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Brain health registry updates: An online longitudinal neuroscience platform

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CONFLICTS OF INTEREST STATEMENT

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CONSENT STATEMENT

All participants in the BHR provided informed consent by signing an electronic consent form.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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Abstract

Introduction: Remote, internet-based methods for recruitment, screening, and longitudinally assessing older adults have the potential to facilitate Alzheimer's disease (AD) clinical trials and observational studies.

Methods: The Brain Health Registry (BHR) is an online registry that includes longitudinal assessments including self- and study partner-report questionnaires and neuropsychological tests. New initiatives aim to increase inclusion and engagement of commonly underincluded communities using digital, community-engaged research strategies. New features include multilingual support and biofluid collection capabilities.

Results: BHR includes > 100,000 participants. BHR has made over 259,000 referrals resulting in 25,997 participants enrolled in 30 aging and AD studies. In addition, 28,278 participants are coenrolled in BHR and other studies with data linkage among studies. Data have been shared with 28 investigators. Recent efforts have facilitated the enrollment and engagement of underincluded ethnocultural communities.

Discussion: The major advantages of the BHR approach are scalability and accessibility. Challenges include compliance, retention, cohort diversity, and generalizability.

Keywords

aging research; Alzheimer's disease; Brain Health Registry; clinical trial recruitment; dementia; diversity; internet; internet registry; neuropsychological tests; neuroscience clinical research studies; online; remote assessment; remote biomarker collection

1 | BACKGROUND

A major obstacle in the development of improved diagnostic methods and treatments for Alzheimer's disease (AD) and other causes of cognitive decline and dementia is the recruitment of sufficient number of participants into clinical research.[1–4] In addition, there is a pressing need for scalable instruments and tests that can be used to assess participants remotely, without the need for in-person visits to clinics.[3] Finally, it has become increasingly obvious that many clinical research studies in the AD field, including clinical trials, predominantly enroll well-educated White individuals, with insufficient enrollment of Black, Latino, and other individuals from underrepresented groups, including those with lower educational attainment and socioeconomic status.[5,6]

A number of local and national US AD-related registries including the Alzheimer's Prevention Registry[7] and the Alzheimer Prevention Trial (APT) webstudy[8,9] exist, and differ in format and purpose.[10–14] Launched in 2014, the Brain Health Registry (BHR) is an online platform for the recruitment and assessment of participants for aging research.[15–45]

By amassing a large pool of prequalified participants, the BHR aims to make clinical trials and neuroscience research studies more efficient and innovative. Longitudinal monitoring of participants helps researchers obtain data to identify, assess, and monitor cognitive changes associated with aging and neurodegenerative disease progression. As the BHR has grown and evolved over the past 8 years, the BHR research team has implemented features to increase enrollment of underrepresented populations (URPs), integrate biomarker data, including genetic, plasma, as well as in-clinic data, and to enable the enrollment of study partners via the Caregiver and Study Partner Portal.[22,29,36,39,41] These enhanced capabilities aim to generate more robust datasets and to increase the generalizability of research findings.

In 2018, we published a summary of BHR methods and activities.[21] Since that time our cohort has grown substantially, and we have new projects, data, and publications. This report summarizes the current status of the BHR.

2 | METHODS

2.1 | BHR

The BHR study is approved by the University of California San Francisco (UCSF) Institutional Review Board. Any individual aged 18 or older who can provide online consent is eligible to participate in the BHR. The BHR includes a public-facing website, participant portal, investigator portal, and secure software platform for study management.

2.1.1 | Software platform—The BHR's software platform, Ebisu, is a web-based software designed by Derek Flenniken, BHR's engineering director, to manage observational studies of human participants. Ebisu has multiple functionalities, including administration of tasks to participants, participant tracking and management, participant communications, study design, and data management. A detailed description of Ebisu's development, maintenance, and capabilities was reported in our previous paper.[21] In addition to the previously described capabilities, updated and new features in Ebisu include: multilingual support, biofluid collection capabilities, payment log, customizable registration page for coenrollments, new interface for datasets, new in-clinic data collection features, enhanced marketing features, and a redesigned user experience. Further details on these updated and new features can be found in Table 1.

2.1.2 | Investigator Portal—Investigators and study coordinators use the Investigator Portal, an independent portal in Ebisu, to perform tasks as well as communicate with BHR staff about the enrollment and randomization of participants referred from BHR.

2.1.3 | Dashboards—The BHR study team uses dashboards to visualize BHR data collected through Ebisu. The data, which are updated daily, pertain to participant and study partner enrollment, demographics including age, geographic location, gender, race, ethnicity, and education, self-reported mild cognitive impairment (MCI) and AD diagnoses, and task completion. Dashboards are customizable across different studies and help track results of recruitment, retention, and marketing efforts. Supplemental Figure S1 shows a screenshot of a dashboard.

2.2 | Recruitment

Participants are recruited to join the BHR through news stories, word of mouth, paid digital ads, social media posts, other registries/research studies, email, and advocacy groups. The BHR's recruitment projects are listed in Table 2. Supplemental Figure S2 shows the overall BHR participant flow starting from recruitment.

2.2.1 | Self-reported recruitment source—Upon registering for the study, participants can select from a dropdown list of recruitment sources. Approximately 16% of participants do not report a recruitment source and about 18% report an unknown source, "Other."

2.2.2 | Trackable links—Trackable links that redirect to the BHR website are included in many digital communications, such as digital advertisements, email, online articles, and social media posts. These links can provide the sources through which participants enrolled.

