need palliative care receive it. There are not enough specialty palliative health care professionals and even fewer specialized neuropalliative health care professionals. The neuropalliative care approach addresses this workforce gap by prioritizing primary neuropalliative care—that is, the integration of palliative care skills into routine clinical practice and involvement of all members of the health care team to provide psychological, social, and spiritual support. While interdisciplinary clinics exist in neurology, they often occur within disease-specific silos and focus on patients with advanced disease. We can do better than this. Prior studies have shown that patients with different neurological conditions experience similar unmet needs, emphasizing the universal nature of suffering with threats to personhood.[6] The implications of this are simple. When planning for clinical services, similar approaches to psychosocial-spiritual support can apply across neurological conditions.

A Call to Action to Scale the Neuropalliative Care Approach

To narrow the quality gap, a continued culture shift is needed. We must broaden our view from seeing disease, dying, and death as physiological events managed by health care professionals to seeing them as processes that are relational and spiritual, managed with a sense of shared responsibility by all. As a result, the path to improved health and well-being will require an informed and activated citizenry and we provide actionable tasks for key stakeholders (**Table**). While the approach will vary by local context, existing capacity, and resources, each has a role to play and levers to pull to advance the neuropalliative care approach.

At a minimum, we recommend that neurology leaders and stakeholders within their own health systems

Corresponding Author: Robert G. Holloway, MD, MPH, Department of Neurology, University of Rochester School of Medicine and Dentistry, Box 673, 601 Elmwood Ave, Rochester, NY 14642.

Table. Actionable Tasks for Stakeholders to Advance the Neuropalliative Care Approach

Stakeholder	Actionable tasks
Health care system leaders	• Recognize the need for adopting a neuropalliative care approach and advocate for resources. • Commit to integrating interdisciplinary team members specializing in behavioral health (psychiatrists, psychologists, mental health counselors), spiritual care (chaplains, faith healers, doulas), and social care (social workers, case managers, community health workers, legal and financial specialists) across neurological populations. • Have the courage to innovate and test novel models of care. • Develop a triage system to trigger specialist neuropalliative care. • Increase fellowship funding and develop alternative pathways to specialist training and certification.
Persons and families living with neurological disease	• Join service organizations and advocate for change. • Demand that behavioral health, spiritual, and social care be better integrated into neurological services. • Become a member of integrated teams and share your lived experiences.
Clinicians and other members of the health care workforce	• Engage in training to improve your primary and specialist palliative care skills. • Look for ways to expand palliative care treatments and services to the patients in your care. • Identify existing resources and incorporate behavioral health, spiritual care, and social care professionals and services into your routine practice. • Be willing to collaborate in a transformed integrated practice.
Educators	• Implement an awareness campaign on the unmet needs of patients with neurological illness and their families. • Educate neurologists, palliative care physicians, and other interdisciplinary team members on primary neuropalliative care skills. • Ensure all training programs teach primary neuropalliative care skills across the career continuum.
Researchers	• Define and measure underuse and overuse of medical care to quantify avoidable harm and benefits. • Test new models of integrated care and become experts in implementation science. • Develop research careers and professional pathways in areas to promote neuropalliative care. • Build the evidence base needed to improve quality and advocate for policy and payment reform.
Administrators	• Continue to advocate for value-based payments. • Develop models to demonstrate the value of neuropalliative care in regard to improved quality of care and cost savings. • In partnership with other stakeholders, develop metrics to measure progress.
Funders	• Increase funding opportunities for pilot projects, career development training, and research networks to support the field. • Evaluate the impact and return on investment of research against progress made.

and communities incorporate the neuropalliative care approach into routine care by enhancing the primary neuropalliative care skills of all neurologists and team members and integrating support services so that they are accessible to patients and families. There are an increasing number of educational resources available to reinforce primary neuropalliative care skills for different learner groups at various stages of their careers.[7] In addition, there are an increasing number of models to assist with integrating behavioral health and social care into medical care, but few have thus far been adapted for neurological programs. The aspirational biopsychosocial-spiritual home for neurology will also aggressively advance health equity, cover the lifespan, facilitate early referrals to specialist neuropalliative care, and embrace the practice of positive medicine.

Keeping the Patient and Family at the Center

We are at a crossroads. Clinicians are emotionally exhausted, there is declining trust in science and the medical profession, gross inequities compound the moral distress many are experiencing, and health systems are challenging themselves to find a better way. The role of academic and health system leaders is to innovate, set direction, align people, secure resources, and motivate change. It is time to lead. There are a growing number of neuropalliative care champions prepared to lead, advocate, teach, conduct research, and disseminate the neuropalliative care approach across the globe. The most important of these are patients and their families. If we have the courage to lean in and deeply listen to what they are saying, the challenge and path before us will become crystal clear.

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VIEWPOINT

Muhammad Ali and Young-Onset Idiopathic Parkinson Disease—The Missing Evidence

Michael S. Okun, MD
Norman Fixel Institute for Neurological Diseases, Departments of Neurology and Neurosurgery, University of Florida, Gainesville; and Associate Editor, *JAMA Neurology*.

Helen S. Mayberg, MD
Departments of Neurology, Neurosurgery, Psychiatry, and Neuroscience, Icahn School of Medicine at Mount Sinai, New York, New York.

Mahlon R. DeLong, MD
Department of Neurology, Emory University School of Medicine, Atlanta, Georgia.

Corresponding Author: Michael S. Okun, MD, Norman Fixel Institute for Neurological Diseases, University of Florida, 3011 SW Williston Rd, Gainesville, FL 32608.

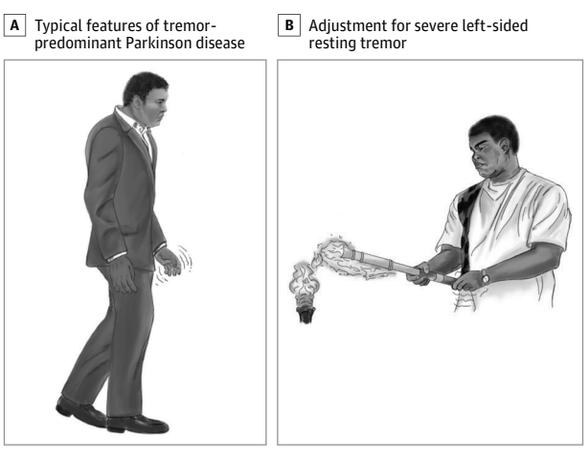
Following Muhammad Ali's death, there has been persistent dialogue about the degree to which Parkinson disease vs repetitive boxing-related head trauma contributed to his progressive motor and cognitive impairments. During one of Ali's most famous public moments, the lighting of the 1996 Olympic torch, Bob Costas from NBC sports commented, "once the most dynamic figure in sports and now trapped by a mask created by parkinson syndrome."[1] Ali manifested a classic Parkinson disease left-arm rest tremor, which was suppressed as he raised his left hand to steady his right arm in order to light the torch.[1] Ali underwent a series of single medical examinations during his professional career from 1981 to 1984 at University of California, Los Angeles, the Mayo Clinic in Rochester, Minnesota, and at Columbia-Presbyterian in New York, New York, which raised the possible diagnoses of both head trauma and Parkinson disease or a parkinsonian syndrome. Postretirement from 1995 until his death, he received his neurological care largely at 1 institution, Emory University in Atlanta, Georgia. He also received local care at the Barrow Neurological Institute in Phoenix, Arizona.

The recent Ken Burns' documentary on the life and boxing career of Ali may have inadvertently, by heavily and graphically focusing on boxing-related trauma, reinforced the idea of a primary diagnosis of dementia pugilistica resulting from repeated head trauma.[2] Ken Burns' documentary and the recent book by Eig[2] on the life and career of Ali both showed and stated that Ali had strong evidence of Parkinson disease, and discussed the possibility of a parkinson syndrome resulting from repeated head trauma. We provide missing and supportive information on Ali's Parkinson disease diagnosis, based on 20 years of clinical follow-up, which occurred between 1995 and 2016. Ali was treated at Emory University with in-person visits, hospitalizations, and testing. These visits collectively informed the nature and course of his medical condition. Here, we add this missing information to the archives of history. The main point of our report is that Muhammad Ali indeed had young-onset levodopa-responsive Parkinson disease with an emergence during the midphase of his boxing career.

In the late 1970s, Ali's family members noted slowness. On October 2, 1980, prior to his last fight against Larry Holmes, because of health concerns, Ali was required to have a prefight medical examination at the Mayo Clinic. Despite an abnormal examination, he was allowed to fight and video footage revealed decreased movement on his left side. In the early 1980s, he was mildly symptomatic with idiopathic Parkinson disease. There was a suspicion of decreased movement, particularly on his left side, which manifested during television interviews including one on May 6, 1981, on NBC where he joined Al Sharpton, James Brown, and reporter Tom Snyder and one with David Letterman on July 9, 1984. There also was a left-sided rest tremor in an interview with Arsenio Hall on June 11, 1991. In the years following, his family, friends, and neurologists observed an intermittent classic parkinsonian rest tremor in the left hand and a slowing of motor function, including softer and dysarthric speech. Moreover, his handwriting became progressively more micrographic, a feature verified by collections of autographs penned over many decades.

Muhammad Ali's disease course, from his late 30s until his death at age 74 years, was chronic and progressive. He manifested fatigue, hypophonia, bradykinesia, and a masked face, as well as many of the visible motor symptoms of Parkinson disease. He was clearly responsive to levodopa, as documented in his several examinations in the early 1980s, a feature usually not present following traumatic brain injury. He was never enrolled in a clinical trial and did not undergo formal on and off medication Unified Parkinson's Disease Rating Scale testing. In 1995, he was first evaluated at Emory University and was followed up there until his death in 2016. A fluorodeoxyglucose positron emission tomography (FDG PET) scan performed in 1997 revealed the Parkinson disease–related pattern of progressive bilateral striatal hyperactivity. A flourodopa F 18 PET scan performed in 1998 showed classic low striatal uptake and, like the FDG PET, this study was consistent with Parkinson disease and not traumatic brain injury. Dopamine transporter (DAT) scanning was not performed. DAT as a diagnostic technology emerged over a decade later with US Food and Drug Administration approval in 2011 for the differentiation of parkinsonism from essential tremor. Ali's brain magnetic resonance imaging scan results revealed no focal abnormalities and was nondiagnostic beyond the presence of brainstem atrophy, third ventricular enlargement, and a cavum septum pellucidum. The Ali hospitalizations were an opportunity to carefully examine and to document his symptoms. Repeated observations confirmed that his prominent left-sided hand tremor, bradykinesia, and rigidity all substantially improved when on medications; all key features in the diagnosis of idiopathic Parkinson.[3] His bradykinesia, rigidity, and tremor progressed gradually and became generalized. Ali showed brisk improvement with various forms of levodopa. Over the course of many years, Ali's face became gradually more masked, his speech more hypophonic, and he developed the classic late-stage symptoms of idiopathic Parkinson disease, including a stooped posture, shuffling steps, postural instability, and falling. Ali developed increasing sleep dys-

Figure. Ali and Parkinson Disease Symptoms



A, Ali with many of the typical features of tremor-predominant Parkinson disease (masked face, resting tremor, stooped posture, and short steps). B, Ali in 1996, overcoming his severe left-sided resting tremor to light the Olympic torch. The video[1] shows a classic unilateral resting Parkinson disease tremor in the left hand and arm, which disappeared as he grabbed onto the bottom of the torch.

function and eventually had diagnostic polysomnography, which confirmed rapid-eye movement sleep behavioral disorder. Ali's weight slowly and gradually declined, another common feature of idiopathic Parkinson disease. His serial neuropsychological testing results showed progressive frontal and memory impairments consistent with classic Parkinson disease. He had mild occasional depression. Ali remained generally positive and embraced his diagnosis, despite the realization it was chronic and progressive. He enjoyed company during his visits, watching videos, performing magic tricks, and mentoring trainees and staff. His disease course also revealed the common reality in tremor-dominant Parkinson disease of a high-functioning and productive life, as evidenced by his many appearances and even by the lighting of the Olympic torch in 1996 (**Figure**). He died of sepsis on June 3, 2016, a common fate in many patients with Parkinson disease.[3]

His medical team discussed autopsy with him. Ali declined a postmortem examination, because Islam forbade the disfigurement or desecration of a dead body. Given the lack of a final tissue diagnosis, we rely on the detailed clinical follow-up and serial PET imaging studies to understand Ali's medical condition. A 34-year chronic progressive presentation with asymmetric levodopa responsive resting tremor, accompanied by other classical features, provides strong evidence for a diagnosis of idiopathic Parkinson disease. In contrast, posttraumatic tremor is commonly transitory, and manifests as a postural and/or kinetic tremor. In addition, posttraumatic tremor is not accompanied by progressive cogwheel rigidity and bradykinesia, both observed in Ali.[3] Head trauma is a known risk factor for the later onset of idiopathic Parkinson disease; however, a causative association in the Ali case cannot be determined.[3,4]

The Muhammad Ali case reinforces the dangers of the press, public, and health care professionals in speculating on medical diagnoses in the absence of an in-person examination. This case highlights the importance of the American Psychiatric Society Goldwater rule; medical professionals should not offer a professional opinion unless an examination is conducted and proper authorization granted for such a statement. In this Viewpoint, we fulfill both Goldwater criteria. Many patients with young-onset idiopathic Parkinson disease presenting like Muhammad Ali have been misdiagnosed or have experienced a delayed diagnosis.[3] Based on extensive long-term clinical and cinematic follow-up, it is clear that Muhammad Ali had young-onset tremor-dominant idiopathic Parkinson disease. The clinical pattern of his symptoms revealed his disease was prolonged, progressive, bilateral but asymmetric, dopa responsive, and was accompanied by serial and classic FDG and DOPA PET imaging. The greater emphasis of the public on his obvious boxing-related sequalae frequently overshadowed the diagnosis of an early-onset case of Parkinson disease. It remains uncertain, as discussed by Eig[2] and others, the extent to which his early onset of Parkinson disease contributed to the progressive impairment in his boxing skills.

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JAMA Neurology | Original Investigation

Long-term Outcomes in Use of Opioids, Nonpharmacologic Pain Interventions, and Total Costs of Spinal Cord Stimulators Compared With Conventional Medical Therapy for Chronic Pain

Sanket S. Dhruva, MD, MHS; Jaime Murillo, MD; Omid Ameli, MD, DrPH; Pamela E. Morin, MBA; Donna L. Spencer, PhD; Rita F. Redberg, MD, MSc; Ken Cohen, MD

IMPORTANCE Spinal cord stimulators (SCSs) are increasingly used for the treatment of chronic pain. There is a need for studies with long-term follow-up.

OBJECTIVE To determine the comparative effectiveness and costs of SCSs compared with conventional medical management (CMM) in a large cohort of patients with chronic pain.

DESIGN, SETTING, AND PARTICIPANTS This was a 1:5 propensity-matched retrospective comparative effectiveness research analysis of insured individuals from April 1, 2016, to August 31, 2018. This study used administrative claims data, including longitudinal medical and pharmacy claims, from US commercial and Medicare Advantage enrollees 18 years or older in Optum Labs Data Warehouse. Patients with incident diagnosis codes for failed back surgery syndrome, complex regional pain syndrome, chronic pain syndrome, and other chronic postsurgical back and extremity pain were included in this study. Data were analyzed from February 1, 2021, to August 31, 2022.

EXPOSURES SCSs or CMM.

MAIN OUTCOMES AND MEASURES Surrogate measures for primary chronic pain treatment modalities, including pharmacologic and nonpharmacologic pain interventions (epidural and facet corticosteroid injections, radiofrequency ablation, and spine surgery), as well as total costs.

RESULTS In the propensity-matched population of 7560 patients, mean (SD) age was 63.5 (12.5) years, 3080 (40.7%) were male, and 4480 (59.3%) were female. Among matched patients, during the first 12 months, patients treated with SCSs had higher odds of chronic opioid use (adjusted odds ratio [aOR], 1.14; 95% CI, 1.01-1.29) compared with patients treated with CMM but lower odds of epidural and facet corticosteroid injections (aOR, 0.44; 95% CI, 0.39-0.51), radiofrequency ablation (aOR, 0.57; 95% CI, 0.44-0.72), and spine surgery (aOR, 0.72; 95% CI, 0.61-0.85). During months 13 to 24, there was no significant difference in chronic opioid use (aOR, 1.06; 95% CI, 0.94-1.20), epidural and facet corticosteroid injections (aOR, 1.00; 95% CI, 0.87-1.14), radiofrequency ablation (aOR, 0.84; 95% CI, 0.66-1.09), or spine surgery (aOR, 0.91; 95% CI, 0.75-1.09) with SCS use compared with CMM. Overall, 226 of 1260 patients (17.9%) treated with SCS experienced SCS-related complications within 2 years, and 279 of 1260 patients (22.1%) had device revisions and/or removals, which were not always for complications. Total costs of care in the first year were $39 000 higher with SCS than CMM and similar between SCS and CMM in the second year.

CONCLUSIONS AND RELEVANCE In this large, real-world, comparative effectiveness research study comparing SCS and CMM for chronic pain, SCS placement was not associated with a reduction in opioid use or nonpharmacologic pain interventions at 2 years. SCS was associated with higher costs, and SCS-related complications were common.

Author Affiliations: University of California, San Francisco School of Medicine, San Francisco (Dhruva); Philip R. Lee Institute for Health Policy Studies, University of California, San Francisco, San Francisco (Dhruva, Redberg); Department of Medicine, San Francisco Veterans Affairs Medical Center, San Francisco, California (Dhruva); Optum Labs, UnitedHealth Group, Eden Prairie, Minnesota (Murillo, Morin, Spencer); Optum Center for Research and Innovation (Ameli, Cohen); Department of Medicine, University of California, San Francisco School of Medicine, San Francisco (Redberg).

Corresponding Author: Sanket S. Dhruva, MD, MHS, University of California, San Francisco School of Medicine, San Francisco Veterans Affairs Medical Center, 4150 Clement St, 111C, San Francisco, CA 94121.

Spinal cord stimulators (SCSs) are neuromodulation devices implanted in the epidural space with the goal of treating chronic pain that fails to respond to conventional treatment. SCSs have been increasingly used in recent years[1,2]; approximately 50 000 are implanted annually in the US[3] at a cost of approximately $3.5 billion.[4] Some have advocated for greater use of SCSs to reduce risks of medications, including opioids and gabapentinoids.[5]

Despite the increasing utilization of SCSs, there are limitations to the evidence supporting its superiority over usual care, which includes conventional medical management (CMM).[6] Most SCS have been authorized by the US Food and Drug Administration (FDA) without clinical data.[7] Approximately 85% of large studies of SCSs (ie, >100 patients) are industry funded.[8] Independent evaluations have generally been small, single-center, and nonrandomized.[9] A recent Cochrane systematic review of randomized trials of SCS found just 1 study (44 patients) examining pain intensity at 1 year or longer follow-up.[10] Although some studies have found benefit in pain relief at 6 months from SCSs compared to CMM, benefits often dissipate after 12 to 24 months.[11] The comparator group in many SCS trials has not adequately masked a placebo effect; when a placebo control is used, treatment effects are smaller.[12]

SCSs have potential complications.[13] In September 2020, the FDA published a letter to health care professionals stating that more than 107 000 medical device adverse-event reports related to SCSs had been filed between July 2016 and July 2020, including patient injury, device malfunction, and 497 deaths.[3] Among 4000 types of medical devices tracked by the FDA, SCSs had the third highest number of adverse events.[14]

Given the limitations in available data, there is a need for data in a larger, contemporary patient cohort to compare the long-term risks, benefits, and cost-effectiveness of SCSs with CMM. Accordingly, we compared the long-term clinical and health care utilization outcomes among patients treated with permanent SCSs compared with CMM.

Key Points

Question What are the outcomes among real-world patients with chronic pain who are treated with spinal cord stimulators compared with conventional medical management?

Findings In this propensity-matched comparative effectiveness research analysis of 7560 insured individuals, treatment with a spinal cord stimulator was not associated with a reduction in use of opioids, pain injections, radiofrequency ablation, or spine surgery at 2 years. Approximately one-fifth of patients treated with spinal cord stimulators experienced complications and required device revision or removal.

Meaning Study results suggest that use of spinal cord stimulators is not associated with reductions in opioid use or nonpharmacologic pain interventions.

Methods

Study Design and Data Source

This was a retrospective comparative effectiveness research study using Optum Labs Data Warehouse (OLDW) data from October 1, 2015, through August 31, 2020. OLDW contains deidentified administrative claims data, including longitudinal medical and pharmacy claims, from US commercial and Medicare Advantage enrollees.[15] Because data were deidentified in compliance with the Health Insurance Portability and Accountability Act, institutional review board approval or waiver of authorization was not required. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

Cohort Selection

Eligible individuals were 18 years or older with an incident diagnosis of failed back surgery syndrome, complex regional pain syndrome, chronic pain syndrome, and other chronic postsurgical back and extremity pain (for the latter diagnosis, history of spine surgery within 6 months of diagnosis was required) between April 1, 2016, and August 31, 2019 (eTable 1 in the Supplement for codes reviewed by multiple authors).[9,16-18] The cohort entry date was defined as the first diagnosis claim meeting any of these criteria after a diagnosis-free clean period of 6 months. If individuals had more than 1 qualifying diagnosis, cohort entry diagnosis and date was based on the following hierarchy: (1) failed back surgery syndrome, (2) complex regional pain syndrome, (3) chronic pain syndrome, and (4) other chronic postsurgical back and extremity pain. Individuals without 6 months of contiguous pharmacy and medical coverage before and 12 months after cohort entry were excluded to ensure consistent ascertainment of treatment patterns. Individuals from the all race and ethnicity groups were included and categorized as the following: Asian, Black, Hispanic, White, and unknown or multiple (refers to patients with unknown race or ethnicity or those included in multiple categories).

Treatments

The exposure of interest was permanent (not trial) SCS implantation within 12 months of cohort entry. Patients were assigned 1 of 2 mutually exclusive treatment cohorts (eFigure 1 in the Supplement): (1) a permanent SCS and (2) CMM only, consisting of pain medications, spine surgery, radiofrequency ablation, epidural and facet corticosteroid injections, and conservative nonpharmacologic therapies (physical therapy, chiropractic treatment, and acupuncture) (eTable 1 in the Supplement). Individuals who received both an SCS and CMM in the 12 months after cohort entry were assigned to the SCS group and baseline use of CMM treatments were evaluated as binary covariates. Individuals with no evidence of an SCS or CMM within 12 months after cohort entry were excluded.

For the SCS group, the index date, ie, treatment initiation, was the date of permanent SCS insertion. Individuals in the CMM group were randomly imputed an index date matching the distribution of index dates in the SCS group.

Six months of continuous pharmacy and medical coverage preindex (baseline) and 24 months of continuous coverage postindex date were required for outcome ascertainment in the primary analysis, with all index dates in the final sample between April 1, 2016, and August 31, 2018 (eFigure 2 in the Supplement). Twelve months of continuous enrollment were allowed to increase sample size for propensity score estimation. From both treatment groups, individuals who received an SCS or care for an SCS, diagnosis of malignancy, possible indications for deep brain stimulation (Parkinson disease) or sacral neuromodulation (urinary or fecal incontinence) to avoid including any non-SCS neuromodulation, disabling neurologic deficits including foot drop, and neurogenic bladder during the baseline period were excluded (eTable 2 in the Supplement). Patients without conversion to permanent SCS within 12 months of trial were excluded.

Outcomes

The primary outcomes were chronic opioid use and epidural and facet corticosteroid injection use, surrogates for primary chronic pain treatment modalities, 1 to 12 months and 13 to 24 months after the index date. Chronic opioid use was defined as a binary outcome during each time window if the total length of opioid possession was 90 days or longer and included either (1) greater than or equal to 120 days' supply or (2) 10 or more fills.[19,20] Other outcomes included long-acting opioid use; greater than 50 morphine milligram equivalent (MME) per day; radiofrequency ablations; new spine surgeries; and any fills for nonsteroidal anti-inflammatory drugs (NSAIDs), systemic corticosteroids, antidepressants, gabapentinoids, and benzodiazepines (eTable 3 in the Supplement). Healthcare utilization, including emergency department visits, hospitalizations, and office visits, were examined. Total costs of care (actual) were also assessed; medical costs included both surgical and medical procedures (and represent approximately 75% of total costs), and pharmacy costs were based on outpatient pharmacy claims. Among patients treated with an SCS, postprocedure complications (lead/generator breakdown, displacement, infection or inflammation, and other mechanical complications), SCS revision, and removal were examined (eTable 4 in the Supplement).

Propensity Matching

To balance baseline characteristics between the treatment groups, the probability of receiving a permanent SCS vs CMM was modeled as a function of 65 baseline predictors among patients with 12 months or longer of follow-up. The following variables were assessed for association with SCS treatment: CMM, which included a comprehensive list of surrogates of baseline pain (total number of filled opioid prescriptions, mean opioid MME, days in possession of opioids, epidural and facet corticosteroid injections, radiofrequency ablation, spine surgery, and nonpharmacologic treatments of painful conditions); index calendar year; demographic characteristics, including race and ethnicity, as assessed in the data source used by the investigators[21] (because these are important demographic variables and studies have shown differences in treatment of pain by race); clinician specialty for cohort entry; 31 medical and mental health comorbidities using the Elixhauser index[22]; and additional pain-related and musculoskeletal conditions using Chronic Conditions Data Warehouse algorithm.[23] A greedy matching algorithm with a caliper width of 20% of the SD of the logit of the propensity score was used.[24] To balance cohort entry diagnosis, matching was performed separately within patients with or without failed back surgery syndrome. Ratio of SCS to CMM matches was 1:5 to achieve optimal power while retaining as many SCS patients as possible. Standardized mean differences were used to evaluate postmatching balance, with values less than 10% considered acceptable.

Statistical Analyses

Patient characteristics for prematch and matched SCS and CMM groups were compared. Using the propensity-matched cohort, outcomes were modeled as a binary variable using generalized linear models with a binomial distribution and a logit link. Total costs of care were modeled using generalized linear models with a gamma distribution and log link. Counts of emergency department visits, hospitalizations, and office visits were modeled using generalized linear models with a Poisson distribution. A generalized estimating equation was used to account for correlation of outcomes within matched clusters during follow-up. Both empirical and robust SEs were examined; as they did not differ, empirical SEs are reported. Outcomes were examined among patients with only either complex regional pain syndrome or chronic pain syndrome at baseline, by patients receiving 7 or fewer days opioids at baseline, and by sex and insurance type. Characteristics of patients excluded due to insufficient post-index follow-up were compared to those included. We also examined the proportion of patients taking opioids at baseline who discontinued these medications at 2 years. All analyses were performed with SAS, version 9.4 (SAS Institute). Significance was considered to be a 2-sided *P* value <.05. Data were analyzed from February 1, 2021, to August 31, 2022.

Results

Study Cohort

There were 6202 patients in the SCS and 215 686 in the CMM group with a diagnosis of failed back surgery syndrome, complex regional pain syndrome, chronic pain syndrome, and other postsurgical extremity or back pain diagnosis and an adequate diagnosis-free clean period and postincident diagnosis continuous enrollment (eFigure 1 in the Supplement). Overall, 1510 of 4731 patients (32%) who had an SCS within 12 months of the cohort entry date were excluded because they received a trial, but not permanent, SCS within 12 months of cohort entry. After excluding patients with indications for other neuromodulation devices, malignancy-related pain, and without 24 months continuous enrollment, 1419 patients in the SCS and 91 307 in the CMM groups composed the final prepropensity score–matched sample. Using

1:5 matching, the final study cohort included 1260 patients who received an SCS and 6300 CMM. Baseline characteristics of retained patients vs those excluded for disenrollment were similar with clinically insignificant differences (eTable 5 in the Supplement). Similarly, patients with permanent SCS did not differ significantly from those with trial SCS only (eTable 6 in the Supplement). At baseline, 1128 of all patients (79%) treated with an SCS also received opioids, and 219 (15.4%) were receiving rehabilitative therapies. Factors associated with SCS treatment are presented in eTable 7 in the Supplement.

Baseline Patient Characteristics

In the matched population of 7560 total patients, all standardized mean differences between patients receiving SCS and CMM were less than 0.1 (eFigure 3 in the Supplement). The mean (SD) age of patients was 63.5 (12.5) years, 3080 (40.7%) were male, and 4480 (59.3%) were female (**Table 1**). Patients belonged to the following race and ethnicity groups: 56 Asian (0.7%), 901 Black (11.9%), 484 Hispanic (6.4%), 5888 White (77.9%), and 231 unknown/multiple (3.1%). Diagnosis at cohort entry included 5352 patients (70.8%) with failed back surgery syndrome, 760 patients (10.1%) with complex regional pain syndrome, 1938 patients (25.6%) with chronic pain syndrome, and 63 patients (0.8%) other postsurgical back or extremity pain. Within 6 months before the index date, 5854 of 7560 patients (77.4%) had received opioids. One-third of patients filled prescriptions for each of NSAIDs, muscle relaxants, and benzodiazepines and half for gabapentinoids. Of the 7560 patients, 3003 (39.7%) received epidural and facet corticosteroid injections, and 1235 (16.3%) received any nonpharmacologic, nonintervention therapy. Only 80 of 1260 patients (6.3%) in the postmatch SCS group did not receive any of the CMM treatments during the 6-month baseline period.

Outcomes of SCS vs CMM

Pharmacologic Treatments for Pain

After achieving baseline balance, during the first 12 months, patients treated with SCSs filled a higher number of opioid prescriptions, were more likely to have chronic opioid use (54.9% vs 51.8%; adjusted odds ratio [aOR], 1.14; 95% CI, 1.01-1.29) (**Table 2** and **Table 3**) and long-acting opioid use (22.5% vs 18.5%; aOR, 1.28; 95% CI, 1.11-1.49) compared with those treated with CMM. During months 13 to 24, there were no significant reductions across pharmacologic treatments for pain among patients treated with SCS; patients treated with SCS had similar adjusted odds of chronic opioid use (49.0% vs 47.6%; aOR, 1.06; 95% CI, 0.94-1.20) and long-acting opioid use (18.3% vs 16.3%; aOR, 1.16; 95% CI, 0.99-1.36). Among patients taking opioids during the 6-month baseline period, SCS was not associated with a higher rate of opioid discontinuation during months 13 to 24 (eTable 8 in the Supplement).

During the first 12 months, there were no significant differences in the use of NSAIDs, muscle relaxants, steroids, TCA/SNRI antidepressants, gabapentinoids, or benzodiazepines. During months 13 to 24, patients treated with SCSs had no difference in the likelihood of receiving NSAIDs or muscle relaxants. However, these patients were more likely to fill a prescription for TCA/SNRI antidepressants (33.3% vs 29.9%; aOR, 1.16; 95% CI, 1.02-1.32) and gabapentinoids (53.3% vs 48.3%; aOR, 1.22; 95% CI, 1.08-1.37), although less likely to fill a benzodiazepine prescription (29.4% vs 32.3%; aOR, 0.87; 95% CI, 0.76-1.00). Results were generally consistent among propensity-matched comparisons by sex and type of insurance coverage (commercial and Medicare Advantage). Results were also consistent when limited to patients matched based on chronic regional pain syndrome or chronic pain syndrome diagnoses (eTable 9 in the Supplement) and when limited to patients who had received opioids for 7 or fewer days during the 6-month baseline period (eTable 10 in the Supplement).

Nonpharmacologic Pain Interventions

Fewer patients with SCSs received epidural and facet corticosteroid injections within the first 12 months compared with CMM (21.7% vs 38.4%; aOR, 0.44; 95% CI, 0.39-0.51) (Table 2 and Table 3), but this difference was not present by months 13 to 24 (24.9% vs 25.1%; aOR, 1.00; 95% CI, 0.87-1.14). Similarly, fewer patients with SCS underwent a radiofrequency ablation within the first 12 months compared with CMM (5.3% vs 9.2%; aOR, 0.57; 95% CI, 0.44-0.72), with no significant difference during months 13 to 24 (5.7% vs 6.7%; aOR, 0.84; 95% CI, 0.66-1.09). Results were consistent by sex and insurance type.

Health Care Utilization and Cost Outcomes

There were no significant differences between patients treated with SCSs or CMM in emergency department visits or hospitalizations in either the first or second year of follow-up (Table 2). The mean (SD) total cost of care per member per month during the first year was $5531 ($4188) for patients treated with SCS vs CMM $2240 ($4008) ($P < .001$); this difference was driven entirely by significantly higher medical costs for patients treated with SCS. Over 12 months, this represents over $39 000 in higher health care costs within the first year post-SCS placement (**Figure**). Stratified by type of insurance coverage, total costs were approximately $60 000 and $33 000 higher for commercially insured and Medicare Advantage enrollees, respectively. During months 13 to 24, the total costs were similar between the 2 groups ($2171 SCS vs $2109 CMM; $P = .51$) and adjusted cost ratios were also similar. Among all patients receiving SCS, out-of-pocket medical (ie, nonpharmacy) costs were approximately $2215 at baseline, increasing to $3695 in the first 12 months after SCS placement, and $1781 in the second year after device placement.

SCS-Related Complications and Removal

Among the 1260 patients treated with SCS, 226 (17.9%) experienced complications within the first 2 years after placement (**Table 4**). These complications included breakdown, displacement, other mechanical complications, and infection of the lead and/or generator. During the first 2 years, 279 patients (22.1%) had an SCS removal and/or revision; 126 (10%) of these were in the absence of a complication, suggesting lack of effectiveness.