2.2.3 | URP recruitment—BHR's failure to adequately recruit and enroll participants from diverse communities (eg, ethnocultural identity, socioeconomic background) is a critical limitation. Starting in 2019, BHR has made significant efforts to develop and evaluate culturally informed, internet-based, scalable methods using a community-engaged research (CER) approach to increase the recruitment and enrollment of individuals from communities that are commonly underincluded in medical research and often experience significant disparities in AD, dementia, MCI, prevalence, incidence, and outcomes.[46–48] Initial efforts focused on recruitment and engagement of Latino participants in the California Latino-BHR (CAL-BHR) study.[41] Our digital CER approach uses multicomponent strategies including (1) a collaboration with marketing professionals experienced in research recruitment in the Latino community; (2) formation of a community science partnership advisory board (CSPB), composed of BHR participants and other community stakeholders, who provide iterative feedback to guide the development and evaluation of all recruitment and enrollment of all strategies; (3) development and deployment of digital culturally and CSPB-informed digital recruitment strategies; and (4) development of multilingual Participant Portal and support to include Spanish.[41] Digital efforts included multilingual and culturally informed messaging and imagery for (1) social media recruitment advertisements, (2) study recruitment landing pages, (3) and referral emails to other studies. In addition, efforts were also tailored to align with different age populations, for example, younger Latino individuals (more likely to be either U.S.-born or first, second, or third generation), middle-aged Latino individuals (more likely to be immigrants or first generation), and (3) older Latino individuals (more likely to be monolingual Spanish speaker). Another current effort, Community Engaged Digital Alzheimer's Research (CEDAR),[49] focuses on improving engagement and research participation of Black BHR participants using similar CER methods. The approach included establishing a Black CSPB, deploying a novel survey focused on facilitators and barriers to research participation, and developing and implementing novel digital engagement strategies (eg, monetary incentives, participant video testimonials, a culturally tailored email campaign). Efforts are under way evaluating the success of this approach, disseminating the findings professionally and in communities, as

well as developing best practices, which can inform the continuous development of BHR and potentially be applied to other studies.

2.3 | Participant Portal

After enrolling, participants are guided to the BHR Participant Portal, which consists of a structured list of study tasks, task descriptions, study dashboards with encouragements, a study navigator page for those enrolled in multiple studies, and a printable completion certificate (see examples in Supplemental Figure S3). A professional web design firm codesigned the Participant Portal to modernize and streamline our interface.

2.4 | Consent forms

To register for BHR, individuals must enter their first and last name, email address, username, password, and month and year of birth on a registration form. All participants in BHR must sign an electronic informed consent form (see Supplemental Figure S3). The BHR platform supports administering multiple online consents for BHR and any related studies and agrees with any of our collaborators to allow the sharing of data between studies. Within their BHR profile, participants can view all the consents they have ever signed and view all the studies they have enrolled in through the platform. Participants have the option to withdraw from individual studies, which will in turn withdraw their associated consents.

2.5 | Questionnaires

BHR participants are asked to complete a series of questionnaires during their baseline and longitudinal follow-up visits. These questionnaires are based on validated instruments that are used verbatim or that are adapted for an online setting.[51–61] Questionnaires undergo periodic review to evaluate the utility and effectiveness of their deployment. Questionnaires are presented in a specified order, but participants may skip individual procedures or deviate from this order.

The initial questionnaire consists of basic demographic information, self-reported diagnoses of MCI, dementia, and AD, family history of AD, self-reported memory concerns, and questions about cognition and mental health. Subsequent questionnaires include measures of everyday cognition (ECog); mood (adapted from the Geriatric Depression Scale Short Form (GDS) and Patient Health Questionnaire (PHQ-8)); medical and depression history; head injuries (adapted from Quality of Life after Brain Injury Scale (QOLIBRI), Rivermead Post-Concussion Symptoms, Satisfaction with Life Scale (SWLS), and Ohio State Traumatic Brain Injury Form (OSU TBI)); family history of AD; hoarding and cluttering (adapted from the Hoarding Rating Scale, Activities of Daily Living for Hoarding Disorder, WHODAS, and Short Form Health Survey SF-12) and quality of life.[54,57–60,62–71] In February 2021, we added a questionnaire asking Latino participants about nativity, immigration, bilingualism, and cross-border ties.[41,53]

2.6 | Neuropsychological tests

The BHR platform currently administers the following online neuropsychological tests: (1) Cogstate Brief Battery[72]; (2) MemTrax Memory Test[73,74]; and (3) Cambridge Cognition Paired Associates Learning,[75] which was added in the summer of 2021. The Lumos Labs

NeuroCognitive Performance Tests[76] was previously administered on the BHR platform for 5 years from 2014 until 2019.

2.7 | Caregiver and Study Partner Portal

The BHR Caregiver and Study Partner Portal (CASPP) is a novel, scalable, web-based tool for remotely obtaining study partner data. Launched in 2016, this tool is a portal within the BHR that allows current participants to nominate a potential study partner by completing a My Study Partner task, which includes a description of the role of a study partner, questions about the potential study partner's relationship to the participant, and a form requesting the name and email address of the potential study partner. Completion of the My Study Partner tasks triggers an automated invitation email to the potential study partner, with a description of the study partner role, instructions on how to enroll, and a link to a custom CASPP registration page within the BHR. From the registration page, the potential study partner creates an account and password, signs an online consent, and completes CASPP-specific tasks. CASPP tasks include study partner demographics, questions about the relationship between the participant and study partner (relationship type, how long they have known each other, whether they live together, how much time they spend together), and online adaptations of the Everyday Cognition Scale (ECog), Functional Activities Questionnaire (FAQ), Cognitive Functional Instrument (CFI), and Mild Behavioral Inventory Checklist.[54,56,61] Study partners are invited to return to the CASPP at 6-month intervals to complete follow-up tasks. Supplemental Figure S4 shows the overall BHR study partner flow. An individual can serve as both a study partner and a participant in BHR. BHR participants can change their study partner at any time through their BHR account and request that a current study partner no longer serve in that role.

2.8 | Participant support

Zendesk Support is a customer service software that uses a ticketing system to support and communicate with customers. Inquiries sent by participants, collaborators, or potential collaborators are forwarded to Zendesk via the info@brainhealthregistry.org email address. Each email is treated as a ticket, which is meant to be solved by designated BHR staff. BHR began using Zendesk Support on March 20, 2018. At any given time, one to three BHR staff members closely monitor and actively respond to participant questions using templated responses. To categorize and more efficiently respond to participant inquiries, tickets are sorted by type. BHR staff aim to respond to participants within 24 to 48 hours of when the participants sent their messages. Zendesk data are useful for tracking and addressing participant responses and attitudes and for identifying bugs or participant-facing issues with the BHR site.