Table 1. Patient Characteristics for Prematch and Postmatched Patient Cohorts

Characteristic	Final prematch cohort 24 mo				Final postmatch cohort 24 mo			
	No. (%)				No. (%)			
	Total (n = 92 726)	SCS (n = 1419)	CMM (n = 91 307)	SMD	Total (n = 7560)	SCS (n = 1260)	CMM (n = 6300)	SMD
Age, mean (SD), y	61.9 (13.3)	64.3 (11.9)	61.9 (13.3)	0.19	63.5 (12.5)	64.0 (12.1)	63.4 (12.5)	0.05
Age category								
18-54	25 048 (27.0)	288 (20.3)	24 760 (27.1)	−0.16	1715 (22.7)	263 (20.9)	1452 (23.1)	−0.05
55-64	25 953 (28.0)	379 (26.7)	25 574 (28.0)	−0.03	2033 (26.9)	342 (27.1)	1691 (26.8)	0.01
65-74	25 321 (27.3)	463 (32.6)	24 858 (27.2)	0.12	2270 (30.0)	400 (31.8)	1870 (29.7)	0.04
75+	16 404 (17.7)	289 (20.4)	16 115 (17.7)	0.07	1542 (20.4)	255 (20.2)	1287 (20.4)	−0.00
Sex								
Male	36 379 (39.2)	561 (39.5)	35 818 (39.2)	0.01	3080 (40.7)	493 (39.1)	2587 (41.1)	−0.04
Female	56 347 (60.8)	858 (60.5)	55 489 (60.8)	−0.01	4480 (59.3)	767 (60.9)	3713 (58.9)	0.04
Insurance type								
Commercially insured	29 417 (31.7)	353 (24.9)	29 064 (31.8)	−0.15	2101 (27.8)	315 (25.0)	1786 (28.4)	−0.08
Medicare Advantage	63 309 (68.3)	1066 (75.1)	62 243 (68.2)	0.15	5459 (72.2)	945 (75)	4514 (71.7)	0.08
Geographic location								
Northeast	7565 (8.2)	76 (5.4)	7489 (8.2)	−0.11	489 (6.5)	74 (5.9)	415 (6.6)	−0.03
Midwest	18 153 (19.6)	411 (29.0)	17 742 (19.4)	0.22	2073 (27.4)	342 (27.1)	1731 (27.5)	−0.01
South	55 794 (60.2)	729 (51.4)	55 065 (60.3)	−0.18	3971 (52.5)	671 (53.3)	3300 (52.4)	0.02
West	11 214 (12.1)	203 (14.3)	11 011 (12.1)	0.07	1027 (13.6)	173 (13.7)	854 (13.6)	0.01
Race and ethnicity								
Asian	1329 (1.4)	<11 (NA)[a]	>1318 (NA)	−0.08	56 (0.7)	<11 (NA)	>45 (NA)	−0.02
Black	15 148 (16.3)	157 (11.1)	14 991 (16.4)	−0.16	901 (11.9)	150 (11.9)	751 (11.9)	−0.00
Hispanic	8016 (8.6)	>90 (NA)	>7926 (NA)	−0.08	484 (6.4)	>85 (NA)	>399 (NA)	0.03
White	65 513 (70.7)	1114 (78.5)	64 399 (70.5)	0.18	5888 (77.9)	973 (77.2)	4915 (78.0)	−0.02
Unknown/multiple[b]	2720 (2.9)	47 (3.3)	2673 (2.9)	0.02	231 (3.1)	41 (3.3)	190 (3.0)	0.01
Index year								
2016	23 689 (25.6)	282 (19.9)	23 407 (25.6)	−0.14	1637 (21.7)	261 (20.7)	1376 (21.8)	−0.03
2017	42 662 (46.0)	664 (46.8)	41 998 (46)	0.02	3553 (47)	595 (47.2)	2958 (47.0)	0.01
2018	26 375 (28.4)	473 (33.3)	25 902 (28.4)	0.11	2370 (31.4)	404 (32.1)	1966 (31.2)	0.02
Cohort entry diagnosis								
Failed back surgery	22 739 (24.5)	1028 (72.5)	21 711 (23.8)	1.12	5352 (70.8)	892 (70.8)	4460 (70.8)	0.00
Complex regional pain	5239 (5.7)	123 (8.7)	5116 (5.6)	0.12	760 (10.1)	94 (7.5)	666 (10.6)	−0.11
Chronic pain	63 790 (68.8)	398 (28.1)	63 392 (69.4)	−0.91	1938 (25.6)	365 (29.0)	1573 (25.0)	0.09
Other chronic back/extremity pain	2775 (3.0)	13 (0.9)	2762 (3.0)	−0.15	63 (0.8)	12 (1.0)	51 (0.8)	0.02
Clinician type on day of cohort entry								
Primary care	41 097 (44.3)	222 (15.6)	40 875 (44.8)	−0.67	1299 (17.2)	207 (16.4)	1092 (17.3)	−0.02
Anesthesiologist	32 020 (34.5)	991 (69.8)	31 029 (34.0)	0.77	4890 (64.7)	847 (67.2)	4043 (64.2)	0.06
Neurosurgeon	4808 (5.2)	141 (9.9)	4667 (5.1)	0.18	745 (9.9)	115 (9.1)	630 (10)	−0.03
Orthopedic surgeon	4600 (5.0)	70 (4.9)	4530 (5.0)	−0.00	394 (5.2)	67 (5.3)	327 (5.2)	0.01
Physiatrist	8317 (9.0)	157 (11.1)	8160 (8.9)	0.07	908 (12.0)	144 (11.4)	764 (12.1)	−0.02
Other medical physician	10 720 (11.6)	65 (4.6)	10 655 (11.7)	−0.26	344 (4.6)	58 (4.6)	286 (4.5)	0.00
Non–medical physician	3973 (4.3)	51 (3.6)	3922 (4.3)	−0.04	305 (4.0)	48 (3.8)	257 (4.1)	−0.01
Surrogates of baseline pain								
Total baseline filled prescriptions for opioids								
Mean (SD)	4.2 (4.2)	4.7 (4.2)	4.2 (4.2)	0.12	4.5 (4.3)	4.6 (4.1)	4.5 (4.3)	0.02
Median (IQR)	3 (1-6)	4 (1-7)	3 (1-6)		4 (1-7)	4 (1-7)	4 (1-7)	
Average opioid MME baseline								
Mean (SD)	29.9 (62.6)	35.5 (68.2)	29.8 (62.5)	0.09	34.9 (69.1)	35.5 (69.7)	34.8 (69.0)	0.01
Median (IQR)	8.0 (0.4-30.7)	12.7 (1.1-38.9)	7.9 (0.4-30.6)		10.1 (0.7-38.0)	12.2 (1.1-38.6)	9.9 (0.6-37.8)	
Baseline opioid days								
Mean (SD)	76.5 (68.3)	85.8 (67.8)	76.3 (68.3)	0.14	81.1 (68.8)	84.3 (67.7)	80.4 (69.0)	0.06
Median (IQR)	61 (3-150)	90 (9-155)	61 (3-150)		76 (5-154)	90 (8-155)	74 (4-154)	
Baseline quartile of days supply of opioids								
Quartile 1	21 980 (23.7)	291 (20.5)	21 689 (23.8)	−0.08	1706 (22.6)	264 (21.0)	1442 (22.9)	−0.05
Quartile 2	22 421 (24.2)	296 (20.9)	22 125 (24.2)	−0.08	1699 (22.5)	270 (21.4)	1429 (22.7)	−0.03
Quartile 3	24 502 (26.4)	406 (28.6)	24 096 (26.4)	0.05	2006 (26.5)	355 (28.2)	1651 (26.2)	0.04
Quartile 4	23 823 (25.7)	426 (30.0)	23 397 (25.6)	0.10	2149 (28.4)	371 (29.4)	1778 (28.2)	0.03

(continued)

Table 1. Patient Characteristics for Prematch and Postmatched Patient Cohorts (continued)

Characteristic	Final prematch cohort 24 mo				Final postmatch cohort 24 mo			
	No. (%)				No. (%)			
	Total (n = 92 726)	SCS (n = 1419)	CMM (n = 91 307)	SMD	Total (n = 7560)	SCS (n = 1260)	CMM (n = 6300)	SMD
Epidural and facet corticosteroid injections	18 178 (19.6)	610 (43.0)	17 568 (19.2)	0.53	3003 (39.7)	507 (40.2)	2496 (39.6)	0.01
Radiofrequency ablation	3325 (3.6)	126 (8.9)	3199 (3.5)	0.22	495 (6.6)	92 (7.3)	403 (6.4)	0.04
Spine surgery	8645 (9.3)	193 (13.6)	8452 (9.3)	0.14	853 (11.3)	159 (12.6)	694 (11.0)	0.05
Other nonpharmacologic, nonintervention treatments during baseline								
Physical therapy	10 170 (11.0)	152 (10.7)	10 018 (11.0)	−0.01	874 (11.6)	139 (11.0)	735 (11.7)	−0.02
Acupuncture	595 (0.6)	<11 (NA)	>584 (NA)	−0.04	27 (0.36)	<11 (NA)	>16 (NA)	0.01
Chiropractor	5672 (6.1)	76 (5.4)	5596 (6.1)	−0.03	422 (5.6)	69 (5.5)	353 (5.6)	−0.01
Any nonpharmacologic, nonintervention treatment	15 047 (16.2)	219 (15.4)	14 828 (16.2)	−0.02	1235 (16.3)	199 (15.8)	1036 (16.4)	−0.02
Pharmacologic treatment during baseline								
Opioids	70 746 (76.3)	1128 (79.5)	69 618 (76.2)	0.08	5854 (77.4)	996 (79.1)	4858 (77.1)	0.05
NSAIDs	29 921 (32.3)	458 (32.3)	29 463 (32.3)	0.00	2507 (33.2)	416 (33.0)	2091 (33.2)	−0.00
Muscle relaxants	27 975 (30.2)	463 (32.6)	27 512 (30.1)	0.05	2526 (33.4)	413 (32.8)	2113 (33.5)	−0.02
TCA/SNRI antidepressants	19 536 (21.1)	446 (31.4)	19 090 (20.9)	0.24	2141 (28.3)	370 (29.4)	1771 (28.1)	0.03
Gabapentinoids	34 732 (37.5)	786 (55.4)	33 946 (37.2)	0.37	3891 (51.5)	674 (53.5)	3217 (51.1)	0.05
Benzodiazepines	29 721 (32.1)	512 (36.1)	29 209 (32.0)	0.09	2615 (34.6)	457 (36.3)	2158 (34.3)	0.04
Oral steroids	22 849 (24.6)	344 (24.2)	22 505 (24.7)	−0.01	1824 (24.1)	316 (25.1)	1508 (23.9)	0.03
Musculoskeletal comorbidities								
Fibromyalgia	7199 (7.8)	114 (8.0)	7085 (7.8)	0.01	542 (7.2)	101 (8.0)	441 (7)	0.04
Spine disk disease	66 987 (72.2)	1339 (94.4)	65 648 (71.9)	0.63	7074 (93.6)	1181 (93.7)	5893 (93.5)	0.01
Traumatic spine injury	6057 (6.5)	129 (9.1)	5928 (6.5)	0.10	595 (7.9)	111 (8.8)	484 (7.7)	0.04
Osteoporosis	5544 (6.0)	89 (6.3)	5455 (6.0)	0.01	486 (6.4)	76 (6.0)	410 (6.5)	−0.02
Osteoarthritis	14 182 (15.3)	320 (22.6)	13 862 (15.2)	0.19	1579 (20.9)	275 (21.8)	1304 (20.7)	0.03
Mental health comorbidities								
Anxiety	23 530 (25.4)	406 (28.6)	23 124 (25.3)	0.07	2124 (28.1)	359 (28.5)	1765 (28.0)	0.01
History of benzodiazepine use disorder	538 (0.6)	11 (0.8)	527 (0.6)	0.02	43 (0.6)	11 (0.9)	32 (0.5)	0.04
Alcohol use disorder	2090 (2.3)	21 (1.5)	2069 (2.3)	−0.06	132 (1.75)	20 (1.59)	112 (1.78)	−0.01
Depression	22 706 (24.5)	660 (46.5)	22 046 (24.1)	0.48	2999 (39.7)	515 (40.9)	2484 (39.4)	0.03
Psychosis	1466 (1.6)	13 (0.9)	1453 (1.6)	−0.06	73 (1.0)	13 (1.0)	60 (1.0)	0.01
Substance abuse disorder	9168 (9.9)	156 (11.0)	9012 (9.9)	0.04	797 (10.5)	136 (10.8)	661 (10.5)	0.01

(continued)

Discussion

In this large, real-world, comparative effectiveness research study comparing well-matched SCS and CMM patients, permanent SCS placement was not associated with a meaningful reduction in use of pharmacologic (including opioids) or nonpharmacologic interventions used for chronic pain at 2 years. Although patients treated with SCS received fewer epidural and facet corticosteroid injections and radiofrequency ablations within the first year after permanent device placement, perhaps due to time spent on efforts to establish SCS effectiveness for pain treatment, these differences were not present in the second year. SCS was also associated with risk, including device removal or revision in more than one-fifth of patients.

The lack of reduction in pharmacotherapy, epidural and facet corticosteroid injections, and radiofrequency ablations at 2 years among patients receiving SCS compared with those receiving CMM suggests that SCS was providing insufficient pain relief to forego other therapies or improve rates of depression or anxiety, as prescriptions for these drug classes did not decline. There is often a significant placebo effect to pain management procedures,[25] including SCS.[12] A systematic review of RCTs of SCS vs placebo found low to very low certainty of benefits on pain intensity.[10] Because most patients still had their permanent SCS in place at 2 years, some may receive prolonged benefit from this modality, although we were not able to identify this through reductions in opioid use or nonpharmacologic pain interventions. Future research should seek to identify these possible subgroups and examine other endpoints that may be important to patients.

These findings also suggest that, despite recommendations that SCS be placed to reduce the need for opioids,[5] this may not occur successfully in most patients who are receiving a contemporary SCS. In May 2018, the FDA announced an initiative to encourage device innovation to target pain[26]; however, all but a single SCS within the past 20 years have been approved based on literature reviews and not original clinical trials[7]; this means limited

Table 1. Patient Characteristics for Prematch and Postmatched Patient Cohorts (continued)

Characteristic	Final prematch cohort 24 mo No. (%) Total (n = 92 726)	SCS (n = 1419)	CMM (n = 91 307)	SMD	Final postmatch cohort 24 mo No. (%) Total (n = 7560)	SCS (n = 1260)	CMM (n = 6300)	SMD
Other comorbidities								
Pregnancy	264 (0.3)	0 (0.0)	264 (0.3)	−0.08	NA (NA)	NA (NA)	NA (NA)	−0.02
Blood loss anemia	1097 (1.2)	12 (0.9)	1085 (1.2)	−0.03	58 (0.8)	11 (0.9)	47 (0.8)	0.01
Cardiac arrhythmias	13 024 (14.1)	222 (15.6)	12 802 (14.0)	0.05	1069 (14.1)	198 (15.7)	871 (13.8)	0.05
Congestive heart failure	8112 (8.8)	114 (8.0)	7998 (8.8)	−0.03	507 (6.7)	107 (8.5)	400 (6.4)	0.08
Coagulopathy	2401 (2.6)	44 (3.1)	2357 (2.6)	0.03	189 (2.5)	37 (2.9)	152 (2.4)	0.03
Chronic pulmonary disease	22 193 (23.9)	341 (24.0)	21 852 (23.9)	0.00	1768 (23.4)	311 (24.7)	1457 (23.1)	0.04
Deficiency anemia	5795 (6.3)	81 (5.7)	5714 (6.3)	−0.02	396 (5.2)	77 (6.1)	319 (5.1)	0.05
Diabetes, uncomplicated	23 380 (25.2)	371 (26.2)	23 009 (25.2)	0.02	1923 (25.4)	336 (26.7)	1587 (25.2)	0.03
Diabetes, complicated	17 133 (18.5)	267 (18.8)	16 866 (18.5)	0.01	1407 (18.6)	243 (19.3)	1164 (18.5)	0.02
Diabetes	27 257 (29.4)	432 (30.4)	26 825 (29.4)	0.02	2227 (29.5)	390 (31.0)	1837 (29.2)	0.04
Fluid and electrolyte disorders	9125 (9.8)	106 (7.5)	9019 (9.9)	−0.09	555 (7.3)	98 (7.8)	457 (7.3)	0.02
HIV	379 (0.4)	<11 (NA)	>368 (NA)	−0.02	21 (0.3)	<11 (NA)	>10 (NA)	−0.01
Hypertension, uncomplicated	55 671 (60.0)	913 (64.3)	54 758 (60.0)	0.09	4684 (62.0)	811 (64.4)	3873 (61.5)	0.06
Hypertension, complicated	9503 (10.3)	126 (8.9)	9377 (10.3)	−0.05	626 (8.3)	116 (9.2)	510 (8.1)	0.04
Hypertension	56 886 (61.4)	934 (65.8)	55 952 (61.3)	0.09	4766 (63.0)	830 (65.9)	3936 (62.5)	0.07
Hypothyroidism	15 392 (16.6)	259 (18.3)	15 133 (16.6)	0.04	1294 (17.1)	230 (18.3)	1064 (16.9)	0.04
Liver disease	4602 (5.0)	73 (5.1)	4529 (5.0)	0.01	382 (5.1)	63 (5)	319 (5.1)	−0.00
Obesity	15 034 (16.2)	251 (17.7)	14 783 (16.2)	0.04	1276 (16.9)	221 (17.5)	1055 (16.8)	0.02
Other neurological deficits	5950 (6.4)	88 (6.2)	5862 (6.4)	−0.01	428 (5.7)	77 (6.1)	351 (5.6)	0.02
Pulmonary circulation disorders	2383 (2.6)	31 (2.2)	2352 (2.6)	−0.03	146 (1.9)	29 (2.3)	117 (1.9)	0.03
Peptic ulcer disease	1091 (1.2)	18 (1.3)	1073 (1.2)	0.01	93 (1.2)	16 (1.3)	77 (1.2)	0.00
Peripheral vascular disease	9948 (10.7)	152 (10.7)	9796 (10.7)	−0.00	733 (9.7)	135 (10.7)	598 (9.5)	0.04
Paralysis	1012 (1.1)	<11 (NA)	>1001 (NA)	−0.06	41 (0.54)	<11 (NA)	>30 (NA)	0.01
Kidney failure	9377 (10.1)	142 (10.0)	9235 (10.1)	−0.00	698 (9.2)	129 (10.2)	569 (9.0)	0.04
Valvular disease	5981 (6.5)	85 (6.0)	5896 (6.5)	−0.02	457 (6.0)	74 (5.9)	383 (6.1)	−0.01
Weight loss	2771 (3.0)	31 (2.2)	2740 (3)	−0.05	166 (2.2)	28 (2.2)	138 (2.2)	0.00
Health care utilization and costs								
All-cause cost of care, $								
Baseline total costs, PMPM								
Mean (SD)	2261 (4639)	2003 (3513)	2265 (4654)	−0.06	2138 (4241)	1993 (3487)	2167 (4376)	−0.04
Median (IQR)	958 (436-2312)	1162 (646-2181)	954 (433-2316)		1060 (557-2253)	1139 (619-2142)	1045 (544-2283)	
Baseline medical costs, PMPM								
Mean (SD)	1718 (4292)	1406 (3288)	1723 (4306)	−0.08	1550 (3570)	1389 (3242)	1582 (3632)	−0.06
Median (IQR)	542 (222-1496)	691 (371-1324)	539 (221-1501)		625 (310-1429)	679 (363-1300)	613 (300-1464)	
Baseline outpatient pharmacy costs, PMPM								
Mean (SD)	543 (1595)	597 (1031)	542 (1603)	0.04	588 (2215)	604 (1064)	585 (2379)	0.01
Median (IQR)	193 (71-532)	275 (107-662)	192 (70-530)		229 (86-602)	281 (102-665)	219 (83-590)	
All-cause health care resource utilization								
Baseline emergency department stays								
Mean (SD)	0.6 (1.4)	0.5 (1.2)	0.6 (1.4)	−0.09	0.5 (1.3)	0.5 (1.2)	0.5 (1.3)	−0.04
Median (IQR)	0 (0-1)	0 (0-1)	0 (0-1)		0 (0-1)	0 (0-1)	0 (0-1)	
Baseline emergency department days								
Mean (SD)	0.7 (3.4)	0.6 (1.5)	0.7 (3.4)	−0.07	0.6 (1.7)	0.5 (1.5)	0.6 (1.8)	−0.06
Median (IQR)	0 (0-1)	0 (0-1)	0 (0-1)		0 (0-1)	0 (0-1)	0 (0-1)	
Baseline inpatient stays								
Mean (SD)	0.2 (0.6)	0.1 (0.4)	0.2 (0.6)	−0.20	0.1 (0.4)	0.1 (0.4)	0.2 (0.4)	−0.09
Median (IQR)	0	0	0		0	0	0	

Abbreviations: MME, morphine milligram equivalent; NA, not available; NSAID, nonsteroidal anti-inflammatory drug; PMPM, per member per month; SMD, standardized mean difference; SNRI, serotonin and norepinephrine reuptake inhibitor; TCA, tricyclic antidepressant.

[a] Small numbers (n <11) cannot be reported according to the Optum Labs cell size suppression policy.

[b] Unknown/multiple refers to patients with unknown race or ethnicity or included in multiple categories.

Table 2. Pain and Health Care Utilization 24 Months After Permanent Spinal Cord Stimulator (SCS) Implantation vs Conventional Medical Management (CMM)

Variable	Follow-up, mo	Total(n = 7560)	SCS (n = 1260)	CMM (n = 6300)
Surrogates of pain				
Average MME	1-12			
Mean (SD)		33.5 (65.5)	33.0 (60.7)	33.6 (66.4)
Median (IQR)		9.6 (0.7-39.1)	11.8 (1.9-38.2)	9.0 (0.5-39.2)
Average MME	13-24			
Mean (SD)		28.3 (55.6)	27.1 (49.2)	28.5 (56.8)
Median (IQR)		5.3 (0.0-35.1)	6.0 (0.0-34.4)	5.2 (0.0-35.1)
No. of opioid scripts	1-12			
Mean (SD)		8.3 (8.2)	8.9 (7.8)	8.2 (8.2)
Median (IQR)		7 (1-13)	7 (2-13)	6 (1-13)
No. of opioid scripts	13-24			
Mean (SD)		7.4 (8.0)	7.4 (7.6)	7.4 (8.0)
Median (IQR)		5 (0-12)	5 (0-12)	5 (0-12)
Chronic opioid use	1-12	3952 (52.3)	692 (54.9)	3260 (51.8)
	13-24	3615 (47.8)	617 (49.0)	2998 (47.6)
Long-acting opioid use	1-12	1449 (19.2)	284 (22.5)	1165 (18.5)
	13-24	1259 (16.7)	231 (18.3)	1028 (16.3)
High MME	1-12	3984 (52.7)	815 (64.7)	3169 (50.3)
	13-24	3318 (43.9)	563 (44.7)	2755 (43.7)
Epidural and facet corticosteroid injections	1-12	2693 (35.6)	273 (21.7)	2420 (38.4)
	13-24	1895 (25.1)	314 (24.9)	1581 (25.1)
Radiofrequency ablation	1-12	644 (8.5)	67 (5.3)	577 (9.2)
	13-24	494 (6.5)	72 (5.7)	422 (6.7)
Advanced imaging	1-12	2440 (32.3)	367 (29.1)	2073 (32.9)
	13-24	2194 (29.0)	357 (28.3)	1837 (29.2)
Spine surgery	1-12	1364 (18.0)	179 (14.2)	1185 (18.8)
	13-24	957 (12.7)	148 (11.8)	809 (12.8)
Pharmacologic treatment during follow-up				
NSAIDs	1-12	2944 (38.9)	476 (37.8)	2468 (39.2)
	13-24	2674 (35.4)	442 (35.1)	2232 (35.4)
Muscle relaxants	1-12	3158 (41.8)	558 (44.3)	2600 (41.3)
	13-24	2909 (38.5)	495 (39.3)	2414 (38.3)
Systemic steroids	1-12	2614 (34.6)	422 (33.5)	2192 (34.8)
	13-24	2532 (33.5)	444 (35.2)	2088 (33.1)
TCA/SNRI antidepressants	1-12	2397 (31.7)	412 (32.7)	1985 (31.5)
	13-24	2305 (30.5)	419 (33.3)	1886 (29.9)
Gabapentinoids	1-12	3996 (52.9)	681 (54.1)	3315 (52.6)
	13-24	3714 (49.1)	671 (53.3)	3043 (48.3)
Benzodiazepines	1-12	2702 (35.7)	451 (35.8)	2251 (35.7)
	13-24	2407 (31.8)	371 (29.4)	2036 (32.3)

(continued)

data support SCS that are used in clinical practice. A prior meta-analysis of 5 clinical trials, 4 of which were industry funded, found a minor reduction in opioid use after SCSs compared with CMM.[27] In contrast, a recent independent study with 1-year follow-up of patients postlaminectomy found small, clinically questionable opioid discontinuation associated with SCSs.[28] We extend these findings to 2 years and several additional endpoints among a broader population receiving SCS for multiple indications.

SCSs may also be associated with harm in some patients. Nearly one-fifth of patients treated with SCSs experienced device-related complications within 2 years. Even more had their devices removed or revised. More than two-fifths of SCS explants are for lack of pain relief.[29] In this context, the greater than 100 000 adverse event reports filed with FDA over the past 4 years[3] and 49 SCS-related recalls in the past 20 years[7] indicate significant risks to patients.

SCS also have high costs: $39 000 more in the first year among patients treated with SCS than CMM. This additional spending was not recouped in the second year after SCS placement because patients continued to receive similar amounts of both pharmacologic and nonpharmacologic treatment. Although we did not conduct a formal cost-effectiveness analysis, some prior research (primarily industry-funded) has found these devices to be cost-effective,[30-32] whereas those conducted by independent investigators have found SCSs to not be cost-effective.[33]

Back pain, with or without extremity pain, has high prevalence: more than one-fourth of patients report back pain within the past 3 months.[34] With more than

Table 2. Pain and Health Care Utilization 24 Months After Permanent Spinal Cord Stimulator (SCS) Implantation vs Conventional Medical Management (CMM) (continued)

Variable	Follow-up, mo	Total(n = 7560)	SCS (n = 1260)	CMM (n = 6300)
Health care utilization and costs, $				
All-cause cost of care				
Total costs, PMPM	Baseline			
Mean (SD)		2138 (4241)	1993 (3487)	2167 (4376)
Median (IQR)		1060 (557-2253)	1139 (619-2142)	1045 (544-2283)
Follow-up total costs, PMPM	1-12			
Mean (SD)		2789 (4220)	5531 (4188)	2240 (4008)
Median (IQR)		1500 (649-3641)	4488 (3319-6436)	1182 (559-2552)
Follow-up total costs, PMPM	13-24			
Mean (SD)		2120 (3682)	2171 (2845)	2109 (3827)
Median (IQR)		1070 (479-2434)	1263 (548-2638)	1035 (464-2398)
Medical costs, PMPM	Baseline			
Mean (SD)		1550 (3571)	1389 (3242)	1582 (3632)
Median (IQR)		625 (310-1429)	679 (363-1300)	613 (300-1464)
Follow-up medical costs, PMPM	1-12			
Mean (SD)		2184 (3492)	4916 (3917)	1638 (3127)
Median (IQR)		921 (362-2932)	3910 (2987-5616)	690 (307-1738)
Follow-up medical costs, PMPM	13-24			
Mean (SD)		1498 (2785)	1557 (2487)	1486 (2840)
Median (IQR)		595 (253-1618)	695 (278-1786)	579 (247-1583)
Outpatient pharmacy costs, PMPM	Baseline			
Mean (SD)		588 (2215)	604 (1064)	585 (2379)
Median (IQR)		229 (86-602)	281 (102-665)	219 (83-590)
Follow-up outpatient pharmacy costs, PMPM	1-12			
Mean (SD)		604 (2249)	615.1 (1120)	602 (2412)
Median (IQR)		240 (93-610)	290 (111-648)	231 (90-601)
Follow-up outpatient pharmacy costs, PMPM	13-24			
Mean (SD)		622 (2282)	614 (1097)	623.6 (2451)
Median (IQR)		232 (87-604)	283 (108-662)	223 (85-590)
All-cause health care resource utilization				
Follow-up inpatient stays	1-12			
Mean (SD)		0.3 (0.8)	0.3 (0.7)	0.3 (0.8)
Median (IQR)		0 (0-0)	0 (0-0)	0 (0-0)
Follow-up inpatient stays	13-24			
Mean (SD)		0.3 (0.8)	0.3 (0.7)	0.3 (0.8)
Median (IQR)		0 (0-0)	0 (0-0)	0 (0-0)
Follow-up ED stays	1-12			
Mean (SD)		1.0 (2.2)	0.9 (2.0)	1.0 (2.2)
Median (IQR)		0 (0-1)	0 (0-1)	0 (0-1)
Follow-up ED stays	13-24			
Mean (SD)		0.9 (2.0)	0.9 (1.8)	0.9 (2.1)
Median (IQR)		0 (0-1)	0 (0-1)	0 (0-1)
Follow-up ED, d	1-12			
Mean (SD)		1.2 (3.0)	1.2 (2.7)	1.2 (3.0)
Median (IQR)		0 (0-1)	0 (0-1)	0 (0-1)
Follow-up ED, d	13-24			
Mean (SD)		1.2 (3.0)	1.1 (2.4)	1.2 (3.1)
Median (IQR)		0 (0-1)	0 (0-1)	0 (0-1)
Office visits	Baseline			
Mean (SD)		12.1 (9.0)	13.3 (8.7)	11.9 (9.0)
Median (IQR)		10 (6-16)	11 (7-17)	10 (6-15)
Follow-up office visits	1-12			
Mean (SD)		22.5 (16.6)	23.0 (16.2)	22.5 (16.7)
Median (IQR)		19 (11-29)	20 (12-30)	19 (11-29)
Follow-up office visits	13-24			
Mean (SD)		21.1 (16.8)	22.4 (18.0)	20.8 (16.5)
Median (IQR)		17 (10-27)	18 (11-29)	17 (10-27)

Abbreviations: ED, emergency department; MME, morphine milligram equivalent; NSAID, nonsteroidal anti-inflammatory drug; PMPM, per member per month; SNRI, serotonin and norepinephrine reuptake inhibitor; TCA, tricyclic antidepressant.

$100 billion in annual total costs,[35] health plans must support use of safe and beneficial evidence-based therapies.[6,36,37] The higher total costs of care that we observed associated with SCSs were primarily borne by health plans, particularly commercial insurance, and could result in higher premiums for all beneficiaries. Clinical practice guidelines provide strong recommendations that patients with chronic low back pain should initially use nonpharmacologic therapies such as exercise, rehabilitation, and cognitive behavioral therapy and then carefully selected pharmacologic treatment.[38] Treatment of concurrent conditions, such as anxiety and depression, is also essential to effective pain treatment. A recent investigation by the US Department of Health and Human Services Office of Inspector General found that Medicare had overpaid by more than $600 million for neurostimulator implantation procedures, primarily because other treatments had not been trialed and a multidisciplinary approach to pain management had not been used.[39]

Limitations

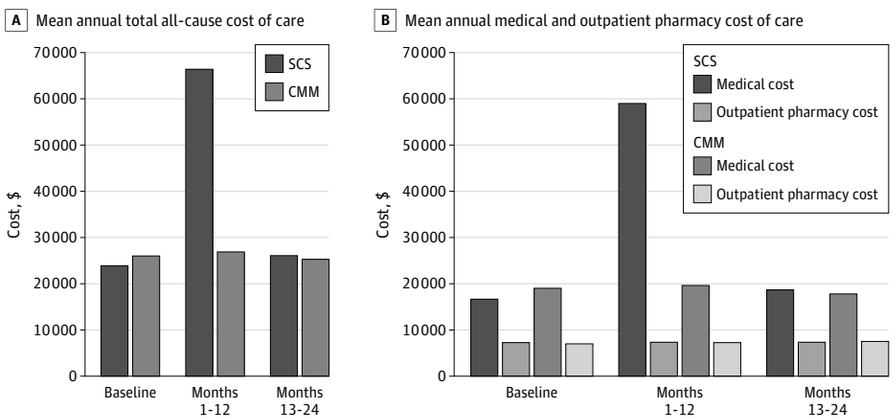
Our findings should be considered in the context of study limitations. First, as with any observational study, results could be subject to residual confounding; patients receiving SCSs were a small group overall and may differ in unmeasured ways from patients who did not receive SCS. However, we used 65 variables for propensity matching. Although we were unable to account for pain scores within the matching process, we did include both pharmacologic and nonpharmacologic treatments that are strong surrogates for pain, with small standardized mean differences indicating a robust match, including by underlying pain diagnosis. Observational studies will be the sole source of long-term comparative data because SCS are widely available, and the FDA has not required new clinical trials for SCS approvals. Second, there is a movement toward ascertaining more holistic outcomes as a composite of multiple factors to evaluate success of SCS.[40] Although these outcomes could

Table 3. Propensity Score–Matched Generalized Estimating Equation Model for Clinical Outcomes Within 24 Months After Permanent Spinal Cord Stimulator Placement vs Conventional Medical Management

Outcome	Follow-up, mo	Odds ratio (95% CI)
Chronic opioid use	1-12	1.14 (1.01-1.29)
	13-24	1.06 (0.94-1.20)
Long-acting opioid use	1-12	1.28 (1.11-1.49)
	13-24	1.16 (0.99-1.36)
High MME	1-12	1.81 (1.60-2.04)
	13-24	1.04 (0.92-1.18)
Epidural and facet corticosteroid injections	1-12	0.44 (0.39-0.51)
	13-24	1.00 (0.87-1.14)
Radiofrequency ablation	1-12	0.57 (0.44-0.72)
	13-24	0.84 (0.66-1.09)
Advanced imaging	1-12	0.84 (0.74-0.96)
	13-24	0.97 (0.85-1.11)
Spine surgery	1-12	0.72 (0.61-0.85)
	13-24	0.91 (0.75-1.09)
NSAIDs	1-12	0.95 (0.83-1.07)
	13-24	0.99 (0.87-1.13)
Muscle relaxants	1-12	1.13 (0.99-1.28)
	13-24	1.03 (0.91-1.17)
Systemic steroids	1-12	0.94 (0.83-1.07)
	13-24	1.09 (0.97-1.24)
TCA/SNRI antidepressants	1-12	1.05 (0.92-1.20)
	13-24	1.16 (1.02-1.32)
Gabapentinoids	1-12	1.06 (0.94-1.20)
	13-24	1.22 (1.08-1.37)
Benzodiazepines	1-12	1.01 (0.88-1.14)
	13-24	0.87 (0.76-1.00)

Abbreviations: MME, morphine milligram equivalents; NSAID, nonsteroidal anti-inflammatory drug; SNRI, serotonin and norepinephrine reuptake inhibitor; TCA, tricyclic antidepressant.