2.9 | Participant engagement

2.9.1 | Email engagement—BHR uses a series of different emails to communicate with participants. Participants receive a welcome email after enrolling in BHR, reminder emails to complete procedures, and a thank you email after completing all procedures. Ahead of 6-month longitudinal follow-up visits, participants receive emails reminding them to return to the website to complete procedures.

Finally, in cases where someone begins enrollment but does not complete this three-step process (registration, account creation, online informed consent), emails are sent asking that they finish enrolling and participate in BHR.

2.9.2 | BHR newsletters—Participants may opt in to receive electronic newsletters that cover developments in the AD research field and update participants on studies conducted by BHR researchers. Since BHR's inception in 2014, newsletters have been in English but have been available in both English and Spanish since September 2021. All newsletters are archived on the BHR website at www.brainhealthregistry.org/newsletter/.

2.9.3 | Social media—BHR uses Facebook and Twitter to share research findings in the greater Alzheimer's field, as well as updates specific to BHR.

2.10 | Types of BHR projects

There are five types of BHR projects: (1) referrals, (2) coenrollments, (3) data sharing, (4) development and validation of online assessments, and (5) software as a service. These BHR projects utilize Ebisu's features to build both internal projects within the BHR team and external collaborative projects involving investigators outside of the BHR team, such as other investigators within UCSF or outside of UCSF, advocacy organizations, and private-sector entities involved in clinical neuroscience studies. All BHR projects are listed in Table 2. The BHR team carefully reviews requests for collaborations and decide which ones are within the capacities of the team based on several factors, including scientific merit, complexity, burden on BHR participants, value of data to the BHR, and cost.

2.10.1 | Referrals

Referrals from BHR to other projects: Referrals originate from the pool of enrolled BHR participants who have completed self-report questionnaires and/or cognitive tests. This allows for screening prior to site referral, to identify likely candidates for the referral study. When participants who have expressed interest in participating in additional research and meets the eligibility criteria for a referral study, they will receive a series of referral emails telling them about the study. If participants are interested, they may sign a data-sharing consent form.

Direct to site referrals: Direct-to-site referrals consist of individuals referred directly to a research clinic site without the requirement to enroll in BHR and complete questionnaires and neuropsychological tests. These are done from a recruitment website, web-based form, or landing page managed by the BHR. Within the web-based form, interested individuals provide their contact information and any other applicable information (eg, birth year or zip codes), which can then be relayed to the site.

2.10.2 | Coenrollments—Coenrollment means that participants are simultaneously enrolled in the BHR (signed the BHR consent) and another study. The goal of coenrollment is to link study data collected by both studies to create a more enriched dataset for analysis, papers, and presentations and to inform participants of future research projects.

2.10.3 | Data sharing—BHR shares its data with interested qualifying researchers outside of the BHR research team, governed by a Data Use Agreement (DUA) and as part of most collaborations. The data-sharing infrastructure includes a secure dataset download portal and scalable, customizable data sets via Ebisu (Table 1). Interested collaborators work with the BHR team to determine the scope of the data shared and premises for potential collaboration in analysis. The BHR data-sharing guidelines are explained on the website at www.brainhealthregistry.org/for-investigators/de-identified-data-sharing/.

2.10.4 | Development and validation of online assessments—Several studies are under way for developing and validating novel online assessments. These studies may include an examination of the feasibility, compliance, and usability of the assessment; investigation of the novel assessment to established in-clinic measures; and comparison of assessment performance in supervised settings versus performance in BHR.

2.10.5 | Software as a service (SaaS)—BHR SaaS is a software platform created and maintained by the BHR team. BHR SaaS allows collaborators to build and manage their own cohorts through recruitment of participants into their online study, longitudinal data capture from participants, and participant communication management.

3 | RESULTS

3.1 | BHR participants

More than 100,000 participants are enrolled in the BHR. This number includes BHR study partners and participants coenrolled in other studies. Future reports will include detailed information on BHR study partners and those coenrolled in other studies. Here, we report data on the remaining 90,650 participants, of whom 67,395 (73.5%) are aged at least 55. Further, 21,938 (24.2%) of participants identify as male, 66,712 (73.6%) identify as female, and <1% as “other” or indicate “prefer not to say” on the gender questionnaire. On the ethnicity question, 12,002 (13.2%) participants marked “Latino,” 4191 (4.6%) identifed as Black or African American, 55,854 (61.6%) of participants reported a 4-year college degree or higher, and 42,520 (49.9%) of BHR participants had a self-reported memory concern. A total of 11,553 study partners are enrolled in the BHR.

The top three metropolitan areas in which BHR participants report residence are San Francisco-Oakland-Hayward, CA; Los Angeles-Long Beach-Anaheim, CA; and New York City-Newark-Jersey City, NY-NJPA. See Figure 1 for more details on BHR participants’ locations across the United States.

See Table 3 for more detailed demographic information on the BHR cohort.

3.2 | Self-report questionnaire completion rates

Among BHR participants, 83,170 (94.2%) completed the initial questionnaire during their baseline time point, and 39,718 (45%) of participants have completed at least two initial questionnaires at any time point, including baseline and subsequent longitudinal time points.

3.3 | Neuropsychological test completion rates

At baseline, 48,581 (55.7%) participants completed at least one neuropsychological test and 18,847 (21.6%) have completed at least two neuropsychological tests. Further, 56,788 (65.1%) have completed at least one neuropsychological test during at least two different time points. Finally, 32,096 (36.8%) of participants completed at least two neuropsychological tests during at least two different time points, including baseline and subsequent longitudinal time points.

3.4 | Participant support

Since 2018, 20,537 tickets (requests for support) have been generated. The three most common ticket categories were General BHR Response, which contains advice for accessing and navigating the BHR portal; Technical Assistance Request, which provides troubleshooting advice if participants encounter issues accessing or completing study tasks; and Account Modification, which relates to account management, such as merging duplicate accounts or participant withdrawal.

Since BHR first began using Zendesk in 2018, 21,739 Zendesk tickets have been created for a total of 90,650 participants enrolled.

3.5 | URP recruitment

The CAL-BHR project (aimed at increased enrollment of older Latino participants in BHR)[41] and the CEDAR project[49] (aimed at increasing engagement by Black BHR participants) represent the major BHR efforts to date. Efforts have resulted in the enrollment of 7013 individuals from underrepresented ethnocultural populations. In addition, a culturally tailored email campaign for recruitment and enrollment of Latino individuals into a remote genetics study increased the percentage of Latino participants from 2% to 21% in this study. More details have been reported in other publications.[41]

3.6 | Referrals (Tables 2 and 4)

A total of 30 studies have established referral programs with the BHR. Over 259,000 referrals to studies were sent out with 25,997 participants enrolled. Successful referral programs include (1) Monell Chemical Senses Center's Smell Study, (2) Online Neuropsychological Test Validation Project with Imaging Pilot, and (3) BHR-GenePool Study.

3.7 | Coenrollments (Tables 2 and 5)

A total of 28,278 BHR participants are coenrolled in 17 other studies. The Head Impact and Trauma Surveillance Study (HITSS), with 1000 enrolled participants, is an example of a successful coenrollment. The BHR platform facilitates the development of a large national cohort of participants who have had a history of head injury and/or are participating in sports or other activities where risk of head injury is high. Marketing activities direct interested participants to the HITSS website, which explains the project, and then the participants register for the BHR user experience.

3.8 | Data sharing

The BHR shares data both as part of larger collaborations and with those interested in pursuing independent analysis questions. As of this writing, the BHR has shared data with 28 research groups.

3.9 | Development and validation of online assessment tools

The BHR began by implementing Cogstate testing for all participants, leading to several publications showing the effects of advanced age and self-reported cognitive impairments,[19] sleep,[20] and depression[26] on the Cogstate Brief Battery. Subsequently, MemTrax and the Cambridge Cognition Paired Associates Learning test were added. This experience with online assessments led to a National Institutes of Health (NIH)-funded project to develop and validate the electronic Clinical Dementia Rating,[39] which is an online version of the widely used gold standard assessment known as the Clinical Dementia Rating. Finally, the BHR population and platform have been used to help validate the recently developed NIH-funded Mobile Toolbox.[77]

4 | DISCUSSION

The major accomplishments of the BHR are as follows: enrollment of over 100,000 participants including over 11,000 study partners and coenrolled participants, over 259,000 referrals to 30 studies, coenrollment of 28,278 participants with 17 other studies, development of improved digital marketing methods for the enrollment of URPs, serving as a platform for the development of novel online assessment tools, and data sharing with collaborators and those requesting data. Major limitations have been high levels of participant dropout and persistent underrepresentation of historically excluded ethnocultural and education groups. Taken together, these accomplishments demonstrate that the BHR provides a unique adjunct for clinical neuroscience research.

4.1 | Caregiver and Study Partner Portal

A unique feature of the BHR is the CASPP, a novel and scalable tool for obtaining dyadic (participant, study partner (SP) pair) data remotely. This approach has many advantages. Dyad report decline: (1) efficiently captures change within a single, cross-sectional assessment by asking about recent changes; (2) provides unique insight into complex activities of daily living that may begin to decline early in the AD continuum, are associated with AD biomarkers,[78–81] and are difficult to assess using neuropsychological testing; and (3) offers good portability across cultures, languages, and educational levels. SP report of cognitive and functional decline has further advantages. The accuracy of self-reporting can be limited by overreporting decline due to being “worried well” or mood and personality traits[82–85] or underreporting decline due to a lack of insight/awareness about one’s condition.[86–88].

4.2 | Referrals into other studies

The major goal of all cohort registries is to provide a reservoir of participants who can join more intensive in-clinic studies, especially randomized clinical trials. A major problem for the BHR and for other registries serving a similar function has been accurately tracking the

success of these referrals. Ideally, the BHR would receive data back from clinics concerning the number of BHR participants who made contact with the site, how many were screened, and how many were finally enrolled by providing informed consent. This data linkage is particularly difficult, and without such linkage it's not possible to quantify the success of the referral program. There are at least two causes of this problem. First, in many cases, especially for industry-sponsored randomized clinical trials, the protocol prevents release of any Protected Health Information to an outside source. Second, the clinic staff are overburdened and focus on recruitment and enrollment; tasking clinic staff with providing information back to the BHR adds a significant time burden. One solution to this problem is to include the BHR and other registries and referral sources in the main protocol of the study, and to require data linkage and accurate reporting of successful referrals by the clinic sites. Such data linkage has been accomplished between the BHR and Alzheimer's Disease Neuroimaging Initiative (ADNI) (because Dr. Weiner is the primary investigator of both studies), demonstrating the feasibility of this approach. Once a successful data linkage approach is implemented, this allows complete tracking of the successes and failures of such an approach, facilitating optimization. Furthermore, data linkage would allow the in-clinic study to utilize information obtained by the referral source. This could be used to reduce screen fails and to provide other data useful to the study.

4.3 | Coenrollments with other studies

A very unique feature of the BHR platform is the ability to conduct coenrollments with other studies. There are many NIH- and industry-funded studies where budget limitations prevent frequent in-clinic or telephone follow-up. Coenrollment with the BHR facilitates long-term follow-up at relatively low cost because most BHR functions are completely automated. Coenrollment also provides a unique opportunity to validate online assessment by examining the relationship between online measures and in-clinic measures.