Figure. Costs of Care Among Propensity-Matched Patients Treated With Spinal Cord Stimulators (SCSs) vs Conventional Medical Management (CMM)



A, Mean annual total all-cause cost of care. B, Mean annual medical and outpatient pharmacy cost of care.

Table 4. Spinal Cord Stimulator (SCS)–Related Complications and Revisions or Removals Among 1260 Patients Within 24 Months After Permanent Device Implantation

Complications/revisions or removals	No. of months after SCS placement	No. (%)
Complications		
Breakdown of lead/generator	1-12	56 (4.4)
	13-24	16 (1.3)
Displacement of lead/generator	1-12	22 (1.8)
	13-24	NA (NA)[a]
Infection/inflammation of lead/generator	1-12	26 (2.1)
	13-24	NA (NA)
Other mechanical complications of lead/generator	1-12	117 (9.3)
	13-24	51 (4.1)
Any complication of lead/generator	1-12	176 (14.0)
	1-24	226 (17.9)
Revision or removals		
Revision of lead/generator	1-12	184 (14.6)
	13-24	75 (6.0)
Lead removal	1-12	95 (7.5)
	13-24	50 (4.0)
Generator removal	1-12	23 (1.8)
	13-24	NA (NA)
Any removal/revision of lead/generator	1-12	217 (17.2)
	1-24	279 (22.1)

Abbreviation: NA, not applicable.

[a] Small numbers (n <11) cannot be reported according to the Optum Labs cell size suppression policy.

not be evaluated using our data source, prospective studies should evaluate the benefits of SCS on holistic outcomes.[40] Third, it is possible that patients with chronic pain could have received benefit from SCS but required medications and procedures for other areas of pain. Fourth, our data set did not include functional measures such as quality of life or ability to return to work, nor the impact of measured complications on patients. However, ascertainment of these outcomes is only possible for prospective studies that have dedicated mechanisms to ascertain these data. Fifth, our study population did not include individuals with Medicare fee-for-service or Medicaid insurance. Sixth, chronic pain is a diagnosis that often lasts longer than the 6-month clean period that we used and some patients were excluded because of insufficient longitudinal data, which may limit study generalizability; however, characteristics between included and excluded patients were not clinically different.

Conclusions

In conclusion, results of this large comparative effectiveness research study examining SCSs compared with CMM for chronic pain suggest a lack of clinical benefit for most patients and possible harm to some. There may be opportunities to redeploy the high—and increasing—use and spending associated with SCS toward more evidence-based interventions for chronic pain relief.

Author Contributions: Dr Ameli and Ms Morin had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Dhruva, Murillo, Ameli, Spencer, Redberg, Cohen.
Acquisition, analysis, or interpretation of data: Dhruva, Murillo, Ameli, Morin, Spencer, Cohen.
Drafting of the manuscript: All authors.
Critical revision of the manuscript for important intellectual content: Murillo, Ameli, Spencer, Redberg, Cohen.
Statistical analysis: Ameli, Morin.
Obtained funding: Redberg.
Administrative, technical, or material support: Spencer, Redberg.
Supervision: Murillo, Ameli, Spencer, Redberg, Cohen.

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JAMA Neurology | Original Investigation

Autoimmune Encephalitis Misdiagnosis in Adults

Eoin P. Flanagan, MD; Michael D. Geschwind, MD, PhD; A. Sebastian Lopez-Chiriboga, MD; Kyle M. Blackburn, MD; Sanchit Turaga, MD; Sophie Binks, MD; Jennifer Zitser, MD; Jeffrey M. Gelfand, MD; Gregory S. Day, MD; S. Richard Dunham, MD; Stefanie J. Rodenbeck, MD; Stacey L. Clardy, MD, PhD; Andrew J. Solomon, MD; Sean J. Pittock, MD; Andrew McKeon, MD; Divyanshu Dubey, MD; Anastasia Zekeridou, MD, PhD; Michel Toledano, MD; Lindsey E. Turner; Steven Vernino, MD, PhD; Sarosh R. Irani, MD, DPhil

IMPORTANCE Autoimmune encephalitis misdiagnosis can lead to harm.

OBJECTIVE To determine the diseases misdiagnosed as autoimmune encephalitis and potential reasons for misdiagnosis.

DESIGN, SETTING, AND PARTICIPANTS This retrospective multicenter study took place from January 1, 2014, to December 31, 2020, at autoimmune encephalitis subspecialty outpatient clinics including Mayo Clinic (n = 44), University of Oxford (n = 18), University of Texas Southwestern (n = 18), University of California, San Francisco (n = 17), Washington University in St Louis (n = 6), and University of Utah (n = 4). Inclusion criteria were adults (age ≥18 years) with a prior autoimmune encephalitis diagnosis at a participating center or other medical facility and a subsequent alternative diagnosis at a participating center. A total of 393 patients were referred with an autoimmune encephalitis diagnosis, and of those, 286 patients with true autoimmune encephalitis were excluded.

MAIN OUTCOMES AND MEASURES Data were collected on clinical features, investigations, fulfillment of autoimmune encephalitis criteria, alternative diagnoses, potential contributors to misdiagnosis, and immunotherapy adverse reactions.

RESULTS A total of 107 patients were misdiagnosed with autoimmune encephalitis, and 77 (72%) did not fulfill diagnostic criteria for autoimmune encephalitis. The median (IQR) age was 48 (35.5-60.5) years and 65 (61%) were female. Correct diagnoses included functional neurologic disorder (27 [25%]), neurodegenerative disease (22 [20.5%]), primary psychiatric disease (19 [18%]), cognitive deficits from comorbidities (11 [10%]), cerebral neoplasm (10 [9.5%]), and other (18 [17%]). Onset was acute/subacute in 56 (52%) or insidious (>3 months) in 51 (48%). Magnetic resonance imaging of the brain was suggestive of encephalitis in 19 of 104 patients (18%) and cerebrospinal fluid (CSF) pleocytosis occurred in 16 of 84 patients (19%). Thyroid peroxidase antibodies were elevated in 24 of 62 patients (39%). Positive neural autoantibodies were more frequent in serum than CSF (48 of 105 [46%] vs 7 of 91 [8%]) and included 1 or more of GAD65 (n = 14), voltage-gated potassium channel complex (LGI1 and CASPR2 negative) (n = 10), *N*-methyl-D-aspartate receptor by cell-based assay only (n = 10; 6 negative in CSF), and other (n = 18). Adverse reactions from immunotherapies occurred in 17 of 84 patients (20%). Potential contributors to misdiagnosis included overinterpretation of positive serum antibodies (53 [50%]), misinterpretation of functional/psychiatric, or nonspecific cognitive dysfunction as encephalopathy (41 [38%]).

CONCLUSIONS AND RELEVANCE When evaluating for autoimmune encephalitis, a broad differential diagnosis should be considered and misdiagnosis occurs in many settings including at specialized centers. In this study, red flags suggesting alternative diagnoses included an insidious onset, positive nonspecific serum antibody, and failure to fulfill autoimmune encephalitis diagnostic criteria. Autoimmune encephalitis misdiagnosis leads to morbidity from unnecessary immunotherapies and delayed treatment of the correct diagnosis.

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Eoin P. Flanagan, MD, Mayo Clinic College of Medicine, Rochester, MN 55905.

Autoimmune encephalitis is increasingly a diagnostic consideration in patients with subacute onset of memory loss, altered mental status, and/or psychiatric symptoms—core features of proposed diagnostic criteria.[1] Detection of autoimmune encephalitis is increasing over time with new neural autoantibody biomarker discovery and greater awareness among clinicians, although the diagnosis remains rare overall.[2] Diagnostic mimics of autoimmune encephalitis are far more prevalent than autoimmune encephalitis, including toxic/metabolic encephalopathies, functional neurological disorders, primary psychiatric disease, neurodegenerative disorders, neoplasms, and epilepsy.[2,3] Although discovery of novel antineuronal and antiglial autoantibodies has improved diagnostic sensitivity for autoimmune encephalitis, specificity varies by antibody type, test methodology, and pretest probability.[4] Thus, there is a potential for false-positive autoantibody results in patients with diseases other than autoimmune encephalitis, which can contribute to misdiagnosis.[5-7] In much of the autoimmune encephalitis literature, there is emphasis on patients in whom the diagnosis of autoimmune encephalitis was initially erroneously overlooked. Yet, there are limited data concerning patients initially incorrectly diagnosed with autoimmune encephalitis and their subsequent correct diagnosis. This is an important topic given the risk of patient harm associated with misdiagnosis, including morbidity from adverse effects of immunotherapies and delay of appropriate treatment.[8] We report data from an international multicenter study of autoimmune encephalitis misdiagnosis across 6 subspecialty centers to analyze patients misdiagnosed with autoimmune encephalitis and identify possible contributors to misdiagnosis.

Key Points

Question What diseases are misdiagnosed as autoimmune encephalitis and which factors contribute to misdiagnosis?

Findings In this case series of 107 outpatients misdiagnosed with autoimmune encephalitis, approximately half had functional neurologic or psychiatric disorders. An insidious rather than subacute onset and lack of magnetic resonance imaging or cerebrospinal fluid findings suggestive of inflammation were clues to misdiagnosis; overinterpretation of serum nonspecific antibodies was a major contributor to misdiagnosis.

Meaning A broad range of disorders are misdiagnosed as autoimmune encephalitis and misdiagnosis occurs in many settings including at specialized centers participating in this study.

Methods

The Mayo Clinic institutional review board approved this multicenter study (#19-004926), and institutional review board approval also occurred at each respective site with all patients either providing written consent or patients included under an institutional review board approved consent waiver for minimal risk retrospective studies. This study was a retrospective multicenter observational study that followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for reporting observational studies.

Inclusion Criteria

Inclusion criteria were adult patients (18 years or older) at the time of neurologic evaluation at a participating site with (1) a prior autoimmune encephalitis diagnosis assigned at another medical center or at the participating site and occurring in the inpatient or outpatient setting and (2) a subsequent alternative diagnosis made at an in-person visit at one of the participating outpatient autoimmune neurology clinics. Alternative diagnoses were defined as a definite alternative diagnosis when diagnostic testing confirmed the diagnosis (eg, brain biopsy revealing tumor) or as a clinical alternative diagnosis when definitive confirmation (eg, biopsy) was not available or it was a purely clinical diagnosis (eg, primary psychiatric disease).

Patient Identification at Participating Centers and Frequency of Misdiagnosis vs Actual Autoimmune Encephalitis Diagnosis

Six academic medical centers with subspecialty expertise in autoimmune neurology participated. These included Mayo Clinic in Rochester, Minnesota (autoimmune neurology clinic); University of Oxford in Oxford, United Kingdom (autoimmune neurology clinic); University of Texas Southwestern in Dallas (autoimmune neurology clinic); University of California, San Francisco in San Francisco (Department of Neurology Multiple Sclerosis/Neuroinflammation clinic, the Memory and Aging Center clinic or through the Memory and Aging Center rapidly progressive dementia research program); Washington University in St Louis, Missouri (rapidly progressive dementia/autoimmune encephalitis clinic); and University of Utah in Salt Lake City (autoimmune neurology clinic). Patients evaluated clinically between January 1, 2014, to December 31, 2020, were considered for study enrollment. Data on 2 patients included in the study were previously published in case reports.[9,10] At the University of California San Fransisco, only patients who received immunotherapy for their presumed autoimmune encephalitis diagnosis were included. Details on numbers of true autoimmune encephalitis over the same study time frame, when available, were also collected to assess its frequency.

Data Collection

Participating centers provided deidentified data detailing age, sex, clinical, and paraclinical variables from patients misdiagnosed with autoimmune encephalitis. Data on race and ethnicity were not collected. Data on the requirements for part 1 and part 2 of the diagnostic criteria for possible autoimmune encephalitis (a requirement for diagnosis of any autoimmune encephalitis category) were also specifically collected and include[1] (1) subacute onset (rapid progression of <3 months) of working memory deficits (short-term memory loss), altered mental status, or psychiatric symptoms and (2) at least one of the following: new focal central nervous system findings, seizures not explained by a previously known seizure

disorder, cerebrospinal fluid (CSF) pleocytosis (white blood cell count of >5 cells/mm^3), or magnetic resonance imaging (MRI) brain features of encephalitis with either hyperintense signal on T2-weighted fluid-attenuated inversion recovery sequences highly restricted to 1 or both medial temporal lobes (limbic encephalitis) or in multifocal areas involving gray matter, white matter, or both compatible with demyelination or inflammation.

Failure to fulfill both part 1 and 2 of the criteria precludes a diagnosis of any category of autoimmune encephalitis. Part 3 of the autoimmune encephalitis diagnostic criteria was not analyzed as this component specifies reasonable exclusion of alternative diagnoses, which by design of the present study would be difficult to quantify retrospectively.

Data collected included age at symptom onset, sex, and time from disease onset to correct diagnosis, insidious (symptoms developing over ≥3 months) vs subacute (<3 months) onset, cancer history, thyroid autoimmunity, or other autoimmune disorders. Results of neuropsychological testing were classified as normal (for age and education) or abnormal. We collected data on elevated IgG index, CSF-restricted oligoclonal bands, electroencephalogram (categorized as normal, showing epileptiform activity [clinical or subclinical seizures, spikes, or sharp waves], slowing or other findings), thyroid peroxidase antibodies, other serologic evidence of systemic autoimmunity, and serum and CSF anti-neural or glial antibodies (including information on titer and assay type when available). Brain biopsy or autopsy details were obtained when applicable. Information on immunotherapies and adverse reactions were also collected.

Participating sites selected from the following potential reasons for misdiagnosis in each patient: (1) overinterpretation of a nonspecific positive antibody; (2) failure to accept an alternative psychiatric diagnosis; (3) misclassification of functional neurologic symptoms as true neurologic abnormalities; (4) overinterpretation of nonspecific cognitive symptoms as encephalitis; or (5) other. There was also a free text section for additional reasons for misdiagnosis.

Statistical Analysis

Descriptive statistics were used. For categorical variables, frequency and percent were used, whereas for continuous variables, median and range or interquartile range were used. JMP Pro, version 14.1.0 (JMP Statistical Discovery LLC) was used.

Results

Demographics and Clinical Characteristics

We included 107 patients misdiagnosed as having autoimmune encephalitis at the 6 participating centers. The median (IQR) age at symptom onset was 48 (35.5-60.5) years and 65 (61%) were female. The median (IQR) time from onset to the correct diagnosis was 16 (7-40) months. A history of any type of autoimmune disease was noted in 44 individuals (41%), of whom 34 (77%) had thyroid autoimmunity. Six patients (6%) had a history of cancer outside of the nervous system. Symptom onset was insidious in 51 of 107 patients (48%), although some had superimposed subacute worsening.

Frequency of Misdiagnosis Compared With Confirmed Diagnoses of Autoimmune Encephalitis

Autoimmune encephalitis misdiagnosis occurred in 107 individuals during a period over which 286 were correctly diagnosed as having autoimmune encephalitis. This included Mayo Clinic (misdiagnosis, 44; true diagnosis, 100); University of Oxford (misdiagnosis, 18; true diagnosis, 125); University of Texas Southwestern (misdiagnosis, 18; true diagnosis, 19); University of California, San Francisco (misdiagnosis, 17; true diagnosis, not available); Washington University in St Louis (misdiagnosis, 6; true diagnosis, 42); and University of Utah (misdiagnosis, 4; true diagnosis, not available).

Disorders Misdiagnosed as Autoimmune Encephalitis

Alternative diagnoses are detailed in **Table 1**, with imaging examples in the **Figure**. Of 107 patients, 17 (16%) had a definite alternative diagnosis confirmed on biopsy (astrocytoma, 6; lymphoma, 2; medulloblastoma, 1; neuronal intranuclear inclusion disease, 1), autopsy (Creutzfeldt-Jakob disease, 1; Alzheimer disease, 1), with genetic testing (mitochondrial encephalomyopathy lactic acidosis and strokelike episodes, 2; behavioral variant frontotemporal dementia with genetic confirmation of a valosin containing protein variant, 1), infectious testing (HIV positive, 1) and other laboratory testing (thiamine deficiency, 1). The remaining 90 alternative clinical diagnoses were often supported by laboratory testing and imaging and are demonstrated by the cases highlighted in Figure E and F.

Fulfillment of Diagnostic Criteria for Possible Autoimmune Encephalitis

Those fulfilling part 1 of the criteria had 1 or more of a clinical presentation of a subacute onset (rapid progression of <3 months) with 1 or more of working memory deficits (short-term memory loss) (36 [34%]), altered mental status (43 [40%]), or psychiatric symptoms (42 [39%]).

Those fulfilling part 2 of the criteria had 1 or more of the following: (1) focal central nervous system findings in 31 patients (29%); (2) seizures not explained by a previously known seizure disorder in 26 patients (24%); (3) CSF pleocytosis in 16 of 84 patients (19%); or (4) MRI brain features suggestive of encephalitis in 19 of 104 patients (18%) with either features of limbic encephalitis in 10 (Figure A) or multifocal abnormalities compatible with demyelination or inflammation in 9 (Figure B-D).

In total, 77 patients (72%) did not fulfill autoimmune encephalitis diagnostic criteria as they lacked requirements for possible autoimmune encephalitis diagnosis, which is a prerequisite for any other autoimmune encephalitis diagnostic category.

Antibody Testing

Thyroid peroxidase antibodies were positive in 24 of 62 individuals (39%). Nineteen patients had coexisting serologic evidence of systemic autoimmunity with antinuclear antibody

Table 1. Alternative Final Diagnoses in Those Initially Misdiagnosed as Autoimmune Encephalitis

Alternative diagnosis	No. (%)	
	Individuals with initial diagnosis (n = 107)	Individuals who fulfilled possible autoimmune encephalitis criteria (n = 30)
Functional neurologic disorder	27 (25)	6 (22)
Neurodegenerative dementia	22 (20.5)	5 (23)
Alzheimer disease[a]	6	0
Dementia with Lewy bodies[b]	4	1
Behavioral variant frontotemporal dementia	4	2
Creutzfeldt-Jakob disease	2	1
Vascular cognitive impairment	1	0
Other[c]	5	1[c]
Psychiatric disease	19 (18)	2 (11)
Depression[d]	7	2
Anxiety	3	0
Schizophrenia	2	0
Bipolar	2	0
Other[e]	5	0
Nonspecific cognitive syndrome in the setting of ≥1 of fibromyalgia, chronic fatigue, sleep disorder, medication adverse reaction, or other comorbidity[f]	11 (10)	1 (9)[f]
Neoplasm	10 (9.5)	7 (70)
Glioma (glioblastoma, astrocytoma, or not otherwise specified)[g]	7	5
Primary central nervous system lymphoma	2	2
Cerebellar medulloblastoma with cerebellar cognitive syndrome	1	0
Seizure disorder, nonimmune-mediated[h]	5 (4.5)	3 (60)
Infectious	3 (2.5)	1 (33)
Residua of prior viral encephalitis	2	1
HIV leukoencephalopathy	1	0
Mitochondrial encephalomyopathy lactic acidosis and strokelike episodes	2 (2)	1 (50)
Other metabolic	2 (2)	1 (50)
Adrenal insufficiency	1	0
Wernicke encephalopathy	1	1
Other	6 (6)	3 (50)
Small vessel vasculitis	2	0
Klein Levin syndrome	1	0
Nonimmunotherapy responsive progressive cerebellar degeneration with cerebellar cognitive syndrome	1	1
Multiple sclerosis and depression	1	1
Nonimmune encephalopathy without further classification	1	1

[a] One individual had coexisting vascular cognitive impairment; 1 patient with prior typical anti-LGI1 encephalitis developed an insidious dementia in follow-up that was suspected to be recurrent autoimmune encephalitis, but repeat LGI1 antibodies testing results were negative (and thus we categorized as antibody negative for this study), and the patient did not respond to immunotherapy and autopsy later confirmed Alzheimer disease as the cause of the insidious dementia.

[b] Two individuals were suspected to have comorbid Alzheimer disease.

[c] Progressive supranuclear palsy, 1; neuronal intranuclear inclusion disease, 1 (this patient fulfilled criteria for possible autoimmune encephalitis); primary lateral sclerosis with cognitive impairment, 1; amnestic mild cognitive impairment, 1; neurodegenerative unclassifiable, 1.

[d] Two individuals had psychosis, one of which also had catatonia.

[e] Depression and anxiety in combination, 1; developmental delay with regression, 1; psychiatric disease without classification, 3.

[f] Other contributors included migraine headaches, insomnia, and psychiatric comorbidity; in this category, there were often multiple combinations of these factors contributing.

[g] In 1 patient, biopsy confirmation was not available.

[h] One from multiple cavernous malformations.

positivity most common. Neural autoantibodies were identified more often in serum (48 of 105 [46%]) than CSF (7 of 91 [8%]) and are outlined in **Table 2**.

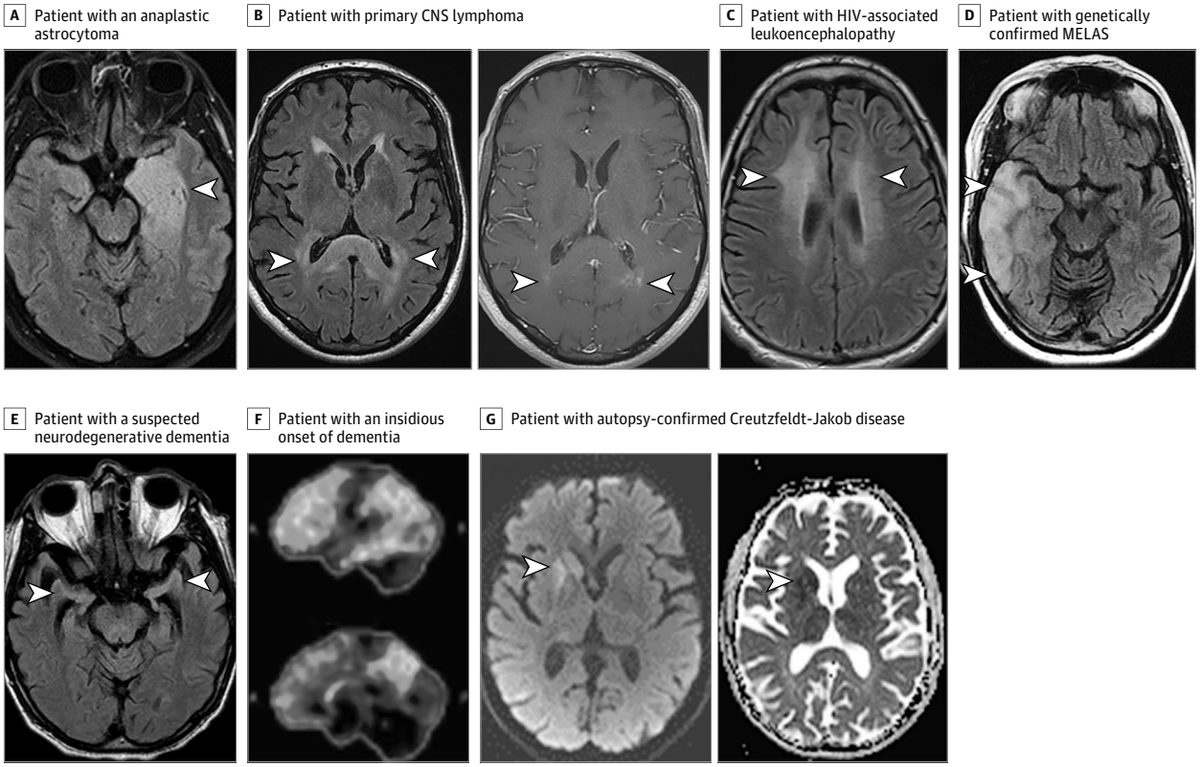
Additional Investigations

Neuropsychological test results were abnormal in 38 of 54 patients (70%). Electroencephalogram findings were abnormal in 31 of 79 (39%) and revealed epileptiform abnormalities in 16 and slowing in 9; details of abnormalities were not available in 6 patients. CSF-restricted oligoclonal bandings or IgG index positivity occurred in 7 of 82 (9%) tested.

Additional Clinical Details on Patients With a CSF Antibody

The 4 patients with *N*-methyl-D-aspartate receptor (NMDAR) antibodies in the CSF without evidence on mouse tissue-based indirect immunofluorescence had HIV-associated leukoencephalopathy (Figure C), pathologically confirmed anaplastic astrocytoma, functional neurologic disorder, and behavioral variant frontotemporal dementia, respectively. In all 4 patients, NMDAR antibodies were also detected in serum. One patient with an unclassified CSF antibody on immunohistochemistry had a progressively enlarging brain mass without immunotherapy response with imaging con-

Figure. Imaging Examples of Patients Who Were Initially Thought to Have Autoimmune Encephalitis but Later Had an Alternative Diagnosis Made



A T2-weighted axial fluid-attenuated inversion recovery (T2-FLAIR) image reveals a left mesial temporal lobe T2-hyperintensity and swelling (A, arrowhead) in a patient with an anaplastic astrocytoma. Note in retrospect the fullness/enlargement of the affected region, possibly suggesting some mass effect. Axial T2-FLAIR image reveals bilateral splenium T2-hyperintensity (B, left panel, arrowheads) with multifocal punctate enhancement (B, right panel, arrowheads) in a patient with primary central nervous system (CNS) lymphoma. An axial T2-FLAIR image reveals bilateral confluent T2-hyperintensity in the subcortical white matter (C, arrowheads) in a patient with HIV-associated leukoencephalopathy. Axial T2-FLAIR image reveals right temporal cortical swelling and T2-hyperintensity (D, arrowheads) in a patient with genetically confirmed mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS). An axial T2-FLAIR image shows disproportionate bilateral hippocampal atrophy (E, arrowheads) in a patient with a suspected neurodegenerative dementia with features potentially consistent with mixed Alzheimer disease and dementia with Lewy bodies. ^{18}F-Fluorodeoxyglucose positron emission tomography reveals reduced uptake of glucose (normal, dark blue/black; mildly reduced, green; moderately reduced, yellow; severely reduced, red) in the frontotemporoparietal region, precuneus and posterior cingulate (F) most suspicious for underlying Alzheimer disease in a patient with an insidious onset of dementia and elevated cerebrospinal fluid phospho-Tau and low cerebrospinal fluid amyloid-β 42 also suggestive of this diagnosis. Axial diffusion weighted hyperintensity (G, left panel) and apparent diffusion coefficient hypointensity (G, right panel) consistent with restricted diffusion in the right caudate and putamen in a patient in whom autopsy later confirmed Creutzfeldt-Jakob disease.

sistent with glioma (final pathology was not available). One patient with CSF GAD65 antibodies (titer, 3.01 nmol/L; normal, ≤0.02 nmol/L) had mixed vascular cognitive impairment and symptomatic Alzheimer disease (CSF biomarker confirmed). Finally, 1 patient with VGKC autoantibodies (LGI1 and CASPR2 negative) had cryptogenic epilepsy (not immune-related).

Treatment Details

One or more immunotherapies were used in 84 of 107 patients (79%) with treatment-related adverse reactions documented in 17 of 84 patients (20%) (**Table 3**).

Reasons for Misdiagnosis

The reasons for misdiagnosis included 1 or more of overinterpretation of a nonspecific positive antibody result (53 [50%]); misinterpretation of nonspecific symptoms as neurologic (19 [18%]); imaging findings felt to be consistent with autoimmune encephalitis (15 [14%]); functional neurologic features mistaken for true neurologic symptoms (14 [13%]); abnormal cerebrospinal fluid findings (9 [8%]); psychiatric manifestations thought to be from autoimmune encephalitis (8 [7%]); failure to accept a psychiatric diagnosis (5 [5%]); or subacute onset or fluctuating course (4 [4%]).

Discussion

This study highlights that misdiagnosis of autoimmune encephalitis is an important and frequent clinical problem. Autoimmune encephalitis misdiagnosis was identified at participating subspecialty outpatient clinics, but the initial incorrect autoimmune encephalitis diagnosis occurred at both outside facilities and participating centers. This shows that mis-

Table 2. Positive Neural Antibodies That Contributed to Misdiagnosis of Autoimmune Encephalitis

Positive neural antibody	No.[a]	Assay detection method	Quantitative results with median (range)[b]	Reference range[b]
Serum				
GAD65	14	RIA	0.10 (0.07-45.6) nmol/L[c]	≤0.02 nmol/L
Voltage-gated potassium-channel-complex (negative for LGI1 & CASPR2)	10	RIA	0.11 (0.07-1.03) nmol/L[c]	≤0.02 nmol/L
NMDAR[d]	10	CBA	High titer in 4; moderate titer in 1; low titer in 1; unavailable titer in 4	Negative
Ganglionic acetylcholine receptor	5	RIA	0.1 (0.05-0.12) nmol/L[e]	≤0.02 nmol/L
CASPR2[f]	2	CBA	Low titer in both	Negative
LGI1[f]	2	CBA	Low titer in both	Negative
Muscle acetylcholine receptor	2	RIA	0.27 and 0.44 nmol/L	≤0.02 nmol/L
Voltage-gated calcium channel (N type)	2	RIA	0.16 and 0.27 nmol/L	≤0.03 nmol/L
Striated muscle	2	ELISA	1:480	<1:240
Glycine receptor	1	CBA	NA	Negative
Amphiphysin[d]	1	WB	NA	Negative
Multiple positive neural antibodies in noncertified laboratory	1	Uncertain	NA	Negative
CSF				
NMDAR[d]	4	CBA	Low titer in 1; unavailable titer in 3	Negative
Voltage-gated potassium-channel-complex (Negative for LGI1, CASPR2)	1	RIA	Not available	≤0.02 nmol/L
GAD65	1	RIA	3.01 nmol/L	≤0.02 nmol/L
Unclassified neural antibody	1	TIFA	Not available	Negative

Abbreviations: CASPR2, contactin-associated protein-like 2; CBA, cell-based assay; CSF, cerebrospinal fluid; ELISA, enzyme-linked immunosorbent assay; GAD65, glutamic acid decarboxylase 65; LGI1, leucine-rich-glioma-inactivated-1; NA, not applicable; NMDAR, *N*-methyl-D-aspartate receptor; RIA, radioimmunoprecipitation assay; TIFA, tissue-based immunofluorescence assay; WB, western blot.

[a] As the exact details of what antibodies were tested in each patient were not always available, no denominator or percentage is given here and some patients had more than 1 antibody detected.

[b] For antibodies detected by RIA and ELISA, only values and reference ranges from the Mayo Clinic neuroimmunology laboratory were used; for CBA, the standard reference range of negative is similar across all laboratories, although for the quantitative result, some report a binary result of positive or negative and others quantify by low, moderate, or high positive, which were provided when available.

[c] Available in 5 individuals.

[d] Not evident on mouse tissue-based immunofluorescence assay.

[e] Available in 3 individuals.

[f] Both patients had final diagnoses of functional neurologic disorder.

diagnosis of autoimmune encephalitis can be encountered in multiple settings, including at autoimmune neurology subspeciality clinics with focused expertise. Many of these patients endured a delay to their correct diagnosis for longer than a year, and one-fifth experienced morbidity related to unnecessary immunotherapy. Overinterpretation of a nonspecific autoantibody was a frequent contributor to misdiagnosis. In 72% of patients, they did not fulfill autoimmune encephalitis diagnostic criteria, suggesting more stringent adherence to these criteria may prevent misdiagnoses. In particular, an insidious onset of symptoms and absence of MRI or CSF findings suggestive of neuroinflammation should raise suspicion for an alternative diagnosis. Yet, patients with LGI1 (the most common form of autoimmune encephalitis), CASPR2m and IgLON5 antibodies can present over long durations with minimal evidence of paraclinical investigation abnormalities, other than the autoantibody itself.[11-14]

Autoimmune encephalitis is a rare condition, with a cumulative incidence of approximately 3 to 9 per million person-years and common conditions accounted for a high proportion of cases mistaken for autoimmune encephalitis.[2,15,16] This is similar to recent data concerning multiple sclerosis misdiagnosis.[17] Functional neurologic disorders and psychiatric diseases are highly prevalent alternative diagnoses whose

Table 3. Treatments Used for Autoimmune Encephalitis and Associated Adverse Reactions

Type of treatment used	No. of patients who received ≥1 of each treatment (n = 84)	Types and frequency of documented adverse reactions[a]
Corticosteroids (intravenous, oral, or both)	78	Steroid-related psychosis or agitation, 5; mania, 1; depression, 1; gastritis, 1; avascular necrosis of the hip, 1; insomnia, 1; heart failure, 1; colonic fistula, 1; myopathy, 1
Intravenous immunoglobulin	30	Aseptic meningitis, 2; alopecia, 1; confusion, 1
Plasma exchange	16	NA
Mycophenolate mofetil	11	NA
Rituximab	10	Headache, 1
Azathioprine	2	Nausea, 1
Cyclophosphamide	2	NA
Methotrexate	1	NA
Adrenocorticotropic hormone	1	NA

Abbreviation: NA, not applicable.

[a] Given the details were obtained from medical record review at the time of misdiagnosis, this could underestimate the number of adverse reactions.