4.4 | Recruitment of underrepresented participants

Like other research studies, the BHR fails to adequately include underrepresented individuals, which is one of the most crucial limitations of research as it impacts the generalizability of research findings and perpetuates health-related inequities.[21,3,5,6,89–91] To address this, the BHR has focused on developing culturally informed digital marketing efforts to include and engage Black and Latino individuals, with website landing pages designed to appeal to these populations. The success of the CAL-BHR and CEDAR projects, which focused on improving diversity in the BHR, has led to the use of similar digital marketing and racial/ethnic designed landing pages for Alzheimer's Disease Neuroimaging Initiative 3 (ADNI3),[92,93] and we are extending this approach for ADNI4. We believe that this digital marketing approach has proven to be a cost-effective adjunct to conventional "boots-on-the-ground" recruitment[94] aimed at underrepresented groups. Although there is still a long way to go in assembling a representative cohort, diversity efforts to date have demonstrated the feasibility of our approach and begun to identify best practices in this area.

4.5 | Development and validation of online assessment tools

The online cohort of the BHR has been a valuable participant pool for the development and validation of online assessments. The advantages of online unsupervised assessments

include efficiency, scalability, reduced cost and resource use, frequent data collection, and ability to include those who cannot take part in in-clinic assessments due to location, competing demands, and other barriers that disproportionately affect URPs. The recent COVID pandemic further highlights the importance of remote assessments.

4.6 | Data sharing with collaborators and those requesting data

As with ADNI, which makes all data available to requestors, the BHR has freely shared data with interested investigators. Our data sharing has led to a number of publications.[15–44] The BHR data are extremely large and complex, especially due to various changes that are made to add or remove various features. For this reason, we recommend that investigators interested in using the BHR dataset to explore or test hypotheses collaborate with BHR scientists who are familiar with the dataset and its limitations.

4.7 | Limitations

The limitations of the BHR include selection biases, issues of data integrity, lack of clinically confirmed data, missing data, and limited ability to engage and retain participants across longitudinal time points. All online research studies have selection biases for individuals with adequate digital devices and internet access and literacy. On the other hand, the online approach permits expanded access to research for individuals who may not be able to participate in in-person studies due to geographic constraints and time burdens. There are likely to be additional selection biases, both for enrollment and retention, related to the health, cognitive, and functional status of participants. In terms of data integrity, we have no way to validate or check the accuracy of the data provided by our participants, and it is possible that, for example, participants get help from others when taking the neuropsychological tests. Another major concern is the very high dropout rate. Furthermore, dropout increases with each successive visit. Nevertheless, many thousands of participants have returned to the BHR twice per year for many years, providing extensive longitudinal data. Related to dropout is the problem of completion. Only a small fraction of participants complete the entire experience. BHR frontloads the initial questionnaire to capture the information deemed most important. A number of methods to reduce dropout and increase completion rates are being considered and tested. Lack of completion and high dropout are clearly major limitations of the BHR and other online registries.

4.8 | Summary

Despite the previously discussed limitations, when taken together, the accomplishments of the BHR (referrals, coenrollments, study partner data, recruitment of underrepresented participants, development/validation of online assessment methods, and data sharing) demonstrate the value of this unique approach to facilitate clinical neuroscience research.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Brain Health Registry (BHR) is an online, longitudinal platform of > 100,000 members.
- BHR made > 259,000 referrals, which enrolled 25,997 participants in 32 studies.
- New efforts increased enrollment and engagement of underincluded communities in BHR.
- The major advantages of the BHR approach are scalability and accessibility.
- BHR provides a unique adjunct for clinical neuroscience research.

RESEARCH IN CONTEXT

Systematic Review:

A review of the literature was conducted using electronic databases and online search engines. A number of different Alzheimer's disease-related local and national registries exist. In 2018, the first publication of the Brain Health Registry (BHR) provided a summary of the methods, activities, and results. Increased BHR participation and referral numbers, as well as new diversity and remote data collection efforts, warrant an update.

Interpretation:

This updated summary of the BHR highlights the registry's success in enrolling participants, referring participants to other studies, coenrolling participants, sharing data, serving as a platform for novel online assessment tools, and increasing the inclusion of ethnoculturally diverse, historically excluded participants in the registry. These accomplishments demonstrate that BHR provides a unique adjunct for clinical neuroscience research.

Future Directions:

Much needed efforts are under way and planned to increase participant engagement and to further increase ethnocultural and socioeconomic diversity of the BHR cohort.