Box. Summary of Red Flags in Autoimmune Encephalitis Diagnosis

Clinical
- Insidious onset
- Multiple comorbidities that cause cognitive deficits such as polypharmacy, chronic pain, fibromyalgia, sleep disorders
- Examination results consistent with functional neurologic disorder
- Features of mitochondrial disease present
- Normal neuropsychological test results

Magnetic Resonance Imaging of the Head
- Normal
- Progressive atrophy without signal abnormalities or enhancement
- Lesion(s) continuing to expand despite immunotherapy

Cerebrospinal Fluid
- Noninflammatory[a]

Serology
- TPO antibodies of any titer
- Low titer–positive GAD65 antibodies
- Voltage-gated potassium channel complex antibodies negative for LGI1/CASPR2
- Low-titer antibody positives by older generation techniques (eg, RIA)
- Isolated serum NMDAR antibody negative in CSF
- Immunoblot or line blot antibody positivity in isolation
- Low titer positive–CASPR2 antibodies
- Antibody detection in noncertified laboratories

Abbreviations: CASPR2, contactin-associated protein-like 2; CSF, cerebrospinal fluid; GAD65, glutamic acid decarboxylase 65; LGI1, leucine-rich-glioma-inactivated-1; NMDAR, *N*-methyl-D-aspartate receptor; RIA, radioimmunoprecipitation assay; TPO, thyroid peroxidase.

[a] Normal white blood cell count and absence of CSF unique oligoclonal bands.

distinction from autoimmune encephalitis can be challenging.[18-21] Autoimmune encephalitis is increasingly considered in patients with psychiatric symptoms as it is potentially treatable with immunotherapy, but autoimmune encephalitis is much less common than primary psychiatric disease, for instance, accounting for less than 1% presenting with a typical first episode of psychosis.[22,23] Psychiatric disease combined with other contributors to cognitive deficits such as chronic pain, sleep disturbance, and medication adverse reactions also led to misdiagnosis. Such patients often had normal neuropsychological testing and did not fulfill autoimmune encephalitis diagnostic criteria due to absence of MRI and CSF findings suggesting classic neuroinflammation.

Neurodegenerative disorders accounted for 20% of misdiagnoses and the insidious onset and absence of neuroinflammation on testing help discriminate from autoimmune encephalitis. However, fluctuations in patients with Lewy body disease and rapid progression with overlapping MRI findings in Creutzfeldt-Jakob disease can make this distinction challenging.[24] Imaging and CSF analysis for amyloid and tau and CSF prion detection with real-time quaking-induced conversion are novel biomarkers that aid diagnosis of Alzheimer disease and Creutzfeldt-Jakob disease, respectively.[25,26]

We found 28% of patients fulfilled autoimmune encephalitis criteria and such patients usually had overlapping MRI or CSF findings with autoimmune encephalitis. Temporal lobe glioma may mimic autoimmune encephalitis; however, the absence of sustained response to immunotherapy, presence of mass effect on MRI (Figure, A) and lack of CSF inflammation may inform the correct diagnosis.[8] The multifocal MRI abnormalities, CSF pleocytosis, and steroid responsiveness of central nervous system lymphoma mimicked autoimmune encephalitis here and previously.[27] The subacute encephalopathy, cortical swelling, and signal abnormality on MRI with mitochondrial encephalomyopathy lactic acidosis and strokelike episodes mimicked autoimmune encephalitis similar to prior reports.[28] Seizure-related MRI signal abnormalities can overlap with autoimmune encephalitis MRI findings and lead to misdiagnosis.[29] Thiamine deficiency and HIV infection are important treatable mimics identified here and reported previously.[30,31] Taken together, the aforementioned cases pose a particular challenge given the paraclinical features in common with autoimmune encephalitis.

Overinterpretation of a nonspecific antibody was the largest potential contributor to autoimmune encephalitis misdiagnosis and a list of the more problematic antibodies are summarized in the **Box**. Thyroid peroxidase antibodies occur in 13% of people and 20% older than 60 years, which drastically diminishes their diagnostic utility in autoimmune encephalitis or Hashimoto encephalopathy and positive results often contribute to misdiagnosis.[5,32] With neural autoantibody biomarkers the diagnostic accuracy varies by pretest probability, sample assessed (serum or CSF), antibody type, assay methodology, and antibody titer.[6] As up to 5% of patients may harbor a positive neuronal antibody, clinically irrelevant results may be frequent if many patients are serologically assessed.[6,33] Indeed, in this study, some positives (eg, ganglionic acetylcholine receptor antibodies) were misinterpreted as being relevant despite autoimmune encephalitis not being the typical phenotype, suggesting that removing problematic antibodies with low specificity from autoimmune encephalitis autoantibody panels could reduce misdiagnosis.[34-37] Low-end titer serum GAD65 antibody positives were often overinterpreted as supporting autoimmune encephalitis but occur in 8% of the population (particularly individuals with diabetes) and typically only high titer (>10 000 IU/mL using enzyme-linked immunosorbent assay or >20 nmol/L using radioimmunoassay)[38,39] serum positives or CSF detection are neurologically relevant.[40-42] Laboratories offering serum GAD65 antibody testing for neurologic indications should consider using these higher cutoffs for neurologically relevant positivity. Voltage-gated potassium channel complex antibody positivity without LGI1 or CASPR2 reactivity are not useful for autoimmune encephalitis diagnosis,[43,44] while low-titer CASPR2 antibodies are also problematic and only high titers support autoimmune encephalitis.[45-47] Serum NMDAR antibodies with negative CSF results were a red flag here, as noted previously.[48] Rarely, CSF NMDAR antibodies by cell-based assay alone led to misdiagnosis. Despite its high specificity, these positive results in CSF

may relate to diffusion of high serum levels, rather than intrathecal synthesis. Detection using a second rodent tissue-based assay enhances CSF NMDAR antibody specificity further.[48] Antibodies detected by western blot/line blot or immunoblot in isolation often yield false positives and require cautious interpretation.[49,50] Moreover, detection of neural antibodies in noncertified laboratories require extreme caution. While this study focused only on autoimmune encephalitis, overinterpretation of nonspecific antibodies is also problematic in other neurologic syndromes in which antibodies are tested (eg, ataxia, myelopathy, stiff person syndrome, peripheral nervous system disorders). Increased education of neurologists on when to order neural autoantibodies and how to interpret positive results is needed to reduce the risk of misdiagnosis and interpretative comments provided by laboratories reporting results can be helpful in this regard.[4,51,52]

Autoimmune encephalitis misdiagnosis is problematic for multiple reasons. First, misdiagnosis of autoimmune encephalitis increases morbidity from failure to treat the actual diagnosis. Second, immunosuppressant treatments commonly have adverse reactions that may be serious, and in this study included infection, psychosis, avascular necrosis of the hip, and heart failure. Moreover, there are many less severe, yet common and bothersome, adverse reactions of corticosteroids including insomnia, weight gain and irritability, some of which may not have been captured in this analysis. Third, during the COVID-19 pandemic, immunotherapies may increase risk of severe COVID-19 infection and hinder vaccine and natural infection responses.[53,54] Finally, increased health care costs may arise from the use of expensive immunosuppressants or unnecessary evaluation for an underlying cancer prompted by nonspecific antibody detection.

Limitations

The retrospective design was a limitation and prospective studies are needed to assess autoimmune encephalitis misdiagnosis frequency and characteristics among new referrals to subspecialty clinics with presumed autoimmune encephalitis. Such studies could incorporate probable and definite categories of autoimmune encephalitis diagnostic criteria to better discriminate true autoimmune encephalitis from autoimmune encephalitis misdiagnosis.[1] The selection bias of analyzing autoimmune encephalitis misdiagnosis identified at subspecialty autoimmune neurology clinics could underestimate the rate of autoimmune encephalitis misdiagnosis and it may exceed true autoimmune encephalitis diagnosis in the general population. There are many potential contributors to underrepresentation of autoimmune encephalitis misdiagnosis including our requirement for an in-person visit as autoimmune encephalitis misdiagnosis can be identified in other settings (eg, video visit, electronic medical record review, other communication between physicians). Moreover, during triage for appointments, true autoimmune encephalitis may be favored over cases suspected to be misdiagnosed. Also, infectious mimics of autoimmune encephalitis are more likely to be encountered in hospitalized patients and our study focused on those identified at outpatient clinics.[55] Finally, differences in rates of autoimmune encephalitis misdiagnosis across centers likely reflect variation in referral patterns. Further studies are needed to better capture autoimmune encephalitis misdiagnosis rates across other settings.

Conclusions

In summary, neurologists should be aware of the potential for autoimmune encephalitis misdiagnosis and consider a broad differential diagnosis including common disorders when evaluating suspected cases. Improved recognition of the clinical, imaging, and serologic red flags in the evaluation of autoimmune encephalitis summarized in the Box may lessen the burden of misdiagnosis in the future.

ARTICLE INFORMATION

Author Affiliations: Laboratory Medicine and Pathology, Mayo Clinic College of Medicine, Rochester, Minnesota (Flanagan, Pittock, McKeon, Dubey, Zekeridou); Center for Multiple Sclerosis and Autoimmune Neurology, Department of Neurology, Mayo Clinic College of Medicine, Rochester, Minnesota (Flanagan, Pittock, McKeon, Dubey, Zekeridou, Toledano); Department of Neurology, University of California, San Francisco (UCSF), San Francisco (Geschwind, Zitser, Gelfand); Department of Neurology, Mayo Clinic, Jacksonville, Florida (Lopez-Chiriboga, Day); Department of Neurology, University of Texas Southwestern Medical Center, Dallas (Blackburn, Vernino); Autoimmune Neurology Group, West Wing, Level 3, John Radcliffe Hospital, University of Oxford, Oxford, United Kingdom (Turaga, Binks, Irani); Movement Disorders Unit, Department of Neurology, Tel Aviv Sourazky Medical Center, Affiliate of Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel (Zitser); Washington University in St Louis, St Louis, Missouri (Day, Dunham); Department of Neurology, University of Utah, Salt Lake City (Rodenbeck, Clardy); Larner College of Medicine at the University of Vermont, Burlington (Solomon); Graduate School of Health Sciences, Mayo Clinic College of Medicine, Rochester, Minnesota (Turner).

Author Contributions: Dr Flanagan had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. These authors contributed equally: Drs Geschwind, Irani, and Vernino.
Concept and design: Flanagan, Lopez Chiriboga, Blackburn, Gelfand.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Flanagan, Lopez Chiriboga, Rodenbeck, Solomon, Irani.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Flanagan.
Administrative, technical, or material support: Lopez Chiriboga, Blackburn, Binks, Zitser, Vernino, Irani.
Supervision: Flanagan, Geschwind, Vernino, Irani.

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Dr Lopez-Chiriboga has served on advisory boards for Genentech and Horizon Therapeutics. Dr Blackburn reported personal fees from Genentech, grants from Siegel Rare Neuroimmune Association outside the submitted work. Dr Binks reported grants from Wellcome Trust during the conduct of the study and had a patent for Ref. JA94536P.GBA pending (diagnostic strategy to improve specificity of CASPR2 antibody detection). Dr Gelfand reported grants from Genentech/Roche for research support to University of California, San Francisco for clinical trials; service on trial steering committees and grants from Vigil Neuroscience for research support to University of California, San Francisco for clinical research study; and personal fees from Biogen for consulting outside the submitted work. Dr Day reported grants from National Institute on Aging (grant K23AG064029) during the conduct of the study; personal fees from PeerView Media, Continuing Education, DynaMed, and Parabon Nanolabs outside the submitted work; is co–principal investigator of the ExTINGUISH Trial (1U01NS120901); owns stock (>$10 000) in ANI Pharmaceuticals; and is the clinical director of the Anti-NMDA Receptor Encephalitis Foundation (uncompensated). Dr Clardy reported being site investigator for an Alexion clinical trial; grants from National Institute of Neurological Disorders and Stroke for the ExTINGUISH Trial, Western Institute for Veteran Research, and Sumaira Foundation for NMO; research support from Siegel Rare Neuroimmune Association Funding and Barbara Gural Steinmetz Foundation Funding; personal fees from American Academy of Neurology (section editor, Neurology Podcast and Neurology Minute), from Alexion, VielaBio/Horizon, Genentech/Roche, Guidepoint, ExpertConnect, and Clarion Healthcare (majority fees to University of Utah); and funding from Viela Bio/Horizon and Alexion/AstraZeneca outside the submitted work. Dr Solomon reported research funding from Bristol Myers Squibb; consulting and nonpromotional speaking for EMD Serono; personal fees from Genentech, Biogen, Alexion, Celgene, Greenwich Bioscience, and Octave Biosciences; expert witness testimony for Jacob D. Fuchsberg Law Firm and Koskoff, Koskoff, and Bieder; served on advisory board of Genentech, Biogen, Alexion, Celgene, Greenwich Biosciences, and TG Therapeutics; and conducted contract research for Sanofi, Biogen, Novartis, Actelion, and Genetech outside the submitted work. Dr Pittock reported grants, personal fees, and nonfinancial support from Alexion and MedImmune/Viela Bio/Horizon (all compensation is paid directly to the Mayo Clinic); grants from the National Institutes of Health, Grifols, NovelMed, and F. Hoffmann-LaRoche/Roche/Genentech (all compensation is paid directly to Mayo Clinic); consulting for Astellas (compensation to Mayo Clinic and personal compensation); personal fees from Sage Therapeutics, UCB, and F. Hoffmann-LaRoche/Roche/Genentech; and had patent #8,889,102 issued, patent #9,891,219B2 issued, and a patent for GFAP-IgG; Septin-5-IgG; MAP1B-IgG; Kelch-like protein 11; PDE10A pending. 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Dr Vernino has served as a consultant for Alterity, Argenx, Catalyst, Genentech, and Sage Therapeutics and has received research support from Dysautonomia International, BioHaven, Grifols, and Quest Diagnostics (through a licensing contract). Dr Irani reported grants from UCB, CSL Behring, and ONO Pharmaceuticals outside the submitted work; had a patent for LGI1/Caspr2 antibodies with royalties paid from EIAG, a patent for Autoantibody diagnostics issued, and a patent for Relapse predictions pending; and honoraria/research support from UCB, Immunovant, MedImmun, Roche, Janssen, Cerebral therapeutics, ADC therapeutics, Brain, CSL Behring, and ONO Pharmaceuticals. No other disclosures were reported.

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JAMA Neurology | Original Investigation

Association of Stroke and Cerebrovascular Pathologies With Scam Susceptibility in Older Adults

Alifiya Kapasi, PhD; Julie A. Schneider, MD; Lei Yu, PhD; Melissa Lamar, PhD; David A. Bennett, MD; Patricia A. Boyle, PhD

IMPORTANCE Scam susceptibility is associated with adverse financial and health outcomes, including an increased risk of cognitive decline and dementia. Very little is known about the role of cerebrovascular pathologies with scam susceptibility.

OBJECTIVE To examine the association of diverse cerebrovascular pathologies (globally and regionally) with scam susceptibility.

DESIGN, SETTING, AND PARTICIPANTS This clinical-pathological cohort study included participants from 2 ongoing studies of aging that began enrollment in 1994 and 1997. In 2010, participants were enrolled in the decision-making and behavioral economics substudy and were followed up for a mean (SD) of 3.4 (2.6) years prior to death. From 1365 older persons with clinical evaluations, 69 were excluded for having dementia at baseline. From 538 older persons who died, 408 had annual assessments for scam susceptibility, cardiovascular risk burden, and cognitive function and consented to brain donation for detailed neuropathologic examination. Data were analyzed from June 2021 through September 2022.

EXPOSURES Neuropathologic examination identified the presence of macroscopic and microscopic infarcts, atherosclerosis, arteriolosclerosis, cerebral amyloid angiopathy, and common neurodegenerative pathologies (Alzheimer disease, limbic-predominant age-related transactive response DNA-binding protein 43 encephalopathy, and Lewy bodies).

RESULTS There was a total of 408 participants. The mean (SD) age at death was 91 (6.1) years, the mean (SD) amount of education was 15.6 (3.1) years, and 297 (73%) were women. Participants included 4 Latino individuals (1%), 7 non-Latino Black individuals (2%), and 397 non-Latino White individuals (97%). The frequency of participants with macroscopic infarcts was 38% (n = 154), microinfarcts was 40% (n = 163), and moderate to severe vessel disease; specifically, atherosclerosis was 20% (n = 83), arteriolosclerosis was 25% (n = 100), and cerebral amyloid angiopathy was 35% (n = 143). In linear regression models adjusted for demographics and neurodegenerative pathologies, macroscopic infarcts were associated with greater scam susceptibility (estimate [SE], 0.18 [0.07]; P = .009). This association persisted after adjusting for cardiovascular risk burden and global cognition. Regionally, infarcts localized to the frontal, temporal, and occipital lobes and thalamus were associated with greater scam susceptibility. Neither arteriosclerosis, atherosclerosis, cerebral amyloid angiopathy, nor microinfarcts were associated with scam susceptibility.

CONCLUSIONS AND RELEVANCE Cerebrovascular pathologies, specifically cerebral infarcts, is linked with greater scam susceptibility in older adults, independent of common neurodegenerative diseases such as Alzheimer disease. Future studies examining in vivo magnetic resonance imaging markers of cerebrovascular pathologies with scam susceptibility and related decision-making outcomes will be important.

Author Affiliations: Rush Alzheimer's Disease Center, Rush University Medical Center, Chicago, Illinois (Kapasi, Schneider, Yu, Lamar, Bennett, Boyle); Department of Pathology (Neuropathology), Rush University Medical Center, Chicago, Illinois (Kapasi, Schneider); Department of Neurological Sciences, Rush University Medical Center, Chicago, Illinois (Schneider, Yu, Bennett); Department of Psychiatry and Behavioral Sciences, Rush University Medical Center, Chicago, Illinois (Lamar, Boyle).

Corresponding Author: Alifiya Kapasi, PhD, Rush Alzheimer's Disease Center, Rush University Medical Center, Jelke Bldg, 1750 W Harrison St, Chicago, IL, 60612.

Each year, millions of individuals in the US devastatingly experience financial exploitations and fraud, with elderly individuals being at a disproportionate risk. Financial exploitation has a direct negative impact on an individual's financial independence, mental and physical well-being, self-esteem, and relationship with others.[1-4] For the older population, recovery from such financial losses can be almost impossible. The enormity of this public health crisis has been further exposed during the COVID-19 pandemic and economic fallout, with a dramatic rise in fraud attempts targeted toward vulnerable at-risk older individuals.[5] In 2020, the US Federal Trade Commission estimated that older adults lost $100 million to COVID-19–related fraud alone.[6] To raise public awareness, the US Senate Special Committee on Aging publishes an annual report on fighting fraud.[6] Further, to combat this problem, the US Department of Justice coordinates efforts to provide support to older individuals who experience fraud and enhance state and local justice efforts.[7]

From a public health perspective, understanding the factors and mechanisms associated with the risk of financial exploitation is of particular interest. Prior studies from our group have shown that susceptibility to scams and in general decision-making are complex behaviors that require multiple resources and that age-associated factors, including cognition,[8-10] psychosocial and contextual factors,[11,12] and personality,[13,14] are important correlates. Further, we show that even among individuals who are cognitively intact, subtle changes in cognition can increase susceptibility to scams.[10] There are very few studies, especially autopsy studies, examining the biological basis for susceptibility to financial exploitation in elderly individuals; however, despite increased awareness that aging increases our vulnerability to financial exploitation[3,15] and now widespread recognition that the aging brain is particularly vulnerable to accumulating Alzheimer disease (AD) pathologic changes and other neurodegenerative processes, such as transactive response DNA-binding protein 43 (TDP-43) and α-synuclein proteinopathies.[16-18]

In recent work, we showed that the accumulation of neurodegenerative pathology, specifically β-amyloid pathology, was associated with greater scam susceptibility, including among persons without dementia.[19] These findings support the notion that age-related changes in the aging brain may be associated with early behavioral changes. Strikingly, almost 90% of postmortem brains from persons older than 65 years harbor cerebrovascular pathologies, with more than 70% having mixed AD with cerebrovascular pathologies[17]; however, the role of vascular pathologies with scam susceptibility has yet to be studied.

In this study, we build on our prior work by examining the association of diverse cerebrovascular pathologies, including macroinfarcts and microinfarcts, atherosclerosis, arteriolosclerosis, and cerebral amyloid angiopathy (CAA) with scam susceptibility among older adults who underwent brain autopsy. Additionally, we further explored regional associations between cerebrovascular pathologies in cortical, subcortical, and watershed-specific brain regions.

Key Points

Question Are cerebrovascular pathologies associated with scam susceptibility in older adults?

Findings In this cohort study, older persons from the community with cerebral infarcts pathologically were found to have a higher susceptibility to scams during life, even after adjusting for common neurodegenerative pathologies and other cerebrovascular pathologies, vascular risk factors, and cognitive function.

Meaning Vascular brain health may play an important role in scam susceptibility.

Methods

Participants

Participants were from 1 of 2 ongoing clinical-pathologic studies of aging, the Religions Orders Study or the Rush Memory and Aging Project. Upon enrollment, which began in 1994 and 1997, participants consented to annual clinical evaluations and brain donation at the time of death. Data on race and ethnicity were collected by self-report. A decision-making substudy, which includes annual assessments scam susceptibility, was added to the Religions Orders Study and Rush Memory and Aging Project in 2010. Studies were approved by the Institutional Review Board of Rush University Medical Center. All participants signed an informed consent and an Anatomical Gift Act for brain donation.[20] Details of studies and inclusion of participants is included in eMethods 1 in the Supplement. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline was followed.

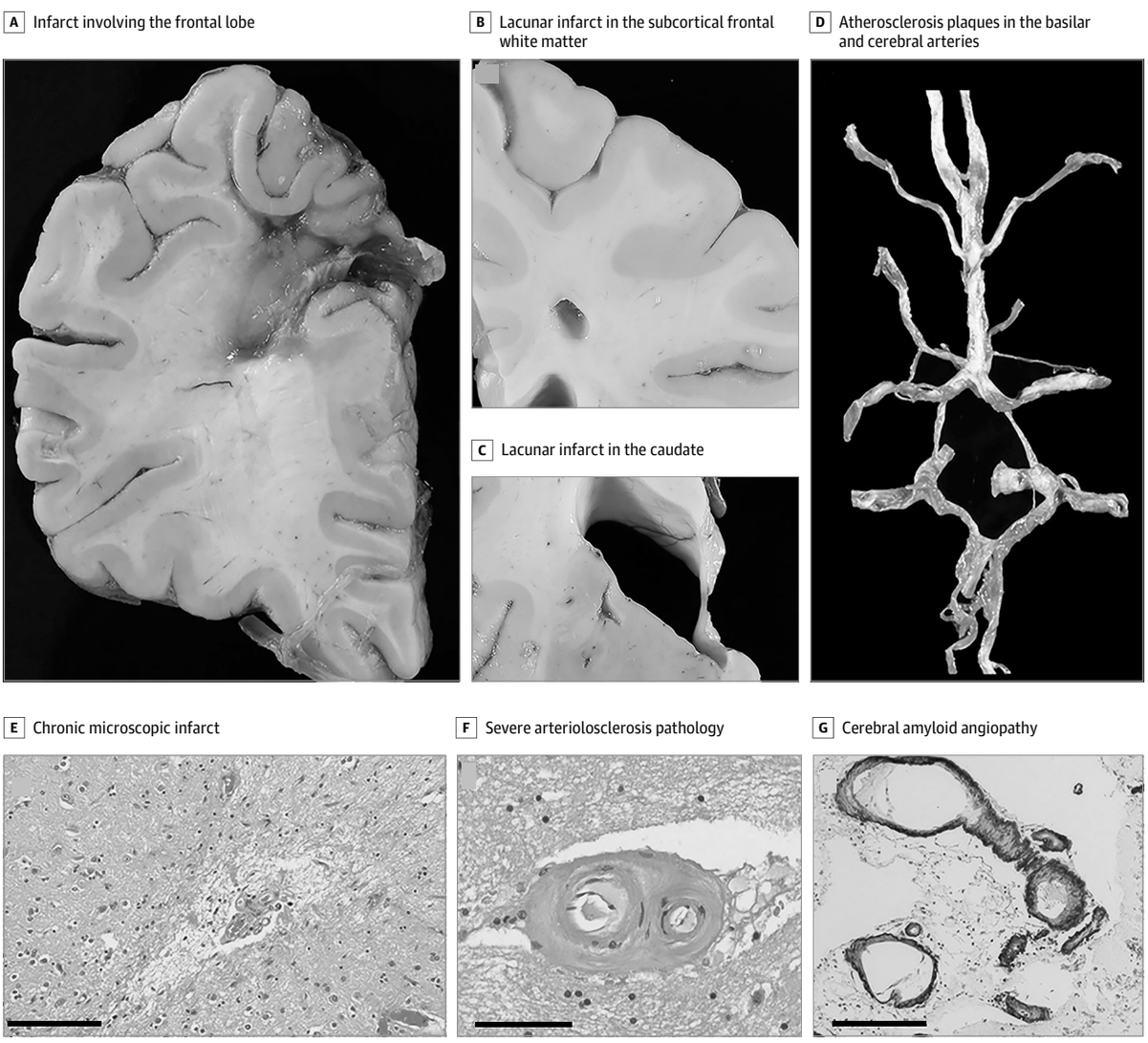
Scam Susceptibility

Participants rated statements that were carefully designed to assess behaviors associated with vulnerability to fraud and scams along a 7-point Likert-type scale ranging from strongly agree (1) to strongly disagree (7). Statements were developed based on findings from the AARP[4] and the Financial Industry Regulatory Authority risk meter,[21] regarding the behaviors commonly associated with exploitation. For example, one item asks participants if they feel like they need to answer the telephone even if they do not know who is calling, and another item asks participants if they usually listen when a telemarketer calls. Participants rated their level of agreement with each item and scam susceptibility was quantified as the mean rating across the 5 items, with higher scores indicating greater susceptibility. For analyses, the mean score for scam susceptibility was derived from all assessments over time (the mean number of visits was 4). Details of scam susceptibility validity is included in eMethods 2 and the eFigure in the Supplement.

Psychosocial Factors

Psychosocial factors include measures of psychological well-being,[14] depressive symptoms,[22] neuroticism, purpose in

Figure 1. Cerebrovascular Pathologies



Representative images showing a macroscopic infarct involving the frontal lobe (A), a lacunar infarct in the subcortical frontal white matter (B), a lacunar infarct in the caudate (C), atherosclerosis plaques in the basilar and associated cerebral arteries (D), a chronic microscopic infarct (E), severe arteriolosclerosis pathology (F), and cerebral amyloid angiopathy (G). Scale bar represents 200 µm (E), 50 µm (F), and 500 µm (G).

life,[23] anxiety, and extraversion.[24] Details included in eMethods 3 in the Supplement.

Global Cognitive Assessment

Scores from a battery of 19 neuropsychological tests were used to create summary indices of global cognitive function, which included assessment in 5 specific cognitive domains: episodic memory, semantic memory, working memory, perceptual speed, and visuospatial ability. Scores were *z*-transformed and averaged to obtain the summary scores for global cognitive function (all 19 tests) and for each individual domain, as previously described.[25,26] For analyses, last valid annual visit scores were used.

Cerebrovascular Pathology

Cerebral Infarcts

Location, age, and size of macroscopic infarcts[27-29] visible on gross examination were documented (**Figure 1**). Subsequently, the age of infarct was confirmed by microscopy and documented as acute, subacute, or chronic. Macroscopic infarcts were categorized into the following regional locations (regions are not mutually exclusive): frontal, temporal, parietal, occipital, basal ganglia, and thalamus. Cortical infarcts included those located in the cortical gray and typically the underlying white matter. Basal ganglia included infarcts in the caudate, putamen, globus pallidus, and internal capsule. Subcortical infarcts (present in subcortical gray or deep white

matter) were further categorized into lacunes (defined as ≤10 mm in size) and nonlacunes (defined as ≥11 mm in size). Microscopic infarcts were not visible to the naked eye and identified by microscopy. Microscopic infarcts were further categorized into watershed microinfarcts if present in watershed brain regions (midfrontal gyrus, anterior watershed, and posterior watershed). For analyses, only chronic infarcts were considered, and all infarct variables categorized into absent vs present.

Arteriolosclerosis

Small vessels in the basal ganglia, anterior watershed, and posterior watershed regions were evaluated on hematoxylin and eosin-stained sections.[30] For analyses, grading used a semiquantitative 4-level rating system (0 = none, 1 = mild, 2 = moderate, and 3 = severe) based on the histological changes of the small arterioles, including intimal deterioration, smooth muscle degeneration, and hyaline concentric thickening with narrowing of the vascular lumen.

CAA

Meningeal and parenchymal vessels from 4 neocortical regions (midfrontal, midtemporal, inferior parietal, and calcarine cortices) were semiquantitatively evaluated on sections immunostained with monoclonal antibodies against β-amyloid.[31]

Atherosclerosis

Large vessel atherosclerosis was semiquantitatively evaluated at the circle of Willis at the base of the brain and included evaluation of the vertebral, basilar, posterior, middle, and anterior cerebral arteries, and their proximal branches.[32] Visual examination included the number of atherosclerotic plaques, extent of vessel involvement, and the degree of vessel occlusion.

Neurodegenerative Pathologies

We quantified 4 neurodegenerative pathologies[28,33-36], including pathologic diagnostic assessment for AD, LATE-NC, dementia with Lewy body disease, and Parkinson disease (eMethods 4 in the Supplement).

Statistical Analyses

We first examined bivariate correlations of demographics, cognitive function, psychosocial factors, vascular risk burden, and neuropathologic characteristics with scam susceptibility. Primary analyses included a single multivariable linear regression model with terms for demographics (age at death, sex, and education) and common age-related neuropathologies (8 neuropathologic indices in total including AD pathology, Lewy bodies, limbic-predominant age-related TDP-43 encephalopathy [LATE-NC], macroscopic and microscopic infarcts, arteriolosclerosis, atherosclerosis, and CAA) to examine vascular pathologic associations with scam susceptibility. Sensitivity analyses included terms for the presence of vascular risk burden (which includes history of smoking, diabetes, and hypertension), global cognition, each individual cognitive domain, well-being, and neuroticism. In secondary analyses, linear regression models examined regional associations of macroscopic infarcts with scam susceptibility that included terms for demographics and AD pathology, as well as watershed microvascular pathology (ie, watershed arteriolosclerosis, watershed microinfarcts, and nonwatershed microinfarcts) with scam susceptibility that included terms for demographics, AD pathology, and macroscopic infarcts. Statistical significance for all analyses was determined at α level of 0.05. Analysis took place between June 2021 and September 2022.

Results

Characteristics of 408 participants are presented in **Table 1**. The mean (SD) age at death was 91 (6.1) years (range, 69.3-104.6 years), the mean (SD) level of education was 15.5 (3.1) years, and 297 (73%) were women. Participants included 4 Latino individuals (1%), 7 non-Latino Black individuals (2%), and 397 non-Latino White individuals (97%). Vascular risk factors were common, with 92 (23%) reporting a history of diabetes, 285 (70%) reporting hypertension, and 162 (40%) reporting being past or current smokers. Presence of cerebrovascular pathologies were common, with the most common vascular pathology being macroscopic and microscopic infarcts. Participants with macroscopic infarcts were more likely to have arteriolosclerosis (odds ratio [OR], 2.3; 95% CI, 1.6-3.4), microinfarcts (OR, 2.2; 95% CI, 1.5-3.4), and atherosclerosis pathology (OR, 3.4; 95% CI, 2.3-5.1).

Scam Susceptibility

Bivariate analyses revealed that older age but not education was correlated with greater scam susceptibility. Men and women did not differ in scam susceptibility. Lower cognitive scores in global cognition and in all 5 cognitive domains, as well as poorer well-being and higher neuroticism, was associated with greater scam susceptibility. Among the vascular risk burden, only smoking was correlated with higher scam. Presence of multiple neuropathologies, including macroscopic and microscopic infarcts, arteriolosclerosis, atherosclerosis, a pathologic diagnosis of AD, and LATE-NC (stage 2 or higher) was correlated with higher scam susceptibility (Table 1).

Cerebrovascular Pathologies With Scam Susceptibility

Linear regression models were used to examine whether cerebrovascular pathologies were associated with scam susceptibility; all models adjusted for demographics and common neurodegenerative pathologies, including AD, TDP-43, and Lewy body pathology. We found that macroscopic infarcts were associated with greater scam susceptibility. There was a positive association between arteriolosclerosis pathology and scam susceptibility, but it was not significant (**Table 2**, model 1). By contrast, we did not find an association of scam susceptibility with other cerebrovascular pathologies, including microscopic infarcts, CAA, or atherosclerosis. In these analyses, AD pathology was associated with scam susceptibility (as previously reported; eTables 3 and 4 in the Supplement). To assess the robustness of the association, sensitivity analyses adjusted for overall vascular risk burden, global cognition (Table 2, models 2 and 3), and specific cognitive

Table 1. Demographics, Clinical, Psychosocial, and Neuropathologic Characteristics and Correlations With Scam Susceptibility

Factor	Mean (SD)	Correlation with scam susceptibility[a]	*P* value
Demographics			
Age at death, y	91.3 (6.1)	0.28	<.001
Men, No. (%)	111 (27)	-0.29	.77
Women, No. (%)	297 (73)		
Education	15.6 (3.1)	0.05	.27
Cognition			
Global cognition	-0.7 (1.0)	-0.35	<.001
Episodic memory	-0.6 (1.2)	-0.34	<.001
Semantic memory	-0.5 (1.1)	-0.35	<.001
Working memory	-0.5 (1.0)	-0.25	<.001
Visuospatial ability	-0.2 (1.0)	-0.28	<.001
Perceptual speed	-1.0 (0.9)	-0.37	<.001
Psychosocial factors			
Depression	1.6 (1.9)	-0.01	.78
Neuroticism	15.0 (6.5)	0.13	.01
Well-being	5.2 (0.6)	-0.25	<.001
Purpose	3.4 (0.5)	-0.06	.21
Anxiety	1.3 (1.5)	0.04	.42
Extraversion	15.7 (3.1)	0.01	.87
Vascular risk burden, No. (%)			
Diabetes	92 (23)	1.39	.17
Hypertension	285 (70)	-0.33	.74
Smoking	162 (40)	3.00	.003
Neuropathology, No. (%)			
Macroscopic infarcts	154 (38)	-2.79	.006
Microinfarcts	163 (40)	-2.03	.04
Arteriolosclerosis (basal ganglia)	100 (25)	-2.97	.003
CAA	143 (35)	-0.79	.43
Atherosclerosis	83 (20)	-2.41	.02
AD pathologic diagnosis	256 (63)	-3.65	.0003
LATE-NC (stage 2/3)	135 (33)	-3.05	.002
Lewy bodies	104 (25)	-1.82	.07

Abbreviations: AD, Alzheimer disease; CAA, cerebral amyloid angiopathy; LATE-NC, limbic-predominant age-related transactive response DNA-binding protein 43 encephalopathy.

[a] Correlations derived from Spearman or *t* tests.

Table 2. Association of Cerebrovascular Pathologies With Scam Susceptibility

	Scam susceptibility					
	Model 1[a]		Model 2[b]		Model 3[c]	
Variable	Estimate (SE)	*P* value	Estimate (SE)	*P* value	Estimate (SE)	*P* value
Macroscopic infarcts	0.18 (0.07)	.009	0.21 (0.07)	.004	0.16 (0.07)	.02
Arteriolosclerosis (basal ganglia)	0.07 (0.04)	.06	0.08 (0.04)	.05	0.07 (0.03)	.05
CAA	-0.04 (0.03)	.25	-0.05 (0.03)	.15	-0.04 (0.03)	.20
Microinfarcts	0.04 (0.07)	.52	0.04 (0.07)	.58	0.04 (0.06)	.52
Atherosclerosis	-0.003 (0.05)	.96	-0.002 (0.05)	.96	-0.03 (0.04)	.50
AD pathology	0.24 (0.06)	<.001	0.24 (0.06)	<.001	0.12 (0.06)	.06
TDP-43	0.04 (0.03)	.15	0.04 (0.03)	15	0.02 (0.02)	.52
Lewy bodies	0.10 (0.07)	.18	0.11 (0.07)	.15	0.04 (0.07)	.56

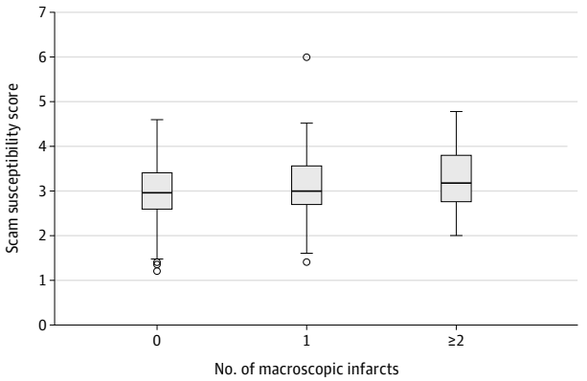
Abbreviations: AD, Alzheimer disease; CAA, cerebral amyloid angiopathy; TDP-43, transactive response DNA-binding protein 43.

[a] β Co-efficient estimates in each cell were obtained from a single linear regression model adjusted for age at death, sex, education, and all neuropathologic indices (11 terms in total).

[b] Regression model further adjusted for vascular risk factor burden (12 terms in total).

[c] Regression model further adjusted for global cognition (13 terms in total).

Figure 2. Scam Susceptibility Across None, Single, and Multiple Macroscopic Infarcts



domains, as well as well-being and neuroticism (eTable 2 in the Supplement). Notably, the associations between macroscopic infarcts with scam susceptibility remained unchanged.

Regional Macroinfarcts With Scam Susceptibility and Cognition

Among those that had macroscopic infarcts, 21% had a single infarct and 17% had multiple (≥2 infarcts). Those who had 2 or more infarcts had a higher scam susceptibility score (**Figure 2**). Macroinfarcts were more frequent in the frontal lobe followed by the basal ganglia, parietal lobe, and thalamus (**Table 3**). Among those with subcortical infarcts (either in subcortical gray or white matter), 119 (82%) had lacunes defined as 10 mm or smaller in size.

Secondary analyses examined the association of regional macroscopic infarcts with scam susceptibility and separately with global cognition. In linear regression models adjusted for demographics and AD pathology, we found that infarcts localized to the frontal, temporal, and occipital lobes and thalamus were related to scam susceptibility. Specifically, infarcts in the thalamus were associated with both scam susceptibility and global cognition, while infarcts in the frontal and occipital lobes were associated with greater scam susceptibility, but not with global cognition nor to any cognitive domain (Table 3 and eTable 1 in the Supplement). Next, we examined whether the association of infarcts differed by size, ie, total lacunes vs nonlacunes. We found that lacunes (<10 mm in size), but not nonlacunes, were associated with both greater scam susceptibility and global cognition (Table 3).

Watershed Microvascular Pathology With Scam Susceptibility

Prior work from our group has shown that watershed brain regions, which lie at the arterial border zones, are more vulnerable to microvascular pathologies.[29,30] In linear regression models adjusted for demographics, macroscopic infarcts, and AD pathology, we found a positive association between arteriolosclerosis pathology in the anterior watershed region and scam susceptibility, but it was not significant. We did not find an association between arteriolosclerosis in the posterior watershed region or between watershed microinfarcts or nonwatershed microinfarcts with scam susceptibility (eTable 5 in the Supplement).

Discussion

To our knowledge, this is the first study examining multiple cerebrovascular pathologies with scam susceptibility in older persons. We found that cerebral infarcts are associated with greater scam susceptibility above and beyond accumulating AD and other neurodegenerative pathologies. Importantly, this association persists after adjusting for vascular risk burden and cognition. Together, our findings suggest that vascular brain health may play an important role in scam susceptibility.

Scam susceptibility is associated with adverse financial and health outcomes, including cognitive decline and dementia.[10,14,37] Understanding brain health in the context of scam susceptibility is a novel area. There are extremely limited data that offer insight into the neurobiological basis underlying scam susceptibility, and in general decision-making processes, in older persons. In a recent study, we showed that accumulating neurodegenerative pathology, specifically β-amyloid, is associated with scam susceptibility, highlighting a specific neurodegenerative-biological footprint with scam susceptibility.[19] Our current study extends these findings in several important ways. First, we examined the association of diverse cerebrovascular pathologies that are commonly found in the aging brain with scam susceptibility, expanding an extremely limited literature regarding vascular brain health as it is associated with scam susceptibility. Second, we found that the association between cerebrovascular pathologies, particularly macroscopic infarcts, is independent of accumulating AD and non-AD proteinopathies. Third, regional vascular changes, including frontal brain regions, may be important for scam susceptibility. Lastly, we observed an association between cerebrovascular pathologies with scam susceptibility independent of cognition, fostering the notion that neural factors may be involved relatively independent of cognition.

The reasons why scam susceptibility (and in general decision-making) are sensitive to specific neuropathologies are unclear. Previous work from our group and others have shown that different neuropathologies in the aging brain can have varying impacts on related behaviors such as cognition.[38-40] Moreover, we have shown that the functional impact of various pathologies depends on combination, severity, and pattern of accumulation of brain pathologies.[41] Decision-making, in particular scam susceptibility, are complex behaviors that involve integration and coordination of diverse cognitive, affective, and socioemotional resources that rely on distributed neural networks.[5,14,42,43] We conceptualize that the presence of macroscopic infarcts (as well as AD pathology) impacts these brain networks and degrades specific abilities that may heighten vulnerability to scams. Neuroimaging studies have identified several interacting brain regions within, or highly connected to the frontal lobe, a brain region particularly vulnerable to infarcts (strokes) and β-amyloid pathology in early stages of AD, are likely involved in eco-

Table 3. Regional Macroscopic Infarcts With Scam Susceptibility and Global Cognition[a]

		Scam susceptibility		Global cognition	
Brain region[b]	No. (%)	β (SE)	*P* value	β (SE)	*P* value
Frontal lobe	65 (16)	0.24 (0.09)	.006	−0.09 (0.12)	.43
Parietal lobe	31 (7.6)	−0.004 (0.12)	.97	−0.39 (0.16)	.02
Temporal lobe	26 (6.4)	0.36 (0.13)	.006	−0.29 (0.18)	.17
Occipital lobe	19 (4.6)	0.47 (0.15)	.002	−0.28 (0.21)	.17
Basal ganglia	61 (15)	0.15 (0.09)	.10	−0.14 (0.12)	.25
Thalamus	30 (7.4)	0.36 (0.12)	.003	−0.33 (0.17)	.04
Lacunar	97 (24)	0.24 (0.07)	.001	−0.25 (0.10)	.02
Nonlacunar	22 (5)	0.04 (0.10)	.67	−0.07 (0.13)	.57

[a] The estimates are derived from linear regression models with scam susceptibility or global cognition as separate outcomes and each individual brain region as the predictor. All models adjusted for age at death, sex, education, and Alzheimer disease pathology.

[b] Brain region(s) are not mutually exclusive.

nomic decision-making and socioemotional abilities.[44,45] Findings from the current study also provides support for a frontal lobe involvement toward decision-making. Accumulating evidence indicates that vascular brain injury is common in older individuals without overt cognitive impairment,[17,46,47] which may impact socio-cognitive and -emotional abilities in early stages of the disease process. Additionally, we and others have shown multiple pathologies coexist in the aging brain. Our prior work shows that mixed pathologies are common and that the combinations/profiles of mixed pathologies,[41] including the combinations of cerebrovascular pathologies, are complex.[48] In the current study, individuals with macroscopic infarcts were more likely to have arteriolosclerosis pathology, microinfarcts, and large vessel disease, and it may be the case that certain combinations of pathologies have stronger impact on scam susceptibility. While we do not have sufficient power to address this now, future studies will examine associations between the specific groups of mixed pathologies with scam susceptibility and decision-making.

Regarding biological and mechanistic pathways, cerebrovascular stress may induce damage to a myriad of white matter networks,[49] disrupt white matter integrity,[50] and initiate inflammatory pathways,[51,52] which in turn can result in brain structural alterations[53,54] and numerous long-term behavioral/decision-making deficits. A robust factor associated with vascular brain injury is inflammation, with evidence to suggest that systemic inflammation triggers a neuroinflammatory response in the brain.[55,56] Chronic inflammation may play a negative role in health outcomes, especially in those with increased vulnerability to vascular brain injuries and has been linked with psychosocial factors and personality traits,[57,58] critical factors that contribute to an individual's decision-making processes. Our current study complements and extends our prior work showing an association between white matter integrity[59] and gray matter volume,[45] detected with in vivo magnetic resonance imaging, with scam susceptibility in the same cohort. Together, these findings pave the way to develop a framework for future longitudinal studies that include in vivo cerebrovascular markers and inflammatory biomarkers with scam susceptibility.

These findings have important clinical implications and suggest that individuals with poor vascular brain health (or numerous strokes) may have a heightened vulnerability to scams. Further, these findings suggest that cerebrovascular disease, specifically cerebral infarcts, impact a broader spectrum of behavior that extends beyond cognition, including decision-making. While the scam susceptibility measure used in this study was developed for an epidemiologic study and is not suitable to predict those individuals with macroscopic infarcts, an appropriately validated measures to assess scam susceptibility in clinical settings may offer very important diagnostic tools. This is the first study, to our knowledge, to link vascular brain injuries with scam susceptibility. Data came from a group of well-characterized, community-based, older persons. We used a well-validated measure of scam susceptibility derived from statements that are widely used in finance studies regarding the behaviors that make individuals more susceptible to scams. Further, we examined a diverse portfolio of cerebrovascular pathologies, including both cerebral infarcts and small- and large-vessel diseases, as well as regional pathologies, revealing nuanced vascular pathologic associations with scam susceptibility.

Limitations

There are some limitations to this work. First, the study cohort consisted of a highly selective group of older adults who were primarily well educated and non-Hispanic White. For the study results to be generalized, the findings should be replicated in a more diverse sample. Second, pathologies are evaluated on small, sampled brain regions; thus, we may be underestimating the burden of specific pathologies. Third, findings from this study are observational and therefore does not infer causality.

Conclusions

Future work exploring mechanistic factors associated vascular brain injury in the context of decision-making will be important to unravel pathways that contribute to decision-making and scams in older persons.

Author Contributions: Drs Kapasi and Boyle had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Kapasi, Boyle.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Kapasi.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Kapasi.
Obtained funding: Bennett, Boyle. *Administrative, technical, or material support:* Kapasi.
Supervision: Schneider, Bennett, Boyle.

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JAMA Neurology | Original Investigation

Association Between Consumption of Ultraprocessed Foods and Cognitive Decline

Natalia Gomes Gonçalves, PhD; Naomi Vidal Ferreira, PhD; Neha Khandpur, ScD; Euridice Martinez Steele, PhD; Renata Bertazzi Levy, PhD; Paulo Andrade Lotufo, MD, PhD; Isabela M. Bensenor, PhD; Paulo Caramelli, MD, PhD; Sheila Maria Alvim de Matos, PhD; Dirce M. Marchioni, PhD; Claudia Kimie Suemoto, MD, PhD

IMPORTANCE Although consumption of ultraprocessed food has been linked to higher risk of cardiovascular disease, metabolic syndrome, and obesity, little is known about the association of consumption of ultraprocessed foods with cognitive decline.

OBJECTIVE To investigate the association between ultraprocessed food consumption and cognitive decline in the Brazilian Longitudinal Study of Adult Health.

DESIGN, SETTING, AND PARTICIPANTS This was a multicenter, prospective cohort study with 3 waves, approximately 4 years apart, from 2008 to 2017. Data were analyzed from December 2021 to May 2022. Participants were public servants aged 35 to 74 years old recruited in 6 Brazilian cities. Participants who, at baseline, had incomplete food frequency questionnaire, cognitive, or covariate data were excluded. Participants who reported extreme calorie intake (<600 kcal/day or >6000 kcal/day) and those taking medication that could negatively interfere with cognitive performance were also excluded.

EXPOSURES Daily ultraprocessed food consumption as a percentage of total energy divided into quartiles.

MAIN OUTCOMES AND MEASURES Changes in cognitive performance over time evaluated by the immediate and delayed word recall, word recognition, phonemic and semantic verbal fluency tests, and Trail-Making Test B version.

RESULTS A total of 15 105 individuals were recruited and 4330 were excluded, leaving 10 775 participants whose data were analyzed. The mean (SD) age at the baseline was 51.6 (8.9) years, 5880 participants (54.6%) were women, 5723 (53.1%) were White, and 6106 (56.6%) had at least a college degree. During a median (range) follow-up of 8 (6-10) years, individuals with ultraprocessed food consumption above the first quartile showed a 28% faster rate of global cognitive decline (β = −0.004; 95% CI, −0.006 to −0.001; *P* = .003) and a 25% faster rate of executive function decline (β = −0.003, 95% CI, −0.005 to 0.000; *P* = .01) compared with those in the first quartile.

CONCLUSIONS AND RELEVANCE A higher percentage of daily energy consumption of ultraprocessed foods was associated with cognitive decline among adults from an ethnically diverse sample. These findings support current public health recommendations on limiting ultraprocessed food consumption because of their potential harm to cognitive function.

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Natalia Gomes Gonçalves, PhD, Department of Pathology, University of São Paulo Medical School, Avenida Doutor Arnaldo, 455, sala 1144, Cerqueira César, São Paulo, SP 01246-903, Brazil.

The prevalence of dementia is estimated to increase from 57 million cases in 2019 to 153 million in 2050 owing to the increase in life expectancy worldwide.[1,2] Dementia is the most important cause of disability in high-income countries, and it is among the 10 most important causes in low-income and middle-income countries.[3] The limited efficacy of available treatments for dementia highlights the importance of identifying interventions that are capable of preventing or delaying dementia onset to decrease the burden caused by this disorder.[4,5] Lifestyle modifications, such as physical activity, healthy dietary habits, and smoking cessation, have been related to dementia prevention.[6] Healthy eating habits, which include a high intake of whole grains, vegetables, fruit, nuts, and fish,[7-11] have been linked to increased brain volume and decreased risk of cognitive decline over time.[8,9,11,12]

In the last 40 years, the food supply industries have increased the commercialization of ultraprocessed foods (UPFs).[13] Such UPFs are formulations of processed food substances (oils, fats, sugars, starch, and protein isolates) that contain little or no whole foods and typically include flavorings, colorings, emulsifiers, and other cosmetic additives.[14] Examples of UPFs are sweet and savory snacks, confectionery, breakfast cereals, ice cream, sugar-sweetened beverages, processed meats, and ready-to-eat frozen meals. Fifty-eight percent of the calories consumed by US citizens, 57% of the calories consumed by British citizens, and 48% of the calories consumed by Canadian citizens come from UPFs.[15-17] In Brazil, this group of foods contributes to 30% of total calorie intake.[18] Consumption of UPFs has been linked to an increased risk of cardiovascular disease, metabolic syndrome, and obesity.[19,20] However, few studies have investigated the association between UPF and cognitive decline in samples from high-income countries.[21-23] Therefore, we aimed to prospectively investigate the association between UPF consumption at baseline and cognitive decline in the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil).

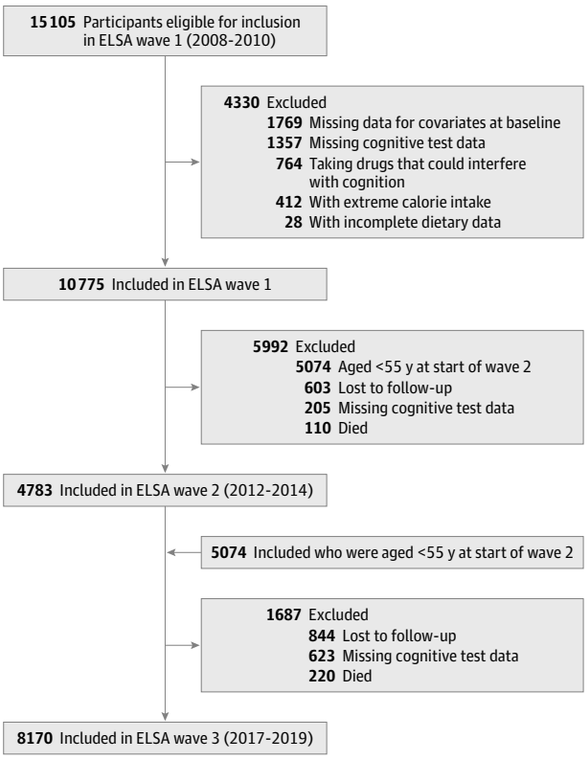
Key Points

Question Is the consumption of ultraprocessed foods associated with cognitive decline?

Findings In a cohort study of 10 775 individuals, higher consumption of ultraprocessed foods was associated with a higher rate of global and executive function decline after a median follow-up of 8 years.

Meaning These findings suggest that limiting consumption of ultraprocessed food could be associated with reduced cognitive decline in middle-aged and older adults.

Figure 1. Flowchart of the Study Sample



ELSA indicates Brazilian Longitudinal Study of Adult Health.

Methods

Participants

The ELSA-Brasil is a multicenter cohort study that comprises public servants aged 35 to 74 years at baseline from 6 Brazilian cities (Belo Horizonte, Porto Alegre, Rio de Janeiro, Salvador, São Paulo, and Vitoria). Data were collected in 3 waves, approximately 4 years apart, starting in 2008 to 2010. The second wave took place in 2012 to 2014, and the third wave was in 2017 to 2019. Inclusion criteria for the ELSA-Brasil study were active or retired employees of the participating institutions. Exclusion criteria were pregnancy, intention to quit working at the institution, cognitive or communication impairment, or, for those retired, residences outside of the study center area. A detailed description of the ELSA-Brasil cohort can be found elsewhere.[24,25]

The current study excluded participants who, at baseline, did not have dietary data, had extreme amounts of energy intake (<600 kcal/day or >6000 kcal/day), had missing data on cognitive tests or covariates, or reported taking medication that could negatively interfere with cognitive performance (**Figure 1**). A comparison between those who were included and excluded from this study analysis can be found in the eAppendix and eTable 1 in the Supplement.

This study was approved by the local ethics committees. The ELSA-Brasil study was conducted according to the guidelines of the Declaration of Helsinki,[26] the procedures were approved by the ethics committees of all study centers, and participants signed an informed consent before participation. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Dietary Assessment

Food and drink consumption in the last 12 months was assessed at baseline using a validated Food Frequency

Questionnaire (FFQ) with 114 items.[27] The frequency of consumption of each item was transformed into grams per day by multiplying the frequency of consumption by the weight of the portion in grams (further details can be found in the eAppendix in the Supplement). Foods were classified according to the extent of industrial processing using the Nova classification system.[14] Nova includes 4 food groups. Group 1 includes unprocessed or minimally processed foods, such as fresh, dry, or frozen fruits or vegetables, grains, legumes, meat, fish, and milk, which have undergone minimal processing like grinding, roasting, pasteurization, or freezing. Group 2 includes processed culinary ingredients, such as table sugar, oils, salt, and other substances that have been extracted, pressed, or centrifuged from group 1 foods or from nature, and are used to make culinary preparations. Group 3 includes processed foods, which are manufactured using unprocessed or minimally processed foods, and ingredients from group 2 are used to prolong the durability of foods and modify their palatability. Examples of foods in group 3 include canned fruits, artisanal bread and cheese, and salted, smoked, or cured meat or fish. Group 4 includes UPFs, which are formulations of several ingredients from group 2 with food additives not used in home preparations, such as flavors, colors, sweeteners, emulsifiers, and other substances used to disguise undesirable qualities of the final product or imitate the sensorial qualities of culinary preparations from group 1.[14] In the current study, foods were classified in 3 groups (eTable 2 in the Supplement): (1) unprocessed or minimally processed foods and processed culinary ingredients (Nova groups 1 and 2), (2) processed foods (Nova group 3), and (3) UPFs (Nova group 4). We calculated the daily energy consumption of UPF by summing the energy consumption in calories of all the foods in that group. Consumption of UPF was then expressed as a percentage of total daily energy consumption because a relative measure can capture the degree to which UPF composes a participant's diet while accounting for individual differences in caloric intake.

Cognitive Assessment

In this longitudinal study, individuals were tested up to 3 times every 4 years (mean [SD] time between visits, 3.3 [0.5] years). The memory domain included the immediate recall, late recall, and recognition word list tests from the Consortium to Establish a Registry for Alzheimer Disease.[28,29] The executive function domain included the semantic and the phonemic verbal fluency tests,[30] and the Trail-Making Test B version.[31] We calculated *z* scores standardized to wave 1 to compare results from different cognitive tests. A detailed description of each test and the *z* score calculation can be found in the eAppendix in the Supplement.

Covariates

Covariates that might confound the association between UPF consumption and cognitive decline included sociodemographic, clinical, and lifestyle variables. The sociodemographic variables were age, sex, monthly income per capita in US dollars, self-reported race and ethnicity (with categories self-reported by the participants as Black or mixed [ie, mixed Black and White], White, and other races, which include Asian and Indigenous), and education (less than college and college degree or more). Race and ethnicity were assessed in this study because they are important social determinants of health that could influence cognitive performance and UPF consumption. Clinical variables included body mass index (calculated as weight in kilograms divided by height in meters squared) categories (underweight, normal weight, overweight, and obese), diabetes, hypertension, cardiovascular disease, and depression. Lifestyle factors included physical activity (light, moderate, or vigorous), smoking (never, former, or current smoker), alcohol consumption (never, former, or current alcohol use), total energy intake (in kilocalories), and adhesion to a healthy diet. Details about the covariates can be found in the eAppendix in the Supplement.

Statistical Analysis

Data were analyzed from December 2021 to May 2022. Descriptive analyses were presented as mean (SD) for continuous variables and as percentages for categorical variables. We grouped the daily energy percentage contribution of UPF in quartiles (0%-19.9%, 20.0%-26.7%, 26.8%-34.1%, and 34.2%-72.7%). Our initial analysis compared each of the quartiles with the first quartile (reference group). Subsequent analysis grouped the 3 highest quartiles and compared them with the first quartile.[32] We used linear mixed-effects models with random intercepts and slopes to assess the association between quartiles of UPF consumption at baseline and change in cognition over time. The timescale was the participant's age in each wave. The longitudinal association between UPF consumption and cognitive decline was evaluated by the interaction of the UPF and the timescale. The linear mixed models were adjusted for sociodemographic, clinical, and lifestyle variables. To calculate the percentage of cognitive decline rate, we subtracted each quartile slope from the first quartile slope, divided this difference by the slope of the first quartile, and multiplied it by 100. We also investigated the modifying effect of age and healthy diet scores on the association between the percentage of daily energy from UPF and cognitive decline by adding a 3-way interaction among the percentage of daily energy from UPF, the timescale, and each modifier on our main models. The significant interactions were assessed in stratified analyses. Inverse probability weighting (IPW) was used to account for nonresponse across waves.[33,34] Details about the IPW calculation can be found in the eAppendix in the Supplement.

We performed 2 sets of sensitivity analyses. First, we repeated the analysis by excluding participants who reported caloric intakes above the 95th percentile (5831 kcal for men and 4607 kcal for women) and without excluding participants because of caloric intake. Moreover, we verified the robustness of our findings despite the missing cognitive data by design in wave 2 by imputing cognitive data using next observation carried backward using the scores from wave 3 in wave 2 for those who were younger than 55 years in wave 2. We assumed this approach is conservative since cognitive performance is expected to decline over time.[35] The α level was set at the 5% level in 2-sided tests. Statistical analyses were performed using R statistical software version 3.6.3 (R Project for Statistical Computing) using the lme4 package.[36,37]

Table 1. Baseline Characteristics of the Study Sample by Quartiles of the Percentage of Daily Energy From UPFs

Characteristic	Participants, No. (%)					
		UPF consumption quartile[a]				
	Total (N = 10 775)	1 (0%-19.9%) (n = 2694)	2 (20.0%-26.7%) (n = 2694)	3 (26.8%-34.1%) (n = 2694)	4 (34.2%-72.7%) (n = 2693)	*P* value
Age, mean (SD), y	51.6 (8.9)	54.2 (8.6)	52.0 (9.0)	50.8 (9.0)	49.6 (9.0)	<.001
Sex						
Female	5880 (54.6)	1392 (51.6)	1443 (53.5)	1501 (55.7)	1544 (57.3)	<.001
Male	4895 (45.4)	1302 (48.4)	1251 (46.5)	1193 (44.3)	1149 (42.7)	
Self-reported race						
Black or mixed[b]	4685 (43.5)	1404 (52.1)	1215 (45.3)	1069 (39.7)	1047 (36.9)	<.001
White	5723 (53.1)	1168 (43.3)	1384 (51.4)	1542 (57.2)	1542 (60.5)	
Other[c]	367 (3.4)	122 (4.6)	95 (3.8)	83 (3.1)	67 (2.6)	
Education (less than college degree)	4669 (43.4)	1390 (51.6)	1154 (42.9)	1037 (38.5)	1088 (40.4)	<.001
Monthly income, mean (SD), $US	983.6 (788.1)	953.5 (797.8)	974.3 (785.8)	997.8 (776.5)	1010.4 (791.8)	.004
Body mass index, mean (SD)[d]	26.9 (4.7)	26.9 (4.6)	27.0 (4.6)	27.0 (4.8)	27.0 (4.8)	.25
Total calorie intake, mean (SD), kcal	2855.9 (991.7)	2813.0 (977.0)	2858.0 (999.0)	2860.0 (993.0)	2894.0 (997.0)	.004
Calories from ultraprocessed foods, mean (SD), kcal	785.0 (419.1)	416.0 (185.0)	667.0 (241.0)	865.0 (308.0)	1192.0 (440.0)	<.001
Calories from Nova groups, % of total calories[e]						
Groups 1 and 2	1873.5 (65.6)	2194.1 (78.0)	1986.3 (69.5)	1790.3 (62.6)	1522.2 (52.6)	<.001
Group 3	197.4 (7.0)	202.9 (7.4)	208.7 (7.3)	203.2 (7.3)	179.8 (6.2)	
Group 4	785.0 (27.4)	416.0 (14.8)	663.0 (23.3)	866.5 (30.3)	1192.0 (41.2)	
Physical activity						
None or light	8197 (76.1)	1968 (73.0)	1996 (74.1)	2062 (76.5)	2171 (80.6)	<.001
Moderate	1539 (14.3)	458 (17.0)	406 (15.1)	383 (14.2)	292 (11.0)	
Vigorous	1039 (9.6)	268 (10.0)	292 (10.8)	249 (9.3)	230 (8.4)	
Hypertension, yes	3704 (34.4)	1100 (41.0)	969 (36.0)	813 (30.2)	822 (30.5)	<.001
Diabetes, yes	2016 (18.7)	701 (26.0)	508 (19.0)	424 (15.7)	383 (14.2)	<.001
Cardiovascular disease, yes	578 (5.3)	165 (6.1)	153 (5.7)	139 (5.1)	121 (4.5)	.04
Depressive symptoms, yes	1263 (11.7)	295 (11.0)	306 (11.3)	285 (10.6)	377 (14.0)	<.001
Alcohol consumption						
Never	1061 (9.8)	301 (11.2)	248 (9.2)	259 (9.6)	253 (9.3)	<.001
Former	1967 (18.3)	467 (17.3)	439 (16.3)	475 (17.7)	586 (21.7)	
Current	7747 (71.9)	1926 (71.5)	2007 (74.5)	1960 (72.7)	1854 (69.0)	
Smoking						
Never	6297 (58.4)	1474 (54.7)	1527 (56.7)	1633 (60.6)	1663 (61.7)	<.001
Former	3165 (29.4)	847 (31.4)	851 (31.6)	748 (27.7)	719 (26.7)	
Current	1313 (12.2)	373 (13.9)	316 (11.7)	313 (11.7)	311 (11.6)	

Abbreviation: UPF, ultraprocessed food.

[a] UPFs are represented as a percentage of total daily energy consumption divided in quartiles.

[b] Includes mixed Black and White.

[c] Includes Asian, Indigenous, or other ethnic groups.

[d] Body mass index calculated as weight in kilograms divided by height in meters squared.

[e] Group 1 includes unprocessed or minimally processed foods. Group 2 includes processed culinary ingredients. Group 3 includes processed foods. Group 4 includes UPFs.

Results

Sample Characteristics

A total of 15 105 individuals were recruited and 4330 were excluded, leaving 10 775 participants. The median (range) duration of follow-up was 8 (6-10) years. At baseline, the mean (SD) age of the participants was 51.6 (8.9) years, 5880 participants (54.6%) were women, 5723 (53.1%) were White, and 6106 (56.6%) had at least a college education. The mean (SD) BMI was 26.9 (4.7), and the mean (SD) total daily calorie intake was 2856 (992) kcal, 27% of which came from UPF (mean [SD], 785.0 [419.1] kcal/day). Compared with the lower quartile of the percentage of daily energy from UPF, those in the fourth quartile (ie, highest UPF consumption) were more likely to be younger, women, White, had higher education and income, were more likely to be nonsmokers, and less likely to be current alcohol consumers. The highest quartile also had a higher total energy intake, lower physical activity, and lower frequency of comorbidities, but a higher frequency of depressive symptoms (**Table 1**).

Table 2. Association Between Baseline Quartiles of the Percentage of Daily Energy From Ultraprocessed Foods and Yearly Cognitive Change During the Study Period

	Change in standardized cognitive score per year						
	Model 1[a]		Model 2[b]		Model 3[c]		
Domain	β (95% CI)	*P* value for trend	β (95% CI)	*P* value for trend	β (95% CI)	*P* value for trend	Difference, %[d]
Memory							
All quartiles							
Quartile 1 × time	0 [Reference]	.88	0 [Reference]	.82	0 [Reference]	.80	0 [Reference]
Quartile 2 × time	0.001 (−0.003 to 0.004)		0.001 (−0.004 to 0.006)		0.001 (−0.002 to 0.004)		6
Quartile 3 × time	0.000 (−0.004 to 0.003)		0.000 (−0.005 to 0.004)		0.000 (−0.004 to 0.003)		0
Quartile 4 × time	0.001 (−0.002 to 0.004)		0.002 (−0.003 to 0.006)		0.001 (−0.002 to 0.005)		6
Lowest × highest quartiles							
Quartile 1 (lowest 25%)	0 [Reference]	.86	0 [Reference]	.77	0 [Reference]	.77	0 [Reference]
Quartiles 2-4 (highest 75%)	0.000 (−0.003 to 0.003)		0.000 (−0.002 to 0.003)		0.000 (−0.002 to 0.003)		0
Executive function							
All quartiles							
Quartile 1 × time	0 [Reference]	.23	0 [Reference]	.12	0 [Reference]	.12	0 [Reference]
Quartile 2 × time	−0.003 (−0.006 to 0.000)		−0.003 (−0.006 to 0.000)		−0.003 (−0.006 to 0.000)		25
Quartile 3 × time	−0.002 (−0.005 to 0.001)		−0.003 (−0.006 to 0.000)		−0.003 (−0.005 to 0.000)		25
Quartile 4 × time	−0.002 (−0.005 to 0.001)		−0.002 (−0.005 to 0.001)		−0.002 (−0.005 to 0.001)		16
Lowest × highest quartiles							
Quartile 1 (lowest 25%)	0 [Reference]	.04	0 [Reference]	.01	0 [Reference]	.01	0 [Reference]
Quartiles 2-4 (highest 75%)	−0.002 (−0.005 to 0.000)		−0.003 (−0.005 to 0.000)		−0.003 (−0.005 to 0.000)		25
Global cognition							
All quartiles							
Quartile 1 × time	0 [Reference]	.06	0 [Reference]	.04	0 [Reference]	.04	0 [Reference]
Quartile 2 × time	−0.003 (−0.006 to 0.000)		−0.003 (−0.006 to 0.000)		−0.003 (−0.006 to 0.000)		21
Quartile 3 × time	−0.004 (−0.007 to −0.001)		−0.004 (−0.007 to −0.001)		−0.004 (−0.007 to −0.001)		28
Quartile 4 × time	−0.003 (−0.006 to 0.000)		−0.003 (−0.006 to 0.000)		−0.003 (−0.006 to 0.000)		21
Lowest × highest quartiles							
Quartile 1 (lowest 25%)	0 [Reference]	.004	0 [Reference]	.003	0 [Reference]	.004	0 [Reference]
Quartiles 2-4 (highest 75%)	−0.003 (−0.005 to −0.001)		−0.003 (−0.006 to −0.001)		−0.003 (−0.006 to −0.001)		28

[a] Model 1 includes linear mixed models adjusted for age, sex, race and ethnicity, education, and income.