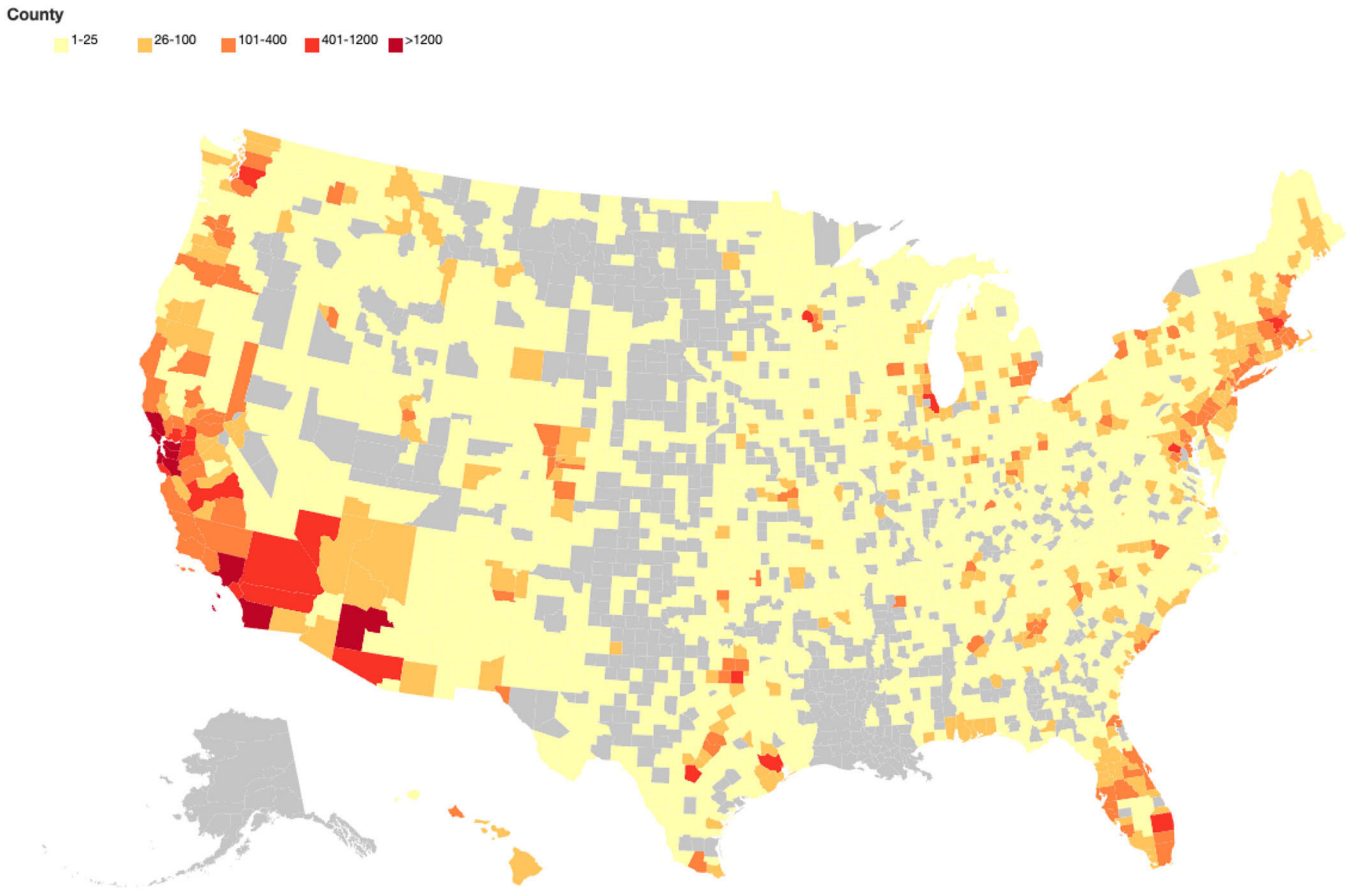

FIGURE 1.
Heatmap of enrolled BHR participants from US counties.

TABLE 1

Updated or new features in Ebisu.

Updated or new feature	Description
Multilingual support	Studies can be configured to set which languages they support to allow participants to view content in their preferred language.
Biofluid collection capabilities	Software features facilitate collection of saliva and blood samples.[29,36] Participants may provide a shipping address and receive a saliva collection kit or be provided with information to visit a local Quest Patient Service Center to have their blood drawn. A Vendor Portal allows fulfillment vendors to log in and download spreadsheets with participant information to create orders and send out saliva kits. The vendors can upload spreadsheets with additional information related to the kits that were sent out. Saliva and blood samples are returned to the BHR specimen bank and shipped out to labs for processing information related to the status of the received samples and can be uploaded into Ebisu. Ebisu captures/monitors data concerning shipment status, collection status, and analysis status. These results are automatically imported into the BHR database, where they are combined with online data collected in BHR.
Payment log	This facilitates disbursement of participant payments upon various events, including task completion, visit completion, and study completion.
Customizable registration page for coenrollments	The software tool for enrolling existing clinical cohorts from other studies into BHR with data linkage now contains a feature for a separate, customizable registration page to join BHR with a study-specific data-sharing consent form. This feature uses the existing BHR protocol and content, thereby reducing effort for new protocol development.
New interface for datasets	Anewinterfaceallows BHR staff to easily build customizable datasets, view the history of a dataset build, and specify data as “identifiable” (Protected Health Information).The interface also allows collaborators to securely download datasets directly from the investigator portal, instead of utilizing a third-party provider for data transfers. The “master data dictionary,” a consolidated list of all variables within a dataset, greatly facilitates data analysis.
New in-clinic data collection features	For projects with in-clinic components, Ebisu schedules in-clinic appointments and manages the collection of in-clinic data. Reports are provided for upcoming and overdue in-clinic appointments. In-clinic data are linked to any corresponding data collected online at home. In-clinic data collection may also include online tasks, to be conducted in a web browser at the clinic without requiring a participant to log in, but instead using a participant-specific appointment code to navigate to the online tasks. This system is used for a current study developing and validating electronic versions of the Clinical Dementia Rating and Financial Capacity Instrument-Short Form.[21]
Enhanced marketing features	New features include the ability to gather and integrate data from Facebook and Google Adwords to analyze advertising efforts to recruit participants.
Redesigned user experience	To enhance the user experience and reduce subject burden, the following features were included: new color scheme, easier navigation and management of main study and substudies, participant-facing messaging with encouragements and guidance points, new task flow with balancing of activity types.

TABLE 2

BHR projects.

Project	Lead institution	Study type, design, population
Recruitment in BHR		
Alzheimer's Prevention Registry (APR)	BAI	Observational, registry recruitment, APR members
California Latino-Brain Health Registry (CAL-BHR) *43	UCSF	Observational, community-engaged registry recruitment, Latino community
Study to expand registry participation of underrepresented populations (STEP-UP) *	BAI	Experimental, registry recruitment, Black, Hispanic, male
Referrals from BHR to other projects		
ALLFTD mobile app study	UCSF	Observational, validation, mobile tests application validation, cognitively unimpaired controls
Alzheimer's Disease Neuroimaging Initiative 3 (ADNI3)[24]	NCIRE	Observational, in-clinic, older adults with or without MCI/AD
Alzheimer's disease neuroimaging initiative-depression (ADNI-D)	UCSF	Observational, in-clinic, older adults with major depressive disorder
Alzheimer Prevention Trials (APT) Webstudy	USC	Observational, online registry recruitment, older adults without dementia
Anti-Amyloid Treatment in Asymptomatic Alzheimer's (A4)	Eli Lilly and Company	Experimental, in-clinic phase 3 secondary AD prevention intervention trial, asymptomatic AD
β Amyloid Production and Effects on Cognition Study	Merck	Experimental, in-clinic phase 3 randomized placebo-controlled drug treatment intervention, older adults with prodromal AD
Butler Alzheimer's Prevention Registry	Butler Hospital	Observational, recruitment to local Alzheimer's prevention registry, older adults
Caregiver Attentional Awareness Pilot Study	UCSF	Experimental, in-clinic, and at-home iPad application intervention, older adult caregivers
Cleveland Clinic Lou Ruvo Center	Cleveland Clinic	Experimental, clinical trial for neurological disease, patients with Alzheimer's, Parkinson's, and Huntington's diseases, multiple sclerosis, and frontotemporal dementia
EMERGE Study	Biogen	Experimental, in-clinic phase 3 randomized placebo-controlled drug treatment intervention, older adults with prodromal AD
Healthy Mind, Healthy You 93	MGH	Experimental, online mindfulness intervention, all BHR participants
Hillblom Healthy Aging Study	UCSF	Observational, in-clinic observational aging/cognition study, cognitively unimpaired older adults
Hoarding behaviors study[28,34,38,40,45]	UF	Observational, online registry assessment of hoarding, adults
Internet-Based Conversational Engagement Clinical Trial (I-CONECT)	OHSU	Experimental, community-based phase II behavioral intervention trial, socially isolated older adults
Phase II RCT of High-dose Vitamin D Supplements in Older Adults	UCD	Experimental, in-clinic, phase II RCT for vitamin D supplements, older adults
Repetitive Transcranial Magnetic Stimulation and Dementia Study	PAVAMC	Experimental, in-clinic repetitive transcranial magnetic stimulation veterans with dementia, MCI, or AD
Repetitive transcranial magnetic stimulation for mild cognitive impairment	PAVIR	Experimental, in-clinic, transcranial magnetic stimulation for mild cognitive impairment, older adults with noticeable decline in memory
Riluzole at Rockefeller	Rockefeller University	Experimental, in-clinic trial, older adults diagnosed with mild AD

Project	Lead institution	Study type, design, population
Smell Study	Monell Chemical Senses Center	Observational, remote smell kit, adults
Study of Aging in Latinas/os for Understanding Dementias	Mount Sinai Medical Center	Observational, older Latino adults with and without HIV
UC Irvine Alzheimer's Disease Research Center	UCI	Observational, in-clinic, neurological, cognitive, specimen collection, older adults
UPenn Healthy Brain Aging Study	UPenn	Experimental, randomized clinical trial, in-clinic, antidepressant medication effects on production of amyloid beta, healthy older adults
Direct-to-Site Referrals		
Alzheimer's Disease Neuroimaging Initiative 3 (ADNI3): ADNI3.org[24]	NCIRE	Observational, recruitment to in-clinic study, older adults
Alzheimer's Disease Neuroimaging Initiative 3 Diversity Task Force (ADNI3 DVT)*95	NCIRE	Observational, culturally tailored recruitment to in-clinic study, older adults without or with MCI/AD from diverse ethnocultural communities (Black/African American, Latino)
Coenrollments		
Alzheimer's Disease Neuroimaging Initiative 3-Brain Health Registry (ADNI3-BHR)[35]	NCIRE	Observational, online longitudinal monitoring, older adults who are cognitively unimpaired, have MCI or AD
Biomarker Prediction Study†[36]	UCSF	Observational, remote blood collection, plasma biomarkers, older adults
Brain Health Registry-Affect: UCSF MAC Collaboration to Study Emotionalityt	UCSF	Survey, online affect-related questionnaires, all BHR participants
Brain Health Registry-GenePool Study*†[29]	UCSF	Observational, remote DNA saliva collection, older adults
Brain Health Registry-Imaging Dementia — Evidence for Amyloid Scanning[25,30,44]	UCSF	Observational, online registry participation, older Medicare beneficiaries with objectively confirmed cognitive impairment by a dementia
Buck Institute	Buck Institute	Recruitment effort with data-sharing consent for future research
Cognition After Surgery & Anesthesia-Brain Health Registry	UCSF	Observational, online longitudinal monitoring, postoperative decline, memory and thinking, MCI, dementia
Community Engaged Digital Alzheimer's Research (CEDAR)* †[49,50]	UCSF	Observational, community-engaged research registry engagement study, African American/ Black BHR participants
Head Impact&Trauma Surveillance Study (HITSS)[26]	BU	Observational, development of online head impact and trauma assessment, soccer and American football players
Healthy Brain Initiative-Brain Health Registry (HBI-BHR)/ageHAPPY (Healthy Ageing Project Population Youth-senior)	University of Melbourne	Observational, online registry for cognitive aging, adults in Australia
Memory assessment results initiative†	UCSF	Observational, pilot study providing unsupervised cognitive assessment results to online registry participants, all BHR participants
Striving Together to Prevent & Treat Alzheimer's Disease	UTHSCSA	Observational, enrollment effort into registry, adults in an ADRC
Study to Evaluate Amyloid in Blood and Imaging Related to Dementia-Brain Health Registry	WashU	Observational, in-clinic, amyloid blood test, older adults
Veteran Brain Health Registry	NCIRE	Observational, online registry, veterans
Development and Validation of Online Assessments		
Cambridge Cognition Paired Associates Learning	UCSF	Observational, remote validation of online unsupervised cognitive assessment, all BHR participants