[b] Model 2 includes linear mixed models additionally adjusted for physical activity, body mass index, hypertension, diabetes, cardiovascular disease, depressive symptoms, alcohol consumption, and smoking.

[c] Model 3 includes linear mixed models additionally adjusted for total calories and healthy eating score.

[d] Difference is between each quartile and the first quartile in model 3.

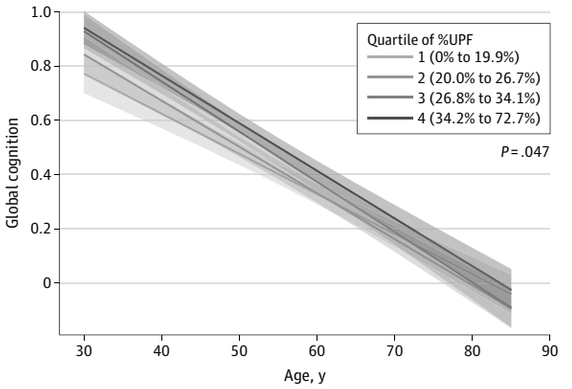
Cognitive Performance and Consumption of UPFs

After a median follow-up of 8 years, participants who reported consumption of UPF of more than 19.9% of daily calories had a 28% faster rate of global cognitive decline compared with those who reported consumption of UPF up to 19.9% of daily calories (β = −0.004; 95% CI, −0.006 to −0.001; *P* = .003) (**Table 2** and **Figure 2**). Moreover, participants who reported consumption of UPF more than 19.9% of daily calories had a 25% faster rate of executive function decline compared with those who reported consumption of UPF less than or equal to 19.9% of daily calories (β = −0.003, 95% CI, −0.005 to 0.000; *P* = .01) (Table 2). We found no association between the percentage of daily energy from UPF and the memory score. Age was an effect modifier in the association of the percentage of daily energy from UPF and cognitive function (*P* for interaction < .001). Participants younger than 60

years with UPF consumption greater than 19.9% showed a faster global cognition decline compared with those with UPF consumption less than 19.9% (β = −0.006; 95% CI, −0.009 to −0.003; *P* < .001) (eTable 3 in the Supplement), whereas there was no association of the percentage of daily energy from UPF and global cognition decline for those aged 60 years or older (eTable 3 in the Supplement). Adhesion to a healthy diet was also an effect modifier on the association of UPF and global cognitive function (*P* for interaction = .04). Participants with low healthy diet scores who consumed more than 19.9% of calories from UPF showed a faster global cognition decline compared with those who consumed less than 19.9% (β = −0.005; 95% CI, −0.009 to −0.002; *P* = .004) (eTable 4 in the Supplement and **Figure 3**A). We found no association between the percentage of daily energy from UPF and global cognition for participants with high healthy diet scores (eTable 4 in the Supplement and Figure 3B).

To assess the robustness of our findings, we performed sensitivity analyses excluding participants who reported caloric intakes above the 95th percentile by sex and without excluding participants because of caloric intake. We also imputed data for cognitive performance for participants younger than 55 years in wave 2. The results of the sensitivity analyses were similar to those found in the main analysis (eTable 5 and eTable 6 in the Supplement).

Figure 2. Trajectories of Global Cognitive Performance Over Time According to Quartiles of the Percentage of Daily Energy From Ultraprocessed Foods (%UPF)



Mixed linear regression models with random intercepts and slopes were adjusted for age, sex, race and ethnicity, education, income, physical activity, body mass index, hypertension, diabetes, cardiovascular disease, depressive symptoms, alcohol consumption, smoking, total calories, and healthy eating score. *P* values were calculated for the interaction between UPF quartiles (ordinal continuous variable) and age as the timescale. Shaded areas indicate 95% CIs.

Discussion

In this cohort study of 10 775 individuals followed for a median of 8 years, we found that consumption of UPF greater than 19.9% of total daily calories was associated with a faster decline in global cognitive performance and executive function compared with consumption less than 19.9% of total daily calories. We also found that the percentage of daily energy from UPF was associated with cognitive decline in participants younger than 60 years, which suggests the importance of preventive interventions in middle-aged adults. Additionally, the percentage of daily energy from UPF was associated with cognitive decline in participants with a low healthy diet score, whereas there was no association in those with a high healthy diet score. Our findings are in line with previous studies linking consumption of UPF and adverse health outcomes, such as the increased risk of overweight and obesity,[38,39] metabolic syndrome,[40] cancer,[41] cardiovascular diseases,[42] and all-cause mortality.[43,44]

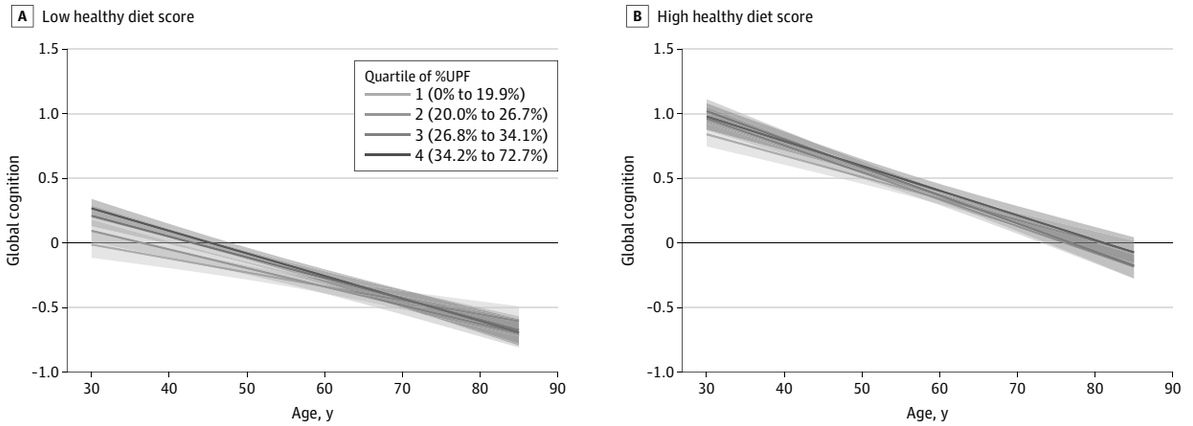
A prior study[21] that investigated the association of UPF and cognition in 568 individuals with type 2 diabetes found no association between total calorie consumption of UPF and cognitive decline, likely because of the small sample size or reverse causation, since individuals who develop diabetes could have reduced their UPF consumption after diagnosis. Our findings are in line with 2 recent studies[22,23] that investigated the association between UPF consumption and cognition. A cross-sectional study[22] of older US adults found an association between UPF consumption and worse verbal fluency performance in participants without preexisting chronic health conditions. Another study[23] investigated the association between consumption of UPF and dementia in 72 083 adults aged 55 years or older from the UK Biobank. Consumption of UPF was associated with a higher risk of all-cause dementia, vascular dementia, and Alzheimer disease after 10 years of follow-up.[23] The association between UPF and cognitive decline found in our study, particularly the decline in executive function, could be secondary to cerebrovascular lesions resulting from UPF consumption, because these functions are particularly sensitive to microvascular lesions.[42,45]

Neuroimaging studies[46,47] have found that high consumption of a Western dietary pattern was related to a reduction in the left hippocampus and gray matter volume in cognitively healthy individuals. Another possible biological mechanism for the decline in executive function and global cognition seen in our study may be related to systemic inflammation caused by the consumption of UPF, because increased levels of circulating proinflammatory cytokines have been associated with cognitive decline.[48-52] On the other hand, healthy dietary patterns were associated with higher gray and white matter volume, total brain volume, and Aβ42/40 ratio, as well as lower oxidative stress and inflammation,[53,54] which could explain our findings that the percentage of daily energy from UPF was associated with cognitive decline in participants with a low healthy diet score, but not in those with a high healthy diet score.

Strengths and Limitations

This study has some strengths. First, this is a large ethnically diverse cohort study from a low- and middle-income country with up to 10 years of follow-up. Second, the diet assessment was conducted using a validated questionnaire.[27] Moreover, we found that UPF consumption was associated with cognitive decline in middle-aged participants. The inclusion of

Figure 3. Trajectories of Global Cognitive Performances Over Time in Participants With Low Healthy Diet Scores and High Healthy Diet Scores



Graphs show trajectories of global cognitive performances over time according to quartiles of the percentage of daily energy from ultraprocessed foods (%UPF). Mixed linear regression models with random intercepts and slopes were adjusted for age, sex, race and ethnicity, education, income, physical activity, body mass index, hypertension, diabetes, cardiovascular disease, depressive symptoms, alcohol consumption, smoking, total calories, and healthy eating score. Shaded areas indicate 95% CIs.

middle-aged participants in studies about risk factors for cognitive decline is particularly important to understand potential preventive targets early in the life course.[55,56]

However, our findings should be considered in light of study limitations. Attrition is a concern for a long-term study, and participants younger than 55 years were not submitted to cognitive assessment during the second visit, because of the study design. Nevertheless, the use of IPW provided some correction for selection bias. Moreover, the imputation of missing cognitive data by design in wave 2 did not change the main study findings. In addition, diet was assessed only at baseline, which may not reflect longitudinal diet changes and may lead to an underestimation of the associations between UPF and cognition.[57] A few food items may have been misclassified because the FFQ was not specifically designed to assess the degree of processing. Because the FFQ was self-reported, the UPF consumption could be underreported owing to social desirability bias, which could have biased associations toward the null. Using the same calorie cutoff interval for men and women may introduce bias due to different caloric intake needs. However, the use of a relative measure as the exposure variable (percentage of the daily energy from UPF) minimizes the effect of extreme total energy intakes on the studied association.[58] Additionally, a sensitivity analysis using different cutoffs for calorie intake in men and women showed similar results to our main analysis. Although the use of software based on North American foods to estimate calorie content may be a limitation, it is unlikely to bias the UPF consumption estimations, because the UPF classification used the composition of products commonly consumed in Brazil and did not consider the nutritional composition from the software. Additionally, our findings may be subjected to selection bias, because the characteristics of those included and those excluded in the study at baseline differed. Although we adjusted the analyses for several sociodemographic and clinical confounders, we cannot exclude the possibility of residual confounding. Furthermore, since neuroimaging is not available in the ELSA-Brasil study, we were not able to investigate possible mechanisms that could explain the association between UPF consumption and cognitive decline in our study.

Conclusions

In this large cohort study, a higher percentage of daily energy from UPF was associated with cognitive decline during 8 years of follow-up. Intact cognitive function is key to successful aging. Therefore, despite the small effect size of the association between UPF consumption and cognitive decline, our findings are meaningful to cognitive health. Limiting UPF consumption, particularly in middle-aged adults, may be an efficient form to prevent cognitive decline. Future studies investigating the mechanism by which UPF may lead to cognitive decline are needed, as well as confirmation of our findings in other longitudinal studies and randomized clinical trials.

ARTICLE INFORMATION

Author Affiliations: Department of Pathology, University of São Paulo Medical School, São Paulo, Brazil (Gomes Gonçalves); Adventist University of São Paulo, Engenheiro Coelho, Brazil (Vidal Ferreira); Division of Geriatrics, University of São Paulo Medical School, São Paulo, Brazil (Vidal Ferreira, Suemoto); Department of Nutrition, School of Public Health, University of São Paulo, São Paulo, Brazil (Khandpur, Martinez Steele, Marchioni); Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, Massachusetts (Khandpur); Department of Preventive Medicine, School of Medicine, University of São Paulo, São Paulo, Brazil (Bertazzi Levy); Center for Clinical and Epidemiological Research, Hospital Universitário, University of São Paulo, São Paulo, Brazil (Andrade Lotufo, Bensenor); Behavioral and Cognitive Neurology Research Unit, Faculdade de Medicina,

Universidade Federal de Minas Gerais, Belo Horizonte, Brazil (Caramelli); Federal University of Bahia, Salvador, Brazil (Alvim de Matos).

Author Contributions: Dr Gomes Gonçalves had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Gomes Gonçalves, Khandpur, Andrade Lotufo, Caramelli, Alvim de Matos, Suemoto.
Acquisition, analysis, or interpretation of data: Gomes Gonçalves, Vidal Ferreira, Khandpur, Martinez Steele, Bertazzi Levy, Andrade Lotufo, Bensenor, Alvim de Matos, Marchioni, Suemoto.
Drafting of the manuscript: Gomes Gonçalves, Martinez Steele, Suemoto.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Gomes Gonçalves, Vidal Ferreira, Khandpur, Martinez Steele, Bertazzi Levy.
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Supervision: Andrade Lotufo, Bensenor, Alvim de Matos, Suemoto.

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JAMA Neurology | Original Investigation

Widening the Spectrum of Risk Factors, Comorbidities, and Prodromal Features of Parkinson Disease

Anette Schrag, MD, PhD; Jens Bohlken, MD; Lotte Dammertz, MD; Stefan Teipel, MD, PhD; Wiebke Hermann, MD; Manas K. Akmatov, PhD; Jörg Bätzing, MD; Jakob Holstiege, PhD

IMPORTANCE The prodromal phase of Parkinson disease (PD) may last for more than 10 years. Recognition of the spectrum and occurrence of risk factors, comorbidities, and prodromal features of PD can increase understanding of the causes and development of the disease and help identify individuals at risk.

OBJECTIVE To identify the association of a subsequent diagnosis of PD with a range of risk factors and prodromal features, including lifestyle factors, comorbidities, and potential extracerebral manifestations of PD.

DESIGN, SETTING, AND PARTICIPANTS This was a case-control study using insurance claims of outpatient consultations of patients with German statutory health insurance between January 1, 2011, and December 31, 2020. Included were patients with incident diagnosis of PD without a previous diagnosis of parkinsonism or dementia and controls matched 1:2 for age, sex, region, and earliest year of outpatient encounter.

EXPOSURES Exposures were selected based on previous systematic reviews, case-control and cohort studies reporting on risk factors, comorbidities, and prodromal features of PD.

MAIN OUTCOMES AND MEASURES Previously postulated risk factors and prodromal features of PD, using the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10)* coding.

RESULTS A total of 138 345 patients with incident PD (mean [SD] age, 75.1 [9.8] years; 73 720 male [53.3%]) and 276 690 matched controls (mean [SD] age, 75.1 (9.8) years; 147 440 male [53.3%]) were identified. Study participants were followed up for a mean (SD) of 6.0 (2.0) years. Consistent with previous reports, risk factors and prodromal features associated with PD included traumatic brain injury, odds ratio (OR), 1.62; 95% CI, 1.36-1.92; alcohol misuse, OR, 1.32; 95% CI, 1.21-1.44; hypertension, OR, 1.29; 95% CI, 1.26-1.31; anosmia, OR, 2.16; 95% CI, 1.59-2.93; and parasomnias (including RBD), OR, 1.62; 95% CI, 1.42-1.84. In addition, there were associations with restless legs syndrome (OR, 4.19; 95% CI, 3.91-4.50), sleep apnea (OR, 1.45; 95% CI, 1.37-1.54), epilepsy (OR, 2.26; 95% CI, 2.07-2.46), migraine (OR, 1.21; 95% CI, 1.12-1.29), bipolar disorder (OR, 3.81; 95% CI, 3.11-4.67), and schizophrenia (OR, 4.48; 95% CI, 3.82-5.25). The following diagnoses were also found to be associated with PD: sensory impairments beyond anosmia, such as hearing loss (OR, 1.14; 95% CI, 1.09-1.20) and changes of skin sensation (OR, 1.31; 95% CI, 1.21-1.43). There were also positive associations with skin disorders (eg, seborrheic dermatitis, OR, 1.30; 95% CI, 1.15-1.46; psoriasis, OR, 1.13; 95% CI, 1.05-1.21), gastrointestinal disorders (eg, gastroesophageal reflux, OR, 1.29; 95% CI, 1.25-1.33; gastritis, OR, 1.28; 95% CI, 1.24-1.33), conditions with a potential inflammatory component (eg, seronegative osteoarthritis, OR, 1.21; 95% CI, 1.03-1.43), and diabetes types 1 (OR, 1.32; 95% CI, 1.21-1.43) and 2 (OR, 1.24; 95% CI, 1.20-1.27). Associations even 5 to 10 years before diagnosis included tremor (odds ratio [OR], 4.49; 95% CI, 3.98-5.06), restless legs syndrome (OR, 3.73; 95% CI, 3.39-4.09), bipolar disorder (OR, 3.80; 95% CI, 2.82-5.14), and schizophrenia (OR, 4.00; 95% CI, 3.31-4.85).

CONCLUSIONS AND RELEVANCE Results of this case-control study suggest that the associations found between PD and certain risk factors, comorbidities, and prodromal symptoms in a representative population may reflect possible early extrastriatal and extracerebral pathology of PD. This may be due to shared genetic risk with PD, medication exposure, or direct causation, or represent pathophysiologically relevant factors contributing to the pathogenesis of PD.

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Anette Schrag, MD, PhD, Department of Clinical and Movement Neurosciences, University College London, U3, Royal Free Hospital School of Medicine, Rowland Hill Street, London, Greater London NW3 2PF, United Kingdom.

Prodromal features of Parkinson disease (PD) can start more than a decade before the typical clinical symptoms allow a diagnosis.[1,2] In addition, there is increasing evidence for a number of possible risk factors that may predispose to the manifestation of the disease or facilitate development or spread of pathological lesions. These risk factors include well-known genetic or environmental risk factors but also diabetes type 2 or gastric pathology, which may increase spread of pathology from the enteric nervous system via the vagal nerve to the central nervous system.[3,4] The recognition of such risk factors and prodromal features of PD together with the presence of Lewy body pathology in peripheral organs and early extrastriatal brain pathology several years before PD diagnosis have widened our understanding of the development of the disease. Specifically, these findings suggest that disease onset may not only occur in the brain but also in gastrointestinal and other extracerebral systems.[5,6] These insights have also offered the opportunity to explore early biomarkers and mechanisms of pathogenesis. To date, the best-established prodromal features are subtle motor symptoms, rapid eye movement sleep behavior disorder (RBD; a rare but highly specific condition),[7,8] hyposmia/anosmia (a common and relatively nonspecific feature),[9,10] neuropsychiatric manifestations (eg, depression and anxiety), autonomic features (eg, constipation and urinary and sexual dysfunction), dizziness and fatigue, and pain.[1] However, other prodromal features have been suggested but with little or divergent evidence. Some may reflect striatal or extrastriatal involvement like restless legs syndrome[11,12] and cognitive changes[13] or early deposition of α-synuclein aggregates in peripheral tissues, including skin.[14-17] Several studies have suggested that infections with cytomegalovirus or Epstein-Barr virus may predate the diagnosis of PD and may represent triggers, risk factors, or causes of the onset of PD.[18-21] Additional associations with potential risk factors include lack of a smoking history, a family history of PD, tremor, or head trauma.[4] Associations are less consistent or divergent with dietary factors,[22] alcohol intake,[23-25] cholesterol levels,[26-28] and hypertension[4,29] as well as with type 2 diabetes,[30-32] osteoarthritis, and inflammatory bowel disease.[33-35] Finally, other studies have suggested associations with schizophrenia,[36,37] bipolar disorder,[38,39] epilepsy,[40,41] and migraine.[42-44] Although some studies indicate that the association with schizophrenia prevails even when excluding drug-induced parkinsonism,[36,37] at least part of the associations with these diseases may be due to medications known to be associated with drug-induced parkinsonism.

Most studies to date include relatively small sample sizes that may have missed subtle associations, included a limited number of exposures precluding comparisons in terms of strength and timeline of association, or are retrospective studies and limited by recall bias. Availability of large data sets, collected in routine care, enables the detection and comparison of subtle associations of multiple risk factors, which may otherwise not be identified. Here, we used a routine-care database comprising insurance claims of outpatient consultations in the German statutory health insurance (covers 87% of all inhabitants of Germany) to analyze data over a 10-year period.

Key Points

Question What risk factors, comorbidities, and prodromal symptoms preceded the diagnosis of Parkinson disease (PD) in a large representative routine-care database?

Findings In this case-control study of 138 345 patients with incident PD and 276 690 matched controls, an increased risk of PD was associated with a range of risk factors, comorbidities, and prodromal features, particularly tremor, restless legs syndrome, and both schizophrenia and bipolar disorder; comorbidities such as diabetes types 1 and 2, epilepsy, sensory skin disturbances, and gastrointestinal disorders; and risk factors such as alcohol misuse and traumatic head injury.

Meaning These associations may reflect possible early extrastriatal and extracerebral pathology of PD; risk factors due to shared genetic risk with PD, medication exposure, or direct causation; or may represent pathophysiologically relevant factors contributing to the pathogenesis of PD.

Methods

Study Design

This was a case-control study using insurance claims of outpatient consultations of patients with German statutory health insurance and incident PD identified between January 1, 2011, and December 31, 2020, using general and specialist practice data from a source population of 72 842 190 people in 2020.[45] The use of claims data for scientific research in Germany is regulated by the Code of Social Law (Sozialgesetzbuch, SGB V). Ethical approval and informed consent are not required for routinely collected pseudonymized data. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

Patients cared for by more than 1 medical professional were only included once. Individuals were included if at least 3 years of outpatient data before diagnosis of PD or index date were available, in order to limit the possibility of including patients with a previous diagnosis of PD that was first recorded by a new treating physician during the patient registration period. Thus, cases of newly diagnosed PD and controls were identified in the data set from January 1, 2014, to December 31, 2020, if they attended 1 or more outpatient visits in the respective year and also received outpatient services at least 1 time 3 years before the index year or earlier. Diagnosis of PD was defined as the presence of an *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10)* diagnostic code (*ICD-10*: G20) in more than 1 insurance claim period (3 months) without a previous diagnosis of parkinsonism (*ICD-10*: G20, G21, or G22) in the preceding 3 years. Patients and controls with a diagnosis of dementia (*ICD-10*: F03, F00) within the 3 years before the index date were excluded. We matched cases to controls (1:2) without a diagnosis of PD (*ICD-10*: G20, G21, or G22) in the index year or the preceding 3 years, with an index date within the same 3-month time period as the case's PD diagnosis, and matched for age, sex, geographic region of residence, and earliest year of outpatient encounter within the study period.

Table. Characteristics of Patients With Incident Parkinson Disease and Controls

Variable	Total		Retrospective data					
			With 1 y		With 2-4 y		With 5-10 y	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
No.	138 345	276 690	138 345	276 690	138 345	276 690	106 957	213 914
Sex, No. (%)								
Female	64 625 (46.7)	129 250 (46.7)	64 625 (46.7)	129 250 (46.7)	64 625 (46.7)	129 250 (46.7)	49 656 (46.4)	99 312 (46.4)
Male	73 720 (53.3)	147 440 (53.3)	73 720 (53.3)	147 440 (53.3)	73 720 (53.3)	147 440 (53.3)	57 301 (53.6)	114 602 (53.6)
Age at index date, mean (SD) [range], y	75.1 (9.8) [40-105]	75.1 (9.8) [40-105]	75.1 (9.8) [40-105]	75.1 (9.8) [40-105]	75.1 (9.8) [40-105]	75.1 (9.8) [40-105]	75.14 (9.8) [40-105]	75.1 (9.8) [40-104]
Follow-up time, mean (SD), y[a]	6.0 (2.0)	6.0 (2.0)	6.0 (2.0)	6.0 (2.0)	6.0 (2.0)	6.0 (2.0)	6.7 (1.6)	6.7 (1.6)

[a] Time from first recorded outpatient visit during observation period to index date.

Data on the presence of defined diagnoses with a potential association with subsequent diagnosis of PD, identified from a review of the literature, were then extracted for each individual from general practice data, both for each year and grouped for the periods less than 1 year, 2 to 4 years, and 5 to 10 years before index date, independent of calendar year and first onset. The time slicing was oriented on previous studies.[1] *ICD* codes for potential prodromal features, risk factors, and comorbidities were defined as described in eTable 1 in the Supplement. This list originated from the literature review and discussion with PD experts. Only prodromal features, risk factors, and comorbidities coded by general practitioners were included in this analysis.

Statistical Analysis

Odds ratios (ORs) were calculated for potential prodromal features of PD in the year before index date and pooled for the periods 2 to 4 years and 5 to 10 years before index date. The 95% CIs were calculated using the method by Altmann[46] with conservative Bonferroni adjustment for multiple comparisons. Statistical significance was assumed when the 95% CI of the OR did not overlap the null value (eg, OR = 1.0). Statistical analyses were performed using SAS, version 9.4 (SAS Institute).

Results

A total of 138 345 patients with incident PD (mean [SD] age, 75.1 [9.8] years; 73 720 male [53.3%]; 64 625 female [46.7%]) in the period between 2014 and 2020 and 276 690 matched controls (mean [SD] age, 75.1 (9.8) years; 147 440 male [53.3%]; 129 250 female [46.7%]) were identified. Their demographic characteristics for each time period are given in the **Table**. Mean (SD) follow-up time was 6.0 (2.0) years in both cases and controls. A total of 102 360 patients (74%) with PD and 27 652 controls (10%) were examined by a neurologist during the insurance quarter of diagnosis. The following presentation of the results is grouped according to the role of a factor as possible prodrome of disease or as risk or comorbid factor.

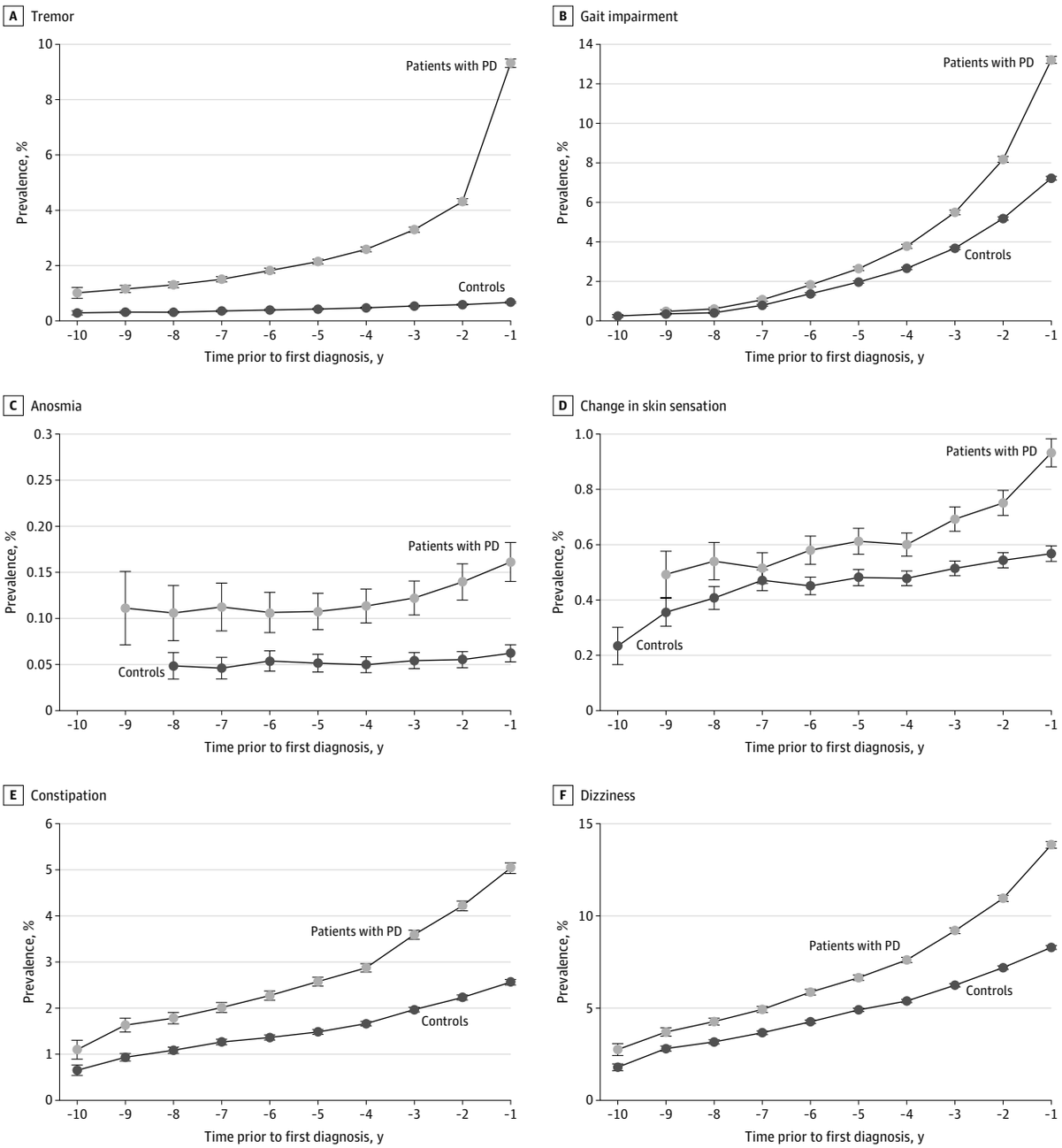
Suspected Prodromal Presentations of PD

There were positive associations for the overall observation period with a subsequent diagnosis of PD for the motor features of tremor (OR, 11.38; 95% CI, 10.51-12.32), gait impairment (OR, 1.90; 95% CI, 1.83-1.98) (**Figure 1**), stiffness of joints (OR, 1.32; 95% CI, 1.17-1.50), shoulder pain (OR, 1.15; 95% CI, 1.06-1.24), and neck pain (OR, 1.16; 95% CI, 1.12-1.20) (eFigure in the Supplement). The autonomic presentations of dizziness (OR, 1.60; 95% CI, 1.55-1.66), postural hypotension (OR, 1.40; 95% CI, 1.32-1.49), constipation (OR, 1.84; 95% CI, 1.76-1.93), features of sexual dysfunction (OR, 1.20; 95% CI, 1.11-1.30), and neurogenic bladder (OR, 1.72; 95% CI, 1.52-1.94) also revealed positive associations with a diagnosis of PD. In addition, there were associations between the following features and PD: fatigue (OR, 1.43; 95% CI, 1.37-1.50); the neuropsychiatric presentations of depression (OR, 1.86; 95% CI, 1.81-1.92) (**Figure 2**), anxiety (OR, 1.65; 95% CI, 1.57-1.74), and memory problems (OR, 1.72; 95% CI, 1.59-1.85); the sleep disorders of restless leg syndrome (OR, 4.19; 95% CI, 3.91-4.50), parasomnias (including RBD; OR, 1.62; 95% CI, 1.42-1.84), sleep apnea (OR, 1.45; 95% CI, 1.37-1.54), insomnia (OR, 1.40; 95% C,I 1.31-1.49), other sleep disorders (OR, 1.41; 95% CI, 1.35-1.47), and, although rare, hypersomnia (OR, 2.16; 95% CI, 1.27-3.68) (eTable 3 in the Supplement). Further, for sensory changes including anosmia (OR, 2.16; 95% CI, 1.59-2.93), hearing loss (OR, 1.14; 95% CI, 1.09-1.20), alterations in skin sensation (OR, 1.31; 95% CI, 1.21-1.43), nonspecific pain (OR, 1.13; 95% CI, 1.09-1.17), and subjective visual disturbance (OR, 1.26; 95% CI, 1.01-1.57) and for diagnoses of the skin conditions seborrheic dermatitis (OR, 1.30; 95% CI, 1.15-1.46) (**Figure 3**), psoriasis (OR, 1.13; 95% CI, 1.05-1.21), and dermatophytosis (OR, 1.25; 95% CI, 1.19-1.32), there were positive associations with a diagnosis of PD.

Association With Suspected Risk Factors and Comorbidities

There was an increased OR for preceding alcohol misuse (OR, 1.32; 95% CI, 1.21-1.44) and traumatic brain injury (OR, 1.62; 95% CI, 1.36-1.92) as well as for hypertension (OR, 1.29; 95% CI, 1.26-1.31) and hypercholesterinemia (OR, 1.11; 95% CI, 1.08-1.13) (**Figure 4**). However, there was a reduced OR for nicotine misuse (OR, 0.92; 95% CI, 0.86-0.98) with PD. In addition, both diabetes type 1 (OR, 1.32; 95% CI, 1.21-1.43) and type 2 (OR, 1.24; 95% CI, 1.20-1.27) were associated with a subsequent diagnosis of PD overall and in all time periods before diagnosis of PD (eTable 2 in the Supplement; Figure 1).