Project	Lead institution	Study type, design, population
Cogstate Brief Battery[19,20,23,26,33]	UCSF	Observational, remote validation of online unsupervised cognitive assessment, all BHR participants
Electric Validation of Online Methods to Predict and Monitor Cognitive Declinet ††‡[27,39]	UCSF	Observational, in-clinic, and remote validation of online unsupervised diagnostic assessment, older adults
Lumos Labs NeuroCognitive Performance Tests[23,26,37]	UCSF	Observational, remote validation of online unsupervised cognitive assessment, all BHR participants
MemTrax Memory Test[23]	UCSF	Observational, remote validation of online unsupervised cognitive assessment, all BHR participants
Mobile Toolbox Study †‡	UCSF	Observational, validation of a remote, smartphone-based cognitive assessment app validation, all BHR participants
Online neuropsychological test validation project with imaging pilot †‡	UCSF	Observational, In-clinic and remote, validation of online unsupervised cognitive assessment, biomarkers, older adults
ReVeRe†‡[31]	UCSF	Observational, in-clinic, and remote validation of online unsupervised cognitive assessment, biomarkers, older adults
Software as a Service (SaaS)		
Alzheimer's Disease Neuroimaging Initiative 4 (ADNI4) * ‡§	NCIRE	Observational, recruitment to in-clinic, observational study, older adultswithout or with MCI/AD
Dutch Brain Health Registry[32]	Amsterdam UMC	Observational, online registry for cognitive aging, adults

- * Focus on URP
- † Also a Referral from BHR toOther Projects
- ‡ Also a Coenrollment
- § Also a Direct-to-Site Referral

Lead Institutions

- BAI: Banner Alzheimer's Institute
- UCSF: University of California, San Francisco
- NCIRE: Northern California Institute of Research and Education
- USC: University of Southern California
- MGH: Massachusetts General Hospital
- UF: University of Florida
- OHSU: Oregon Health and Science University
- UCD: University of California, Davis
- PAVAMC: Palo Alto Veterans Affairs Medical Center
- PAVIR: Palo Alto Veterans Institute for Research
- UCI: University of California, Irvine
- UPenn: University of Pennsylvania

Alzheimers Dement. Author manuscript; available in PMC 2024 February 16.

Project	Lead institution	Study type, design, population
• BU: Boston University • UTHSCSA: University of Texas Health Science Center at San Antonio • WashU:Washington University in St. Louis • Amsterdam UMC: Amsterdam University Medical Center		

TABLE 3

Demographics of BHRcohort.

Demographics	***N***	**%**
Total	90,650	
Age, *n* = 89,315		
<50	15,165	17.0%
50–59	16,632	18.6%
60–69	27,827	31.2%
70–79	22,185	24.8%
>80	7,506	8.4%
Gender, *n* = 90,650		
Female	66,712	73.6%
Male	21,938	24.2%
Other	45	<1%
Prefer not to say	45	<1%
Ethnicity, *n* = 90,650		
Latino	12,002	13.2%
Not Latino	71,376	78.7%
Prefer not to say	2,372	2.6%
Unknown	4,900	5.4%
Race, *n* = 90,650		
Asian	3,138	3.5%
Black or African American	4,191	4.6%
Native American	2,697	3.0%
Pacific Islander	429	<1%
White	71,716	79.1%
More than 1 race	3,384	3.7%
Not collected	1,658	1.8%
Other	5,997	6.7%
Prefer not to say	1,572	1.7%
Education, *n* = 90,650		
High school or less	6,837	7.5%
Some college	16,759	18.5%
2-year college degree	7,994	8.8%
4-year college degree	26,206	28.9%
Prefer not to say	222	<1%
Advanced degree	29,648	32.7%
Memory concern and family history, *n* = 85,197; MCI, AD, dementia diagnosis, *n* = 63,103		
Memory concern	42,520	49.9%
Family history of AD	18,982	22.3%
Diagnosed with MCI	3,658	5.8%
Diagnosed with AD	518	<1%

Demographics	***N***	**%**
Diagnosed with dementia	805	1.3%
Medical condition, *n* = 54,675		
Parkinson's	1,783	3.2%
Movement disorder	2,499	4.6%
Motor neuron disease	313	<1%
Stroke	1,807	3.3%
Schizophrenia	102	<1%
Heart disease	3,185	5.8%
High blood pressure	18,715	34.2%
Cholesterol	22,025	40.3%
Diabetes	5,028	9.2%
Cancer	9,043	16.5%
Alcohol abuse	6,664	12.1%
Drug abuse	3,993	7.3%
Smoking	20,867	38.2%

TABLE 4

Summary of referral programs.

Referral program	Referred	Responded	Response rate	Enrolled	Enrollment rate
ALLFTD Mobile App Study	298	148	50%	40	13%
Alzheimer's Disease Neuroimaging Initiative 3 (ADNI3)	16153	3033	19%	82	1%
Alzheimer's Disease Neuroimaging Initiative-Depression (ADNI-D)	1528	369	24%	25	2%
Alzheimer Prevention Trials Webstudy (APT)	31317	4739	15%	1872	6%
Anti-Amyloid Treatment in Asymptomatic Alzheimer's (A4)	1212	297	25%	11	1%
β Amyloid Production and Effects on Cognition Study	139	48	35%	0	0%
Biomarker Prediction Study	7147	1308	18%	864	12%
Brain Health Registry-Affect: UCSF MAC Collaboration to Study Emotionality	73795	11871	16%	10233	14%
Brain Health Registry-GenePool Study	10675	2158	20%	1690	16%
Butler Alzheimer's Prevention Registry	2384	484	20%	23	1%
Caregiver Attentional Awareness Pilot Study	14	4	29%	0	0%
Community Engaged Digital Alzheimer's Research (CEDAR)	3802	434	11%	384	10%
Cleveland Clinic Lou Ruvo Center	497	84	17%	0	0%
Electric Validation of Online Methods to Predict and Monitor Cognitive Decline	3098	580	19%	152	5%
EMERGE Study	385	39	10%	1	0%
Healthy Mind, Healthy You	32200	4258	13%	0	0%
Hillblom Healthy Aging Study	1512	144	10%	39	3%
Hoarding Behaviors Study	13878	6290	45%	1303	9%
Internet-Based Conversational Engagement Clinical Trial (I-CONECT)	36	7	19%	0	0%
Memory Assessment Results Initiative	1304	415	32%	380	29%
Mobile Toolbox Study	48109	10099	21%	7161	15%
Online neuropsychological test validation project with imaging