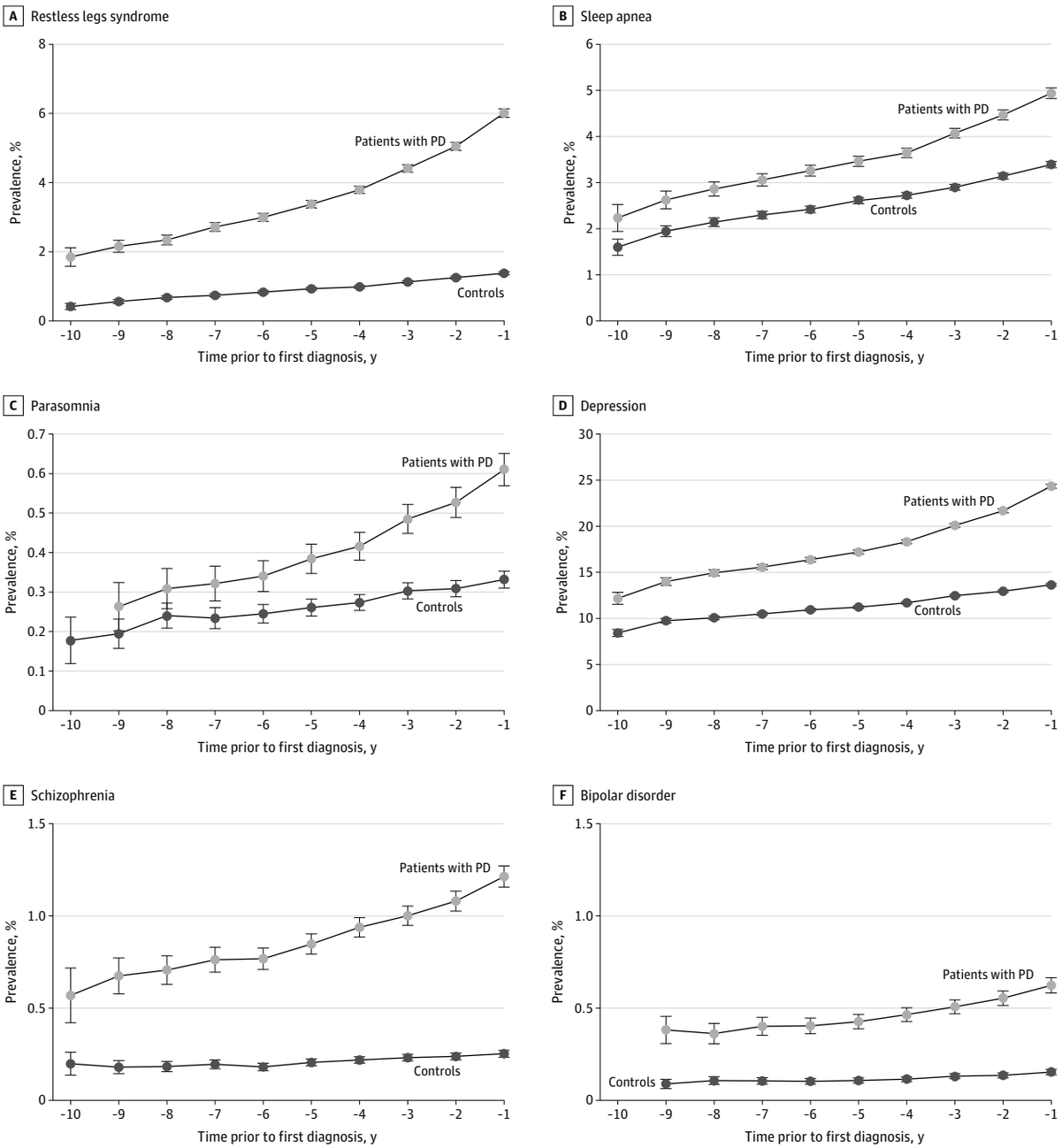
Figure 1. Prevalence of Motor, Sensory, and Autonomic Presentations Most Strongly Associated With Parkinson Disease (PD) by Year Before Diagnosis Compared With Controls



Prevalence of tremor (A), gait impairment (B), anosmia (C), skin sensation (D), constipation (E), and dizziness (F) associated with PD by year before diagnosis.

Associations for comorbidities with PD were found for the diagnoses of schizophrenia (OR, 4.48; 95% CI, 3.82-5.25) and bipolar disorder (OR, 3.81; 95% CI, 3.11-4.67), with increased ORs also for epilepsy (OR, 2.26; 95% CI, 2.07-2.46), migraine (OR, 1.21; 95% CI, 1.12-1.29), osteoarthritis (OR, 1.20; 95% CI, 1.17-1.23), seropositive inflammatory arthritis (OR, 1.21; 95% CI, 1.03-1.43), and other inflammatory arthritis (OR, 1.19; 95% CI, 1.11-1.27). There was also an increased OR for the gastrointestinal comorbidities of gastroesophageal reflux disease (OR, 1.29; 95% CI, 1.25-1.33), gastritis (OR, 1.28; 95% CI, 1.24-1.33), and gastric ulcer (OR, 1.24; 95% CI, 1.12-1.37), with less-consistent associations over time periods for duodenal ulcer (OR, 1.13; 95% CI, 1.00-1.29), Crohn disease (OR, 1.21; 95% CI, 0.99-1.48), and ulcerative colitis (OR, 1.23; 95% CI, 1.06-1.43). There was no significant association in any time period for gastrojejunal

Figure 2. Prevalence of Sleep and Psychiatric Presentations Associated With Parkinson Disease (PD) by Year Before Diagnosis Compared With Controls



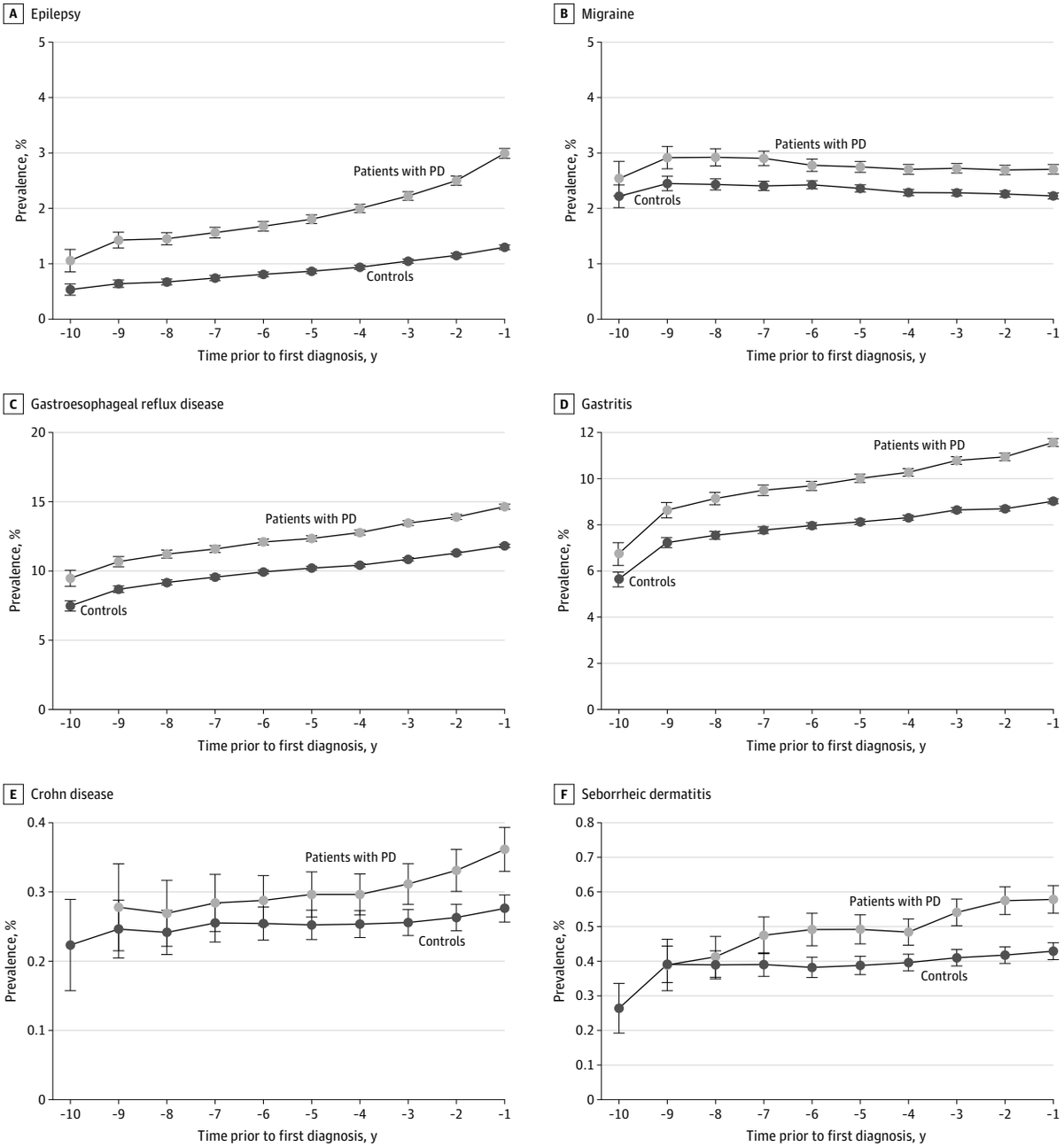
Prevalence of restless legs syndrome (A), sleep apnea (B), parasomnia (C), depression (D), schizophrenia (E), and bipolar disorder (F) associated with PD by year before diagnosis.

ulcer (OR, 1.25; 95% CI, 0.81-1.92) and peptic ulcer (OR, 1.34; 95% CI, 0.97-1.86). There was no significant association for cytomegaloviral disease (OR, 1.05; 95% CI, 0.61-1.79) and infectious mononucleosis (OR, 1.46; 95% CI, 0.94-2.25), but these were rare.

Discussion

In this large, representative, case-control study of PD based on claims data, we found a number of previously known

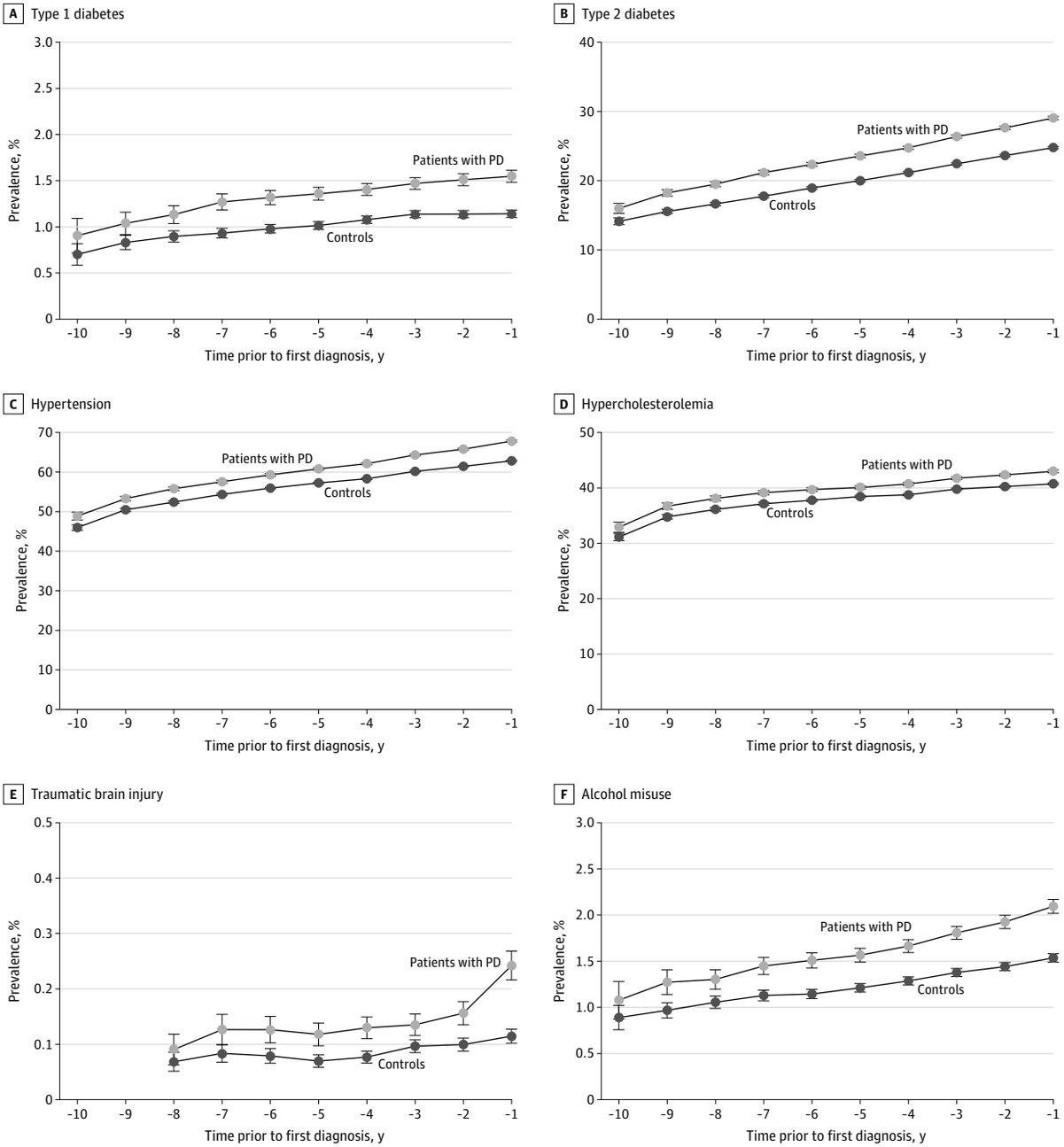
Figure 3. Prevalence of Some Comorbidities Associated With Parkinson Disease (PD) by Year Before Diagnosis Compared With Controls



Prevalence of epilepsy (A), migraine (B), gastroesophageal reflux disease (C), gastritis (D), Crohn disease (E), and seborrheic dermatitis (F) associated with PD by year before diagnosis.

early features and a range of previously unreported or controversial associations with subsequent diagnosis of PD. Among the early motor features, there were associations observed for tremor, which had a relatively high prevalence in those with a subsequent diagnosis of PD but rarely occurred in the control population (<1%). Changes in gait were common in both the PD and the control population but, together with shoulder pain and neck pain, were already increased 5 years before diagnosis, whereas detection of joint stiffness as a marker of rigidity was relatively uncommon before diagnosis. Consistent with previous reports,[1] we found associations with neuropsychiatric features of early and prodromal PD, including depression and less commonly, anxiety,[1] notably even in the earliest prediagnostic period. Interestingly, these neuropsychiatric features included memory complaints even more than 5 years before diagnosis,

Figure 4. Prevalence of Other Risk Factors Associated With Parkinson Disease (PD) by Year Before Diagnosis Compared With Controls



Prevalence of type 1 diabetes (A), type 2 diabetes (B), hypertension (C), hypercholesterolemia (D), traumatic brain injury (E), and alcohol misuse (F) with 95% CI error bars for each year before diagnosis of PD.

albeit much less commonly than depression or anxiety. Among the autonomic features, dizziness was present in more than 10% of patients more than 5 years before diagnosis of PD. Hypotension was relatively rare overall but more frequent in subsequent PD cases than in controls in all time periods. Possible interactions of hypotension with medication could not be assessed with our data. Constipation was only present in a relatively small proportion of patients before diagnosis of PD in this study, which was lower than in previous studies[1,2] and may be due to underreporting. Sexual dysfunction and symptoms of neurogenic bladder disturbances had a low prevalence but were more frequently reported than in controls across all time periods. All sleep disorders were more common in the group with subsequent PD than in controls, including diagnostic codes used for parasomnias. This diagnostic code also covers RBD for which no

specific code was available. However, other sleep disturbances, including insomnia, were also more commonly diagnosed before PD diagnosis as previously reported.[1,47] RBD is thought to affect approximately 1% of the general population,[48] but the condition is probably undiagnosed in the majority of patients because symptoms of RBD or other sleep disturbances are often underreported and undervalued in routine care. Furthermore, it is possible that diagnoses of sleep disorders, including parasomnias, nightmares, and insomnia, reflect underlying RBD, which would require specific questioning and polysomnography for a definite diagnosis. Sleep apnea has also been reported to be increased in patients with PD and been associated with risk of subsequent PD.[49,50] Although information on diagnostic test results was not available, our study results also suggested an associated increased risk of a clinical diagnosis of sleep apnea in cases with a subsequent diagnosis of PD. Hypersomnia, although more common in those with subsequent diagnosis of PD, was not frequently diagnosed. This may have been due to low prevalence, underdiagnosis, or underreporting of symptoms by patients. The most common occurrence of all sleep disorders associated with subsequent PD occurred for restless legs syndrome, which was at least 4 times more commonly diagnosed in those with subsequent PD than in controls and was also relatively frequent (4%-6% of patients). Although restless legs syndrome is recognized as a feature of PD (it may be of heterogeneous origin[51]), it is also common in the general population. Thus far, there has been controversial evidence for an association of restless legs syndrome and subsequent PD.[11,12,52] Among the sensory systems, hyposmia is recognized to be almost universally present in established PD and predates the diagnoses often by many years or decades.[10,53-55] However, it rarely leads to subjective complaints severe enough to require medical attention. Nevertheless, we found that anosmia, the most severe form of loss of sense of smell, was more common in those with subsequent diagnosis of PD, albeit rare (<1%), in all examined time periods. We also found that hearing loss, a relatively common disorder in the general population, was more prevalent in those with subsequent diagnosis of PD than in controls, even more than 5 years before diagnosis. Although an association of hearing loss with Alzheimer disease has long been recognized,[56,57] this has only rarely been reported for PD.[41,58] Subjective visual complaints, which are also common in PD,[59] were not a common feature associated with subsequent PD. Unspecified pain, another common sensory feature of PD,[60] was present in a large number of patients before the diagnosis of PD and more common than in controls in all examined time periods as has been previously reported.[1] To our knowledge, a new finding of this study was an association with diagnoses reflecting changes in skin sensation. Such sensations have been reported in established PD before[61,62] but not as a prodromal feature of PD. If confirmed in future studies, this may indicate early sensory changes that reflect central changes in skin perception similar to pain but may also be linked with skin disorders as outlined subsequently. However, as the diagnostic codes used may reflect a number of different complaints, further research is needed to identify whether there is a more specific association for some of these sensory complaints.

Consistent with previous reports,[4] results of our study suggest that risk factors such as traumatic brain injury and alcohol misuse were positively associated with a diagnosis of PD, and nicotine use was negatively associated with PD. There was also an increased OR for previous diagnoses of hypertension and hypercholesterinemia in those with subsequent diagnosis of PD, in keeping with some but not other previous reports.[26-29] Diabetes type 2 has previously been reported to be associated with subsequent diagnosis of PD, although more and larger-scale studies were thought to be required,[31] and diabetes type 1 has not been previously reported to be increased in patients with PD or before diagnosis. If confirmed, these associations may represent potentially modifiable risk factors for PD and may also suggest potential mechanisms contributing to the evolution of PD. Although vascular pathology may lead to development of parkinsonian syndromes not related to an underlying α-synucleinopathy, mendelian randomization and preclinical studies have suggested that diabetes is causally related to occurrence and progression of PD.[30,31,63]

Comorbidities

We found associations of schizophrenia and bipolar disorder with a subsequent diagnosis of PD, with a 4- to 5-fold increase in risk across all time periods. Although a proportion of these cases may be due to use of dopamine antagonistic medications, which cannot always be discontinued when parkinsonism occurs, there is also increasing evidence that the use of antidopaminergics may not be the only driver of these associations[36,37] but rather other factors such as a shared genetic background of both disorders.[36,64] A recent study[37] that used several approaches to investigate the association of schizophrenia with subsequent development of PD (including clinical records and diagnoses made by neurologists based on the UK Brain Bank or the Movement Disorder Society clinical criteria with follow-up over several years, the use of time limits for diagnosis and patient age, and the exclusion of patients with secondary parkinsonism) showed a clear associated increased risk of PD in those with schizophrenia, with abnormal DaTscans in those examined. Our own study, however, did not allow us to identify the medication of the cases to test this assumption further, and it is likely that at least some of the association is nevertheless secondary to the use of dopamine antagonistic medication. Similar confounding may partly contribute to the greater than 2-fold increased associated risk of epilepsy in the prediagnostic period, related to the use of the antiepileptic sodium valproate, and the less-pronounced but consistent increased rate of migraine in all prediagnostic time periods. It is also possible that patients with these diagnoses are more likely to be diagnosed with PD as they are already under neurologic or other medical follow-up care explaining some of the increase in risk.

In addition to the changes in skin sensation previously discussed, there was an association with a number of skin disorders that were examined because of their previously reported association with established or prodromal PD.[15,65] These included not only seborrheic dermatitis, which is common in

PD, but also psoriasis and dermatophytosis, reflecting fungal infection of the skin. Although the diagnostic certainty of these diagnoses is not known, these findings suggest early skin involvement, eg, through deposition of α-synuclein, which has been suggested to provide a means for early diagnosis through skin biopsy.[17,66,67] Given the interest in the early involvement of the gastrointestinal system, with possible infectious etiology and the possible propagation of PD-related pathology through the vagal nerve, we examined associations of a number of gastrointestinal diagnoses with subsequent diagnosis of PD. We did not find a significant association with cytomegalovirus disease or infectious mononucleosis, which had been previously postulated[19-21] during the observation period. However, the rarity of these diagnoses precludes firm conclusions. On the other hand, we found that gastritis, gastroesophageal reflux, gastric ulcer, and, in the most recent time period, duodenal ulcer, Crohn disease, and ulcerative colitis were associated with subsequent PD. This suggests that gastrointestinal pathology beyond constipation can occur in the prodrome of PD and may reflect early changes in gut motility, changes in constitution of gastric fluid, altered composition of the gastrointestinal microbiome, gastric infections, or other pathologies (in particular, inflammatory disorders). This may also underlie the association with osteoarthritis and seronegative arthritis, which occurred even more than 5 years before diagnosis, although misattribution of some early PD symptoms to these diagnoses cannot be excluded. Overall, it is possible that patients who present in the prodromal phase of PD receive other diagnoses related to increased medical attention. This possibility of a surveillance bias is an important consideration that has been highlighted previously[68] and may account for some of the less-pronounced associations in the years leading up to the diagnosis of PD. Taken together with the large sample size of this study, we therefore suggest cautious interpretation in terms of etiologic inference. Nonetheless, even these associations still highlight the value of an approach based on these presentations for identifying persons at higher risk of PD. Although at present these associations do individually not allow use for clinical diagnosis or counseling, several approaches exist that use a combination of prodromal features and risk factors for research purposes,[69-71] and the associations found in this study could enhance these approaches as well as support exploration of different phenotypes of PD even at the earliest stages. Further research should also explore whether associations found are particularly relevant to subgroups of patients with PD, such as those with RBD or anosmia, or whether a more generalizable, multisystem prodrome exists in the majority of patients with PD.

Strengths and Limitations

This study had several strengths. This was a large case-control study of PD and is representative of the general population of Germany in primary care. It also included information on diagnosis of PD from general and specialist practices, independent of health care professional, providing a comprehensive data set of those with a diagnosis of PD. This extends and confirms our previously reported analysis of some of the included risk factors and prodromal features of PD in the German specialist practices.[2]

This study also had limitations, as it relied on diagnosis of PD using patient medical records, and application of diagnostic criteria was not possible. Although other electronic health care databases, such as The Health Improvement Network in the UK, have shown acceptable accuracy of primary care diagnosis of PD using a single diagnostic code,[1] albeit with slightly higher incidence rates,[72] no validation study is available in this data source. The diagnostic codes used for prodromal features and risk factors may also not always be accurate or precise, given that the medical records used were based on a routine care database. These diagnostic limitations should be taken into account as detailed in the discussion. We were also not able to access information on medication and tried to interpret findings cautiously, where a suspected medication-induced effect is possible. However, equally unrecognized medication effects may not be acknowledged, eg, for medications used to treat gastritis or gastroesophageal reflux. Furthermore, the database only includes diagnoses made according to *ICD-10* codes. More subtle symptoms or features are likely to have been underrecognized. It is also important to note that secondary analysis of claims data is not meant to confirm, but rather to generate, hypotheses on potential associations that can be tested in subsequent primary studies.

Conclusions

Given the size and study period, we believe that this case-control study has generated valuable hypotheses on the associations found between PD and certain risk factors, comorbidities, and prodromal symptoms in a representative population. These associations may reflect possible early extrastriatal and extracerebral pathology of PD due to shared genetic risk with PD, medication exposure, or direct causation, or represent pathophysiologically relevant factors contributing to the pathogenesis of PD. Subtle associations require future testing in prospective controlled studies.

ARTICLE INFORMATION

Author Affiliations: Department of Clinical and Movement Neurosciences, University College London, London, United Kingdom (Schrag); Institut für Sozialmedizin, Arbeitsmedizin und Public Health der Medizinischen Fakultät der Universität Leipzig, Leipzig, Germany (Bohlken); Central Research Institute of Ambulatory Health Care in Germany, Department of Epidemiology and Healthcare Atlas, Berlin, Germany (Dammertz, Akmatov, Bätzing, Holstiege); Deutsches Zentrum für Neurodegenerative Erkrankungen Rostock/Greifswald, Rostock, Germany (Teipel); Department of Psychosomatic Medicine, University of Rostock, Rostock, Germany (Teipel); Department of Neurology, University of Rostock, Rostock, Germany (Hermann).

Author Contributions: Dr Schrag had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Schrag, Bohlken, Teipel, Akmatov, Bätzing, Holstiege.

Acquisition, analysis, or interpretation of data: Schrag, Dammertz, Hermann, Akmatov, Bätzing, Holstiege.
Drafting of the manuscript: Schrag, Dammertz, Teipel.
Critical revision of the manuscript for important intellectual content: Bohlken, Teipel, Hermann, Akmatov, Bätzing, Holstiege.
Statistical analysis: Schrag, Akmatov, Holstiege.
Administrative, technical, or material support: Dammertz, Bätzing.
Supervision: Schrag, Bohlken, Teipel, Bätzing, Holstiege.

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JAMA Neurology | Original Investigation

Association Between Antiepileptic Drugs and Incident Parkinson Disease

Daniel Belete, MBChB; Benjamin M. Jacobs, MSc; Cristina Simonet, MD; Jonathan P. Bestwick, MSc; Sheena Waters, PhD; Charles R. Marshall, PhD; Ruth Dobson, PhD; Alastair J. Noyce, PhD

IMPORTANCE Recent studies have highlighted an association between epilepsy and Parkinson disease (PD). The role of antiepileptic drugs (AEDs) has not been explored.

OBJECTIVE To investigate the association between AEDs and incident PD.

DESIGN, SETTING, AND PARTICIPANTS This nested case-control study started collecting data from the UK Biobank (UKB) in 2006, and data were extracted on June 30, 2021. Individuals with linked primary care prescription data were included. Cases were defined as individuals with a Hospital Episode Statistics (HES)–coded diagnosis of PD. Controls were matched 6:1 for age, sex, race and ethnicity, and socioeconomic status. Prescription records were searched for AEDs prescribed prior to diagnosis of PD. The UKB is a longitudinal cohort study with more than 500 000 participants; 45% of individuals in the UKB have linked primary care prescription data. Participants living in the UK aged between 40 and 69 years were recruited to the UKB between 2006 and 2010. All participants with UKB-linked primary care prescription data (n = 222 106) were eligible for enrollment in the study. Individuals with only a self-reported PD diagnosis or missing data for the matching variables were excluded. In total, 1477 individuals were excluded; 49 were excluded due to having only self-reported PD, and 1428 were excluded due to missing data.

EXPOSURES Exposure to AEDs (carbamazepine, lamotrigine, levetiracetam, and sodium valproate) was defined using routinely collected prescription data derived from primary care.

MAIN OUTCOMES AND MEASURES Odds ratios and 95% CIs were calculated using adjusted logistic regression models for individuals prescribed AEDs before the first date of HES-coded diagnosis of PD.

RESULTS In this case-control study, there were 1433 individuals with an HES-coded PD diagnosis (cases) and 8598 controls in the analysis. Of the 1433 individuals, 873 (60.9%) were male, 1397 (97.5%) had their race and ethnicity recorded as White, and their median age was 71 years (IQR, 65-75 years). An association was found between AED prescriptions and incident PD (odds ratio, 1.80; 95% CI, 1.35-2.40). There was a trend for a greater number of prescription issues and multiple AEDs being associated with a greater risk of PD.

CONCLUSIONS AND RELEVANCE This study, the first to systematically look at PD risk in individuals prescribed the most common AEDs, to our knowledge, found evidence of an association between AEDs and incident PD. With the recent literature demonstrating an association between epilepsy and PD, this study provides further insights.

Author Affiliations: Preventive Neurology Unit, Wolfson Institute of Population Health, Faculty of Medicine and Dentistry, Queen Mary University of London, London, United Kingdom (Belete, Jacobs, Simonet, Bestwick, Waters, Marshall, Dobson, Noyce); Department of Neurology, Royal London Hospital, Barts Health NHS Trust, London, United Kingdom (Jacobs, Marshall, Dobson, Noyce).

Corresponding Author: Alastair J. Noyce, PhD, Preventive Neurology Unit, Wolfson Institute of Preventive Medicine, London EC1M 6BQ, United Kingdom.

There is evidence for an association between Parkinson disease (PD) and epilepsy.[1-3] Recent observational studies have also established a temporal association between epilepsy and incident PD.[3,4] The mechanism underlying this association remains unclear.

It is plausible that antiepileptic drugs (AEDs) may account for some or all of the apparent association between epilepsy and PD. Various AEDs list movement disorders (such as parkinsonism, postural tremor, and dystonia) as possible adverse events, but the association between AEDs and PD has not been well studied.[5] It remains unclear whether AEDs may partly explain recently reported associations between epilepsy and PD. We used the UK Biobank (UKB) and linked primary care medication data to investigate the association between AED prescriptions and incident PD.

Key Points

Question Are antiepileptic drugs (AEDs) associated with increased risk of developing Parkinson disease (PD)?

Findings In this case-control study of 1433 individuals with a Hospital Episode Statistics–coded diagnosis of PD and 8598 controls in the UK Biobank, prescription of an AED was associated with an increased risk of subsequent PD.

Meaning The findings of this study suggest an association between certain AEDs and PD; the relative contribution of epilepsy and AEDs should be further examined in light of these findings.

Methods

Cohort

The UKB is a large cohort study that includes data on more than 500 000 participants from the UK. The methods of data collection have been described elsewhere.[6] In 2019, the UKB released linked primary care data for 45% of its participants. This included prescription data in the form of Read version 2, the *British National Formulary*, and the *NHS Dictionary of medicines and devices* codes. Where available, drug names and quantities were also provided.

Exposure and Outcome Definitions

We conducted a nested case-control study in the UKB. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline. We defined PD cases as individuals with a Hospital Episode Statistics (HES) (field identification [ID] 41270, *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* code G20). Controls were matched to year of birth (field ID 34), sex (field ID 31), socioeconomic class quartiles measured using the Townsend deprivation index (field ID 189), and race and ethnicity (field ID 21000). Risk factors for PD may be associated with race and ethnicity; therefore, we controlled for race and ethnicity in this study. Race and ethnicity were self-reported by participants. Participants were asked "What is your ethnic group?" Options were White, mixed, Asian or Asian British, Black or Black British, Chinese, other ethnic group, do not know, or prefer not to answer. Sequential questions further clasifying race and ethnicity were then asked.

Individuals with a self-reported PD diagnosis but no HES diagnostic code were excluded from the primary analysis. Six controls were matched for each case. Date of diagnosis was set to the first date an HES PD code was found in hospital records. This was used as an index date for cases. Controls were assigned an index date set to the date of diagnosis of their matched case.

Medications were searched for using Read version 2 codes and drug names and descriptions (eTable 1 in the Supplement). The first prescription issue date was used as the date of starting an AED. Prescriptions after the index date were excluded from the analysis. Individuals were divided into quartiles based on the number of prescription issues for all AEDs, with those in the first quartile with the fewest issues and those in the fourth quartile with the most issues. We searched for the 4 most commonly prescribed AEDs in the UK (sodium valproate, lamotrigine, carbamazepine, and levetiracetam).[7] We also conducted a wider search of AEDs in the cohort (eTable 2 in the Supplement).

Sensitivity analyses were performed. We excluded prescriptions issued within 1-, 2-, and 5-year windows prior to the index date. The association with self-reported PD (field ID 20002) was also studied. For this analysis, all individuals with a self-reported PD diagnosis were included; individuals with an HES PD code but no self-reported PD diagnosis were excluded. The self-reported date of diagnosis (field ID 20008) was used as the date of diagnosis. We also conducted a further sensitivity analysis with a more stringent definition of PD; HES diagnosis and 2 or more prescriptions for PD medications (levodopa, dopamine receptor agonists, and monoamine oxidase B inhibitors).

Informed written consent was obtained from all participants on enrollment in the UKB. Participants were free to withdraw their consent at any time, at which time their data were censored and excluded from future analysis. The UKB has approval from the North West Multicentre Research Ethics Committee.

Statistical Analysis

Statistical analysis was performed in R, version 3.6.1 (R Project for Statistical Computing). R scripts used in this study are available at GitHub.[8] Logistic regression models, adjusting for age, sex, and Townsend deprivation index, were used to calculate odds ratios (ORs) and 95% CIs. A second logistic regression model was built adjusting for age, sex, Townsend deprivation index, and HES epilepsy diagnosis to investigate epilepsy as a potential confounding factor. Individuals with missing data for matching variables were excluded from the analysis.

Results

Demographic Characteristics

There were 222 106 individuals in the UKB with linked primary care medication data. In total, 1477 individuals were

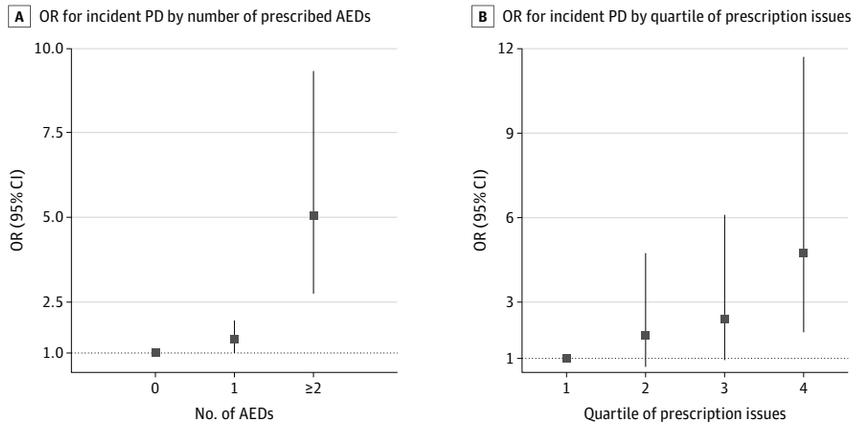
Table. ORs of Antiepileptic Drugs and Their Association With PD

Medication	Cases (n = 1433)	Controls (n = 8598)	OR for PD (95% CI)	*P* value[a]
Any antiepileptic drug	62	211	1.80 (1.35-2.40)	6.93×10^{-5}
Carbamazepine	32	135	1.43 (0.97-2.11)	.07
Lamotrigine	15	32	2.83 (1.53-5.25)	9.29×10^{-4}
Levetiracetam	12	24	3.02 (1.51-6.05)	1.85×10^{-3}
Sodium valproate	30	48	3.82 (2.41-6.05)	1.17×10^{-8}

Abbreviations: OR, odds ratio; PD, Parkinson disease.

[a] Asymptotic *P* values were calculated from the *z* statistic.

Figure. Forest Plot of Odds Ratios (ORs) of Number of Different Antiepileptic Drugs (AEDs) and Number of AEDs Issues for Parkinson Disease (PD)



excluded; 49 were excluded due to having only self-reported PD, and 1428 were excluded due to missing data for matching variables. Of 1443 individuals with an HES-coded PD diagnosis, 1433 had complete data for year of birth, sex, Townsend deprivation index, and race and ethnicity. There were 8598 matched controls. The median age at PD diagnosis was 71 years (IQR, 65-75 years). Of the 1433 participants with PD (cases) 873 (60.9%) were male, and 1397 (97.5%) had their race and ethnicity recorded as White (eTable 3 in the Supplement).

In this nested case-control cohort study, there were 62 individuals (4.3%) with an AED prescription prior to their date of PD diagnosis. In the control group, there were 211 individuals (2.5%) prescribed an AED before the index date (eTable 4 in the Supplement). In the cases, 63 (4.4%) had an epilepsy diagnosis compared with 113 (1%) of the controls. Of the individuals with 2 or more issues of a PD medication, 96% had an HES-coded PD diagnosis. The remaining 4% had a self-reported PD diagnosis.

Association Between AED and PD

There was evidence of an association of lamotrigine, levetiracetam, and sodium valproate with PD, with weaker evidence for carbamazepine (**Table**). The OR for PD following prescription of any AED was 1.80 (95% CI, 1.35-2.40). The odds of incident PD were higher among individuals prescribed more than 1 AED and among individuals with higher numbers of issues (**Figure**). The number of prescriptions issued for AEDs ranged from 1 to 1354, with a median of 10. Evidence of an association remained between sodium valproate and PD in the model adjusting for age, sex, Townsend deprivation index, and epilepsy (eTable 5 in the Supplement).

Sensitivity Analyses

Excluding prescriptions issued 1, 2, and 5 years before the date of PD diagnosis did not alter the strength of any association between individual AEDs and PD except for carbamazepine at 1 year (eTable 6 in the Supplement). There were 410 individuals with a self-reported PD diagnostic code. As with HES-coded PD, being prescribed an AED was associated with an increased risk of an incident self-reported PD diagnosis (OR, 2.23; 95% CI, 1.11-4.48). Of those with a PD diagnosis, 913 of 1433 individuals (63.7%) had a record of 2 or more issues of a PD medication. With this more stringent definition of PD, strong evidence of an association remained for sodium valproate (eTable 7 in the Supplement).

Discussion

Using linked prescription records and health care data from UKB, we found an association between AED use and incident PD. We used a nested case-control design to identify 1433 PD cases and 8598 matched controls. The magnitude of the association increased with the number of discrete AEDs prescribed and the number of prescription issues. Having multiple discrete AEDs or multiple prescription issues over time is a useful proxy for long-term exposure to AEDs in the absence of accurate information on duration of medication use.

On an individual drug level, we observed associations of the use of lamotrigine, levetiracetam, and sodium valproate with PD. The association between sodium valproate and incident PD was most robust and remained even after adjusting for epilepsy diagnosis.

These findings are consistent with previous reports of an association between epilepsy and PD.[1-4] One explanation for the association between epilepsy and PD is that medications prescribed to treat epilepsy may increase PD risk.

It is plausible that AEDs are associated with drug-induced parkinsonism, which is misdiagnosed (or misrecorded) as idiopathic PD. We tried to mitigate the risk of misclassification in our analysis by using stringent definitions of incident PD incorporating multiple sources of diagnostic codes and prescription of PD treatments. Furthermore, to exclude cases of transient drug-induced parkinsonism, which may abate on cessation of the drug, we excluded AED prescriptions within 1, 2, and 5 years of the PD diagnosis date. Although this analysis would not remove individuals with tardive parkinsonism, this condition is relatively rare with AED use and is unlikely to be a major source of bias.[9] The latter analysis also reduces the possibility of reverse causation, in which some patients with PD may have been treated with selected AEDs for early mood or neuropsychiatric symptoms.

Studies have shown that AEDs have the potential to interfere in dopamine pathways. Both carbamazepine and sodium valproate are associated with downregulation of dopamine receptors and dopamine insensitivity.[10,11] While this may explain drug-induced parkinsonism, it is likely that other factors may contribute to PD pathogenesis. In a case series with extended follow-up, Dal and Whyte[12] found that patients who initially experienced remission of drug-induced parkinsonism symptoms after stopping AED treatment later developed PD. This may suggest that these patients had subclinical PD or were at risk of PD. While we are not aware of prospective data to support or refute this observation, it is supported by postmortem studies showing that individuals with drug-induced parkinsonism have reduced levels of homovanillic acid and dopamine in the striatum.[13] It has also been observed that individuals taking levetiracetam were at higher risk of psychotropic adverse effects if they had genetic variants associated with decreased dopamine activity.[14]

Limitations

A major limitation of the study is that epilepsy is a common reason for admission to the hospital. In HES data, ascertainment of PD may contribute to the observed associations simply because patients with epilepsy had been admitted to the hospital more than patients without epilepsy. Our study was likely to be underpowered to detect effects in some of our sensitivity analysis. In particular, further work in larger cohorts is needed to fully assess the effects of AEDs on individuals without epilepsy. Although we studied the 4 most commonly prescribed AEDs in the UK, these findings cannot be generalized to other AEDs. Other limitations of this study include the generalizability of the UKB cohort to a wider UK population (although it should be noted that the prevalence of epilepsy in the control group closely matched that in the UK more generally[15]), that medication data are available only for roughly 45% of the UKB cohort, and that data quality and missingness meant that overall lifetime dose exposure was difficult to determine.

Conclusion

To the best of our knowledge, this is the first observational study to investigate a range of AEDs and their association with incident PD. As such, it sets the scene and highlights the need for further work to corroborate our findings in other large data sets because these findings could have important implications for clinical decision-making. The underlying reasons for an association between AEDs and PD should be further explored.

ARTICLE INFORMATION

Author Contributions: Drs Belete and Noyce had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Belete, Jacobs, Simonet, Dobson, Noyce.
Acquisition, analysis, or interpretation of data: Belete, Jacobs, Bestwick, Waters, Marshall, Noyce.
Drafting of the manuscript: Belete, Jacobs, Noyce.
Critical revision of the manuscript for important intellectual content: Belete, Jacobs, Simonet, Bestwick, Waters, Marshall, Dobson.
Statistical analysis: Belete, Jacobs, Bestwick, Waters, Noyce.
Obtained funding: Marshall, Noyce.
Administrative, technical, or material support: Belete, Jacobs, Waters, Dobson, Noyce.
Supervision: Jacobs, Marshall, Dobson, Noyce.

Conflict of Interest Disclosures: Dr Waters reported receiving grants from UK Research and Innovation. The Innovate UK grant was received by his supervisor and funded his Research Associate position during the conduct of the study. Dr Marshall reported receiving grants from Tom and Sheila Springer Charity and grants from Barts Charity during the conduct of the study; grants from the National Institute for Health and Care Research (NIHR), grants from Innovate UK, grants from the Michael J. Fox Foundation, and grants from Alzheimer's Research UK outside the submitted work. Dr Dobson reported grants from the Multiple Sclerosis Society of Great Britain and Northern Ireland, grants from the National Multiple Sclerosis Society, grants from the BMA Foundation, grants from the Horne Family Charitable Trust, grants from the Medical Research Council, grants from the NIHR, grants from Biogen, grants from Merck, grants from Celgene (now Bristol Myers Squibb), and personal fees from Novartis, Janssen Biogen, Merck, Teva, and Roche. Dr Noyce reported receiving grants from Barts Charity, Parkinson's UK, Cure Parkinson's, the Michael J. Fox Foundation, Innovate UK, Solvemed, and Alchemab and personal fees from AstraZeneca, AbbVie, Zambon, BIAL, uMedeor, Alchemab, Britannia, and Charco Neurotech outside the submitted work. No other disclosures were reported.

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JAMA Neurology | Brief Report

Predictors of Atrial Fibrillation in Patients With Stroke Attributed to Large- or Small-Vessel Disease

A Prespecified Secondary Analysis of the STROKE AF Randomized Clinical Trial

Lee H. Schwamm, MD; Hooman Kamel, MD; Christopher B. Granger, MD; Jonathan P. Piccini, MD; Jeffrey M. Katz, MD; Pramod P. Sethi, MD; Evgeny V. Sidorov, MD, PhD; Scott E. Kasner, MD; Scott B. Silverman, MD; Theodore T. Merriam, MS; Noreli Franco, PhD; Paul D. Ziegler, MS; Richard A. Bernstein, MD, PhD; for the STROKE AF Investigators

IMPORTANCE The Stroke of Known Cause and Underlying Atrial Fibrillation (STROKE AF) trial found that approximately 1 in 8 patients with recent ischemic stroke attributed to large- or small-vessel disease had poststroke atrial fibrillation (AF) detected by an insertable cardiac monitor (ICM) at 12 months. Identifying predictors of AF could be useful when considering an ICM in routine poststroke clinical care.

OBJECTIVE To determine the association between commonly assessed risk factors and poststroke detection of new AF in the STROKE AF cohort monitored by ICM.

DESIGN, SETTING, AND PARTICIPANTS This was a prespecified analysis of a randomized (1:1) clinical trial that enrolled patients between April 1, 2016, and July 12, 2019, with primary follow-up through 2020 and mean (SD) duration of 11.0 (3.0) months. Eligible patients were selected from 33 clinical research sites in the US. Patients had an index stroke attributed to large- or small-vessel disease and were 60 years or older or aged 50 to 59 years with at least 1 additional stroke risk factor. A total of 496 patients were enrolled, and 492 were randomly assigned to study groups (3 did not meet inclusion criteria, and 1 withdrew consent). Patients in the ICM group had the index stroke within 10 days before insertion. Data were analyzed from October 8, 2021, to January 28, 2022.

INTERVENTIONS ICM monitoring vs site-specific usual care (short-duration external cardiac monitoring).

MAIN OUTCOMES AND MEASURES The ICM device automatically detects AF episodes 2 or more minutes in length; episodes were adjudicated by an expert committee. Cox regression multivariable modeling included all parameters identified in the univariate analysis having *P* values <.10. AF detection rates were calculated using Kaplan-Meier survival estimates.

RESULTS The analysis included the 242 participants randomly assigned to the ICM group in the STROKE AF study. Among 242 patients monitored with ICM, 27 developed AF (mean [SD] age, 66.6 [9.3] years; 144 men [60.0%]; 96 [40.0%] women). Two patients had missing baseline data and exited the study early. Univariate predictors of AF detection included age (per 1-year increments: hazard ratio [HR], 1.05; 95% CI, 1.01-1.09; *P* = .02), CHA_2DS_2-VASc score (per point: HR, 1.54; 95% CI, 1.15-2.06; *P* = .004), chronic obstructive pulmonary disease (HR, 2.49; 95% CI, 0.86-7.20; *P* = .09), congestive heart failure (CHF; with preserved or reduced ejection fraction: HR, 6.64; 95% CI, 2.29-19.24; *P* < .001), left atrial enlargement (LAE; HR, 3.63; 95% CI, 1.55-8.47; *P* = .003), QRS duration (HR, 1.02; 95% CI, 1.00-1.04; *P* = .04), and kidney dysfunction (HR, 3.58; 95% CI, 1.35-9.46; *P* = .01). In multivariable modeling (n = 197), only CHF (HR, 5.06; 95% CI, 1.45-17.64; *P* = .05) and LAE (HR, 3.32; 1.34-8.19; *P* = .009) remained significant predictors of AF. At 12 months, patients with CHF and/or LAE (40 of 142 patients) had an AF detection rate of 23.4% vs 5.0% for patients with neither (HR, 5.1; 95% CI, 2.0-12.8; *P* < .001).

CONCLUSIONS AND RELEVANCE Among patients with ischemic stroke attributed to large- or small-vessel disease, CHF and LAE were associated with a significantly increased risk of poststroke AF detection. These patients may benefit most from the use of ICMs as part of a secondary stroke prevention strategy. However, the study was not powered for clinical predictors of AF, and therefore, other clinical characteristics may not have reached statistical significance.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT02700945

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The STROKE AF Investigators are listed in Supplement 3.

Corresponding Author: Lee H. Schwamm, MD, Department of Neurology, Massachusetts General Hospital, Department of Neurology, 55 Fruit St, Boston, MA 02114.

Atrial fibrillation (AF) is the most common cardiac arrhythmia newly diagnosed after stroke and likely includes cases of preexisting AF that had escaped detection before stroke as well as new-onset AF after stroke or stroke-induced AF.[1-3] The recent Stroke of Known Cause and Underlying Atrial Fibrillation (STROKE AF) trial, which included participants with stroke due to large- or small-vessel disease, found AF detected by insertable cardiac monitors (ICMs) at a rate of 12.1% at 1 year.[4] We sought to determine the association between commonly assessed risk factors and poststroke detection of new AF in the STROKE AF cohort.

Key Points

Question Are there commonly assessed risk factors associated with undiagnosed atrial fibrillation (AF) in patients with ischemic stroke attributed to large- or small-vessel disease?

Findings In this prespecified analysis of a randomized clinical trial that included 242 patients monitored with insertable cardiac monitors, the annual risk of detecting AF was significantly higher in patients with congestive heart failure and/or left atrial enlargement (23.4%) compared with patients without either condition (5.0%).

Meaning If these findings are replicated in other cohorts, the associations of congestive heart failure and left atrial enlargement with AF may be useful when considering an insertable cardiac monitor in routine poststroke clinical care.

Methods

Study Population

The STROKE AF trial has been previously described (Supplement 1).[4,5] Briefly, at baseline (April 1, 2016-July 12, 2019), 496 patients with an index ischemic stroke classified by the enrolling investigator as being due to large- or small-vessel disease using the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria[6] were included from 33 clinical research sites in the US. In total, 492 patients were randomly assigned to groups (3 did not meet inclusion criteria, and 1 withdrew consent) (eFigure in Supplement 2). All participants provided written informed consent, and the study was approved by all relevant institutional review boards. Patients were 60 years or older or aged 50 to 59 years with at least 1 stroke risk factor.[4,5] Participants were randomly assigned (1:1) to AF monitoring using an ICM (Reveal LINQ [Medtronic]) within 10 days of index stroke vs site-specific usual care. The ICM detects AF episodes of 2 minutes or longer, and first episodes of AF were adjudicated by a clinical events committee to confirm its diagnosis.

Statistical Analysis

This analysis was a prespecified ancillary outcome of the trial to identify variables associated with a first-detected AF episode through 12 months. Exposure variables were electrocardiographic and echocardiographic predictors of AF (**Table 1**). All participants randomly assigned to the ICM group were included, and only those with complete predictor data were included in the multivariable models.

To address high rates (40.8%) of missing left atrial volume index (LAVI) values, a post hoc composite variable for left atrial enlargement (LAE) was created and used for the primary analysis. Participants were classified as having LAE if they met any of the following accepted criteria[7-9]:

- LAVI greater than 28 mL/m^2.
- Male participant with LA diameter greater than 41 mm.
- Female participant with LA diameter greater than or equal to 39 mm.
- No measurements for LA volume or diameter, but LAE was documented in the echocardiography report.

LAE was classified as missing if none of this information was available. Variable selection for multivariable models was based on the outcomes of univariate models. Cox proportional-hazards regression models were fitted to various baseline characteristics for the prediction of AF. Predictors with *P* values <.10 in univariate models were included in a multivariable Cox model using a complete case data set. In all regression models, predictors were analyzed using 2-sided *P* values. A significance level of .05 was used in the multivariable Cox models, and hazard ratios (HRs) were calculated along with their 95% CIs. Data were analyzed from October 8, 2021, to January 28, 2022, using SAS software, version 9.4 (SAS Institute).

Results

The analysis included the 242 participants randomly assigned to the ICM group in the STROKE AF study. The mean (SD) age was 66.6 (9.3) years; 96 participants (40.0%) were women, and 144 (60.0%) were men (2 patients had missing baseline data and exited the study early). The eTable in Supplement 2 shows baseline characteristics for patients randomly assigned to ICM vs those with successful insertion (n = 221), and no meaningful differences were observed between the groups. Follow-up continued through August 2020 (from randomization to 12 months) for a mean (SD) duration of 11.0 (3.0) months. AF was detected in 27 patients in the ICM group (11.2%), and 26 first episodes (96.3%) were asymptomatic. None of the 7 patients who crossed over to the control group had AF detected.

Table 1 shows the univariate HR and 95% CI of AF detection at 12 months for each potential predictor. LAE was available for 214 participants (89.1%). Variables identified as univariate predictors of AF (based on a nominal *P* value <.10) included LAVI per 10-mL increments (HR, 2.30; 95% CI, 1.58-3.34; *P* < .001), LAE (HR, 3.63; 95% CI, 1.55-8.47; *P* = .003), chronic obstructive pulmonary disease (HR, 2.49; 95% CI, 0.86-7.20; *P* = .09), CHF (with preserved or reduced ejection fraction: HR, 6.64; 95% CI, 2.29-19.24; *P* < .001), kidney dysfunction (HR, 3.58; 95% CI, 1.35-9.46; *P* = .01), age (per 1-year increments: HR, 1.05; 95% CI, 1.01-1.09; *P* = .02), CHA_2DS_2-VASc score (per point: HR, 1.54; 95% CI, 1.15-2.06; *P* = .004), QRS duration (HR, 1.02; 95% CI, 1.00-1.04; *P* = .04), and LA diameter (per millimeter: HR, 1.05; 95% CI, 0.99-1.11; *P* = .08).

In the multivariable analysis (n = 197) shown in **Table 2**, only CHF (HR, 5.06; 95% CI, 1.45-17.64; *P* = .05) and LAE (HR,

Table 1. Univariate Analysis for Predictors of Atrial Fibrillation Detection at 12 Months in Participants of the Stroke of Known Cause and Underlying Atrial Fibrillation (STROKE AF) Trial

Predictor	No.	Hazard Ratio (95% CI)	*P* value
Age/y	240	1.05 (1.01-1.09)	.02[a]
Sex	240	1.40 (0.66-2.97)	.39
BMI	240	1.04 (0.98-1.10)	.20
Blood pressure			
Diastolic	240	0.98 (0.96-1.01)	.20
Systolic	240	1.01 (0.99-1.03)	.19
CHA2DS2-VASc score/point	240	1.54 (1.15-2.06)	.004[a]
Cerebral artery stenosis	240	1.18 (0.35-3.91)	.79
Chronic obstructive pulmonary disorder	240	2.49 (0.86-7.20)	.09[b]
Congestive heart failure	240	6.64 (2.29-19.24)	<.001[a]
Coronary artery disease	240	0.98 (0.34-2.84)	.98
Coronary artery bypass graft	240	1.35 (0.32-5.68)	.69
Coronary artery intervention	240	0.80 (0.19-3.36)	.76
Diabetes	240	1.37 (0.63-2.95)	.43
Heart rate	238	1.00 (0.97-1.03)	.87
Hypertension	240	1.35 (0.47-3.90)	.58
Left atrial diameter	166	1.05 (0.99-1.11)	.08[b]
Left atrial enlargement	214	3.63 (1.55-8.47)	.003[a]
Left atrial volume index (+10 mL/m^2)	142	2.30 (1.58-3.34)	<.001[a]
Myocardial infarction	240	0.50 (0.07-3.66)	.49
Peripheral vascular disease	240	1.81 (0.63-5.24)	.27
Kidney dysfunction	240	3.58 (1.35-9.46)	.01[a]
Sleep apnea	240	1.98 (0.68-5.73)	.21
PR interval/ms	218	1.00 (0.98-1.01)	.51
QRS duration/ms	219	1.02 (1.00-1.04)	.04[a]
QTc interval/ms	219	1.00 (1.00-1.01)	.35
RR interval/ ms	180	1.00 (1.00-1.00)	.26
Stroke/TIA prior to qualifying event			
Stroke or stroke-related event	240	0.76 (0.31-1.88)	.55
Ischemic stroke, of known origin	240	1.23 (0.49-3.04)	.66
Transient ischemic attack	240	0.76 (0.18-3.23)	.72
Modified Rankin Score	239	1.05 (0.82-1.34)	.71
NIHSS	240	1.02 (0.94-1.12)	.63
Qualifying stroke infarction location			
Brainstem	240	1.17 (0.44-3.08)	.76
Cerebellum	240	0.33 (0.04-2.42)	.28
Cerebral artery			
Anterior	240	1.25 (0.38-4.17)	.71
Middle	240	1.12 (0.52-2.38)	.77
Posterior	240	1.94 (0.82-4.59)	.13
Qualifying stroke side (left vs right)	240	1.00 (0.47-2.12)	>.99
Qualifying stroke type (small vessel vs large vessel)	242	1.14 (0.53-2.43)	.74

Abbreviations: BMI, body mass index; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attack.

[a] Significant at $P \leq .05$.

[b] Significant at $P < .10$ (cutoff for inclusion in multivariable models).

3.32; 95% CI, 1.34, 8.19; $P = .009$) were associated with an increased likelihood of detecting AF during 12 months of monitoring, with a trend toward significance for QRS duration (HR, 1.02; 95% CI, 1.00-1.04; $P = .06$). There was no statistically significant interaction between CHF and LAE. The rate of AF detection at 12 months among patients with either CHF and/or LAE (40 of 142 patients) was significantly higher compared with patients with neither attribute (23.4% vs 5.0%; HR, 5.1; 95% CI, 2.0-12.8; $P < .001$) (**Figure**).

Discussion

In this prespecified analysis of the STROKE AF randomized clinical trial of patients with ischemic stroke due to large- or small-vessel disease, those with CHF and/or LAE had an annual risk of AF that was substantially elevated compared with patients without CHF or LAE, with rates of 23.4% vs 5.0%, respectively. This translates to a number needed to monitor of

Table 2. Multivariable Analysis for Predictors of Atrial Fibrillation Detection at 12 Months in Participants of the Stroke of Known Cause and Underlying Atrial Fibrillation (STROKE AF) Trial

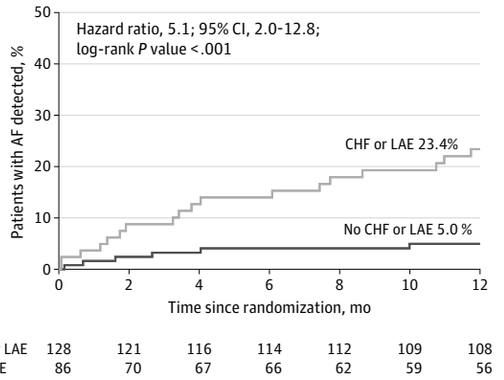
Stroke AF complete case ICM group (N = 197[a])		
Predictor	Hazard ratio (95% CI)	*P* value
Age/y	1.00 (0.94-1.06)	.98
CHA_2DS_2-VASc score/point	1.29 (0.83-2.02)	.26
Chronic obstructive pulmonary disorder	1.59 (0.41-6.19)	.51
Congestive heart failure	5.06 (1.45-17.64)	.05[b]
Left atrial enlargement	3.32 (1.34-8.19)	.009[b]
QRS duration/ms	1.02 (1.00-1.04)	.06
Kidney dysfunction	2.33 (0.76-7.18)	.14

Abbreviation: ICM, insertable cardiac monitor.

[a] 197 patients with ICM had complete case data for all predictors and outcome.

[b] Significant at $P \leq .05$.

Figure. Rate of Atrial Fibrillation (AF) Detection at 12 Months Among Patients With Congestive Heart Failure (CHF) or Left Atrial Enlargement (LAE)



No. at risk

No CHF or LAE	128	121	116	114	112	109	108
CHF or LAE	86	70	67	66	62	59	56

Increased AF detection in patients with CHF and/or LAE in participants randomized to insertable cardiac monitor (ICM) in the Stroke of Known Cause and Underlying Atrial Fibrillation (STROKE AF) trial through 12 months compared with participants without either condition (23.4% vs 5%; $P < .001$).

just over 5 to detect AF in the first 12 months. Using an ICM to continuously monitor these patients also showed the rate of AF detection over time. Selecting individuals with risk factors such as CHF and LAE for monitoring could lead to higher rates of AF detection.

Most patients with ischemic stroke are treated with antiplatelet agents. Detection of AF after stroke is important regardless of whether it predated the index stroke because it often leads to an evidence-based change in therapy. However, the optimal management of patients with AF and symptomatic atherosclerotic disease is unknown. Likewise, the efficacy and safety of oral anticoagulant (OAC) therapy is not established in patients with large- and small-vessel atherosclerotic disease and coexisting AF. It is well established that antiplatelet therapy alone is inadequate for recurrent stroke prevention in AF.[10] To answer these questions, randomized clinical trials are necessary.

An overemphasis on monitoring for AF only in patients with an index cryptogenic embolic stroke may be doing patients a disservice by failing to detect and intervene on clinically meaningful AF in patients with other index stroke subtypes. Given the high rates of recurrent stroke among patients in general, and particularly in those with AF, identifying the subset of patients with the greatest probability of future AF detection should be the focus rather than relying solely on the index stroke mechanism. This concept is supported by the nearly identical rates of AF detected by ICM at 1 year in the STROKE AF[4] and Cryptogenic Stroke and Underlying AF (CRYSTAL AF)[11] trials (12.1% and 12.4%, respectively), suggesting that stroke mechanism alone does not explain the likelihood of underlying AF.

Currently, it remains unclear whether OAC for poststroke AF detected by ICM is beneficial to prevent secondary strokes and what AF burden is sufficient to produce benefit from OAC. However, early detection of poststroke AF would allow for continued close monitoring to detect when patients cross the threshold to a clinically meaningful AF burden before a recurrent stroke occurs. Future studies are needed to determine the proper thresholds for initiating OAC therapy in patients with ICM-detected AF after stroke.

Limitations

Our study has several important limitations. Although the data were acquired prospectively and in a randomized clinical trial setting with adjudicated end points, the trial was not powered to detect clinical predictors of AF, and therefore, other clinical characteristics may not have reached statistical significance. Our limited sample size may explain why variables such as age and CHA_2DS_2-VASc score did not reach statistical significance in our modeling.

Conclusions

In summary, in this prespecified analysis of patients from the STROKE AF randomized clinical trial who were continuously monitored for AF, participants with CHF or LAE were at greater risk of having AF detected at 12 months than those without either and may represent an enriched population for monitoring with ICM. Although preliminary in nature, if the findings from our study are replicated in other cohorts, then the associations of CHF and LAE with AF may be useful when considering an ICM in routine poststroke clinical care.

ARTICLE INFORMATION

Author Affiliations: Department of Neurology, Massachusetts General Hospital, Boston (Schwamm); Department of Neurology, Weill Cornell Medicine, New York, New York (Kamel); Deputy Editor, *JAMA Neurology* (Kamel); Duke Clinical Research Institute, Duke University Medical Center, Durham, North Carolina (Granger, Piccini); Department of Neurology and Radiology, North

Shore University Hospital, Manhasset, New York (Katz); Guilford Neurology Associates, Moses H. Cone Hospital, Greensboro, North Carolina (Sethi); Department of Neurology, The University of Oklahoma Health Sciences Center, Oklahoma City (Sidorov); Perelman School of Medicine, University of Pennsylvania, Philadelphia (Kasner); Department of Neurology, Massachusetts General Hospital, Boston (Silverman); Clinical Department, Medtronic, Minneapolis, Minnesota (Merriam, Franco); Research Department, Medtronic, Minneapolis, Minnesota (Ziegler); Davee Department of Neurology, Feinberg School of Medicine of Northwestern University, Chicago, Illinois (Bernstein).

Author Contributions: Drs Schwamm and Bernstein had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Schwamm, Granger, Katz, Ziegler, Bernstein.
Acquisition, analysis, or interpretation of data: Schwamm, Kamel, Piccini, Sethi, Sidorov, Kasner, Silverman, Merriam, Franco, Ziegler, Bernstein.
Drafting of the manuscript: Schwamm, Merriam, Franco.
Critical revision of the manuscript for important intellectual content: Kamel, Granger, Piccini, Katz, Sethi, Sidorov, Kasner, Silverman, Merriam, Franco, Ziegler, Bernstein.
Statistical analysis: Merriam.
Administrative, technical, or material support: Sidorov, Silverman, Franco, Ziegler.
Supervision: Schwamm, Sethi, Sidorov, Franco, Bernstein.

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Data Sharing Statement: See Supplement 4.

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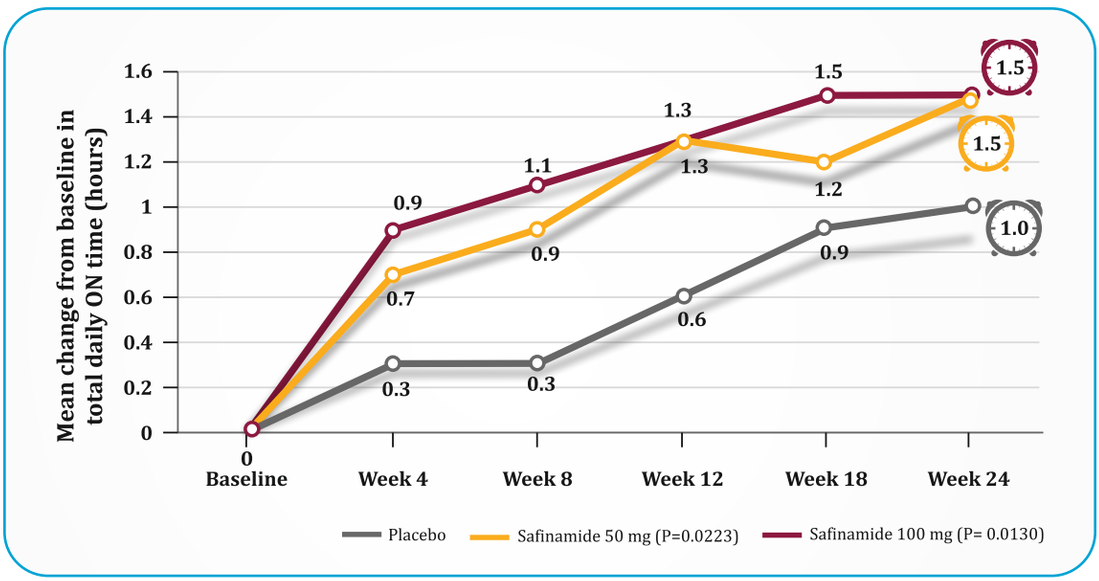

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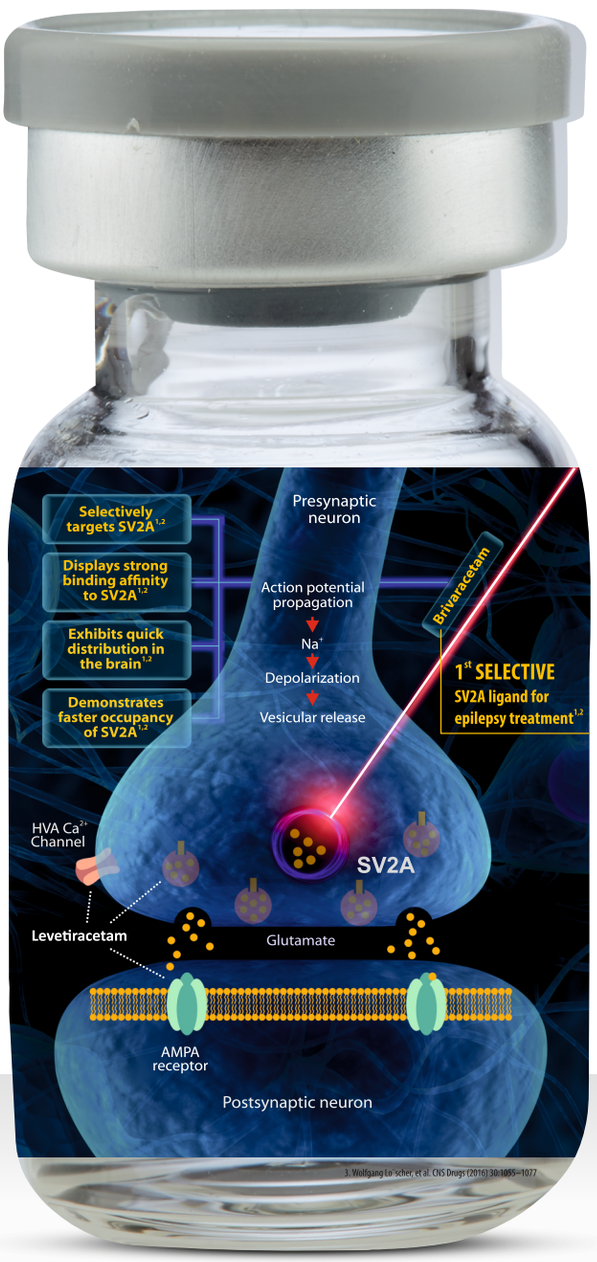

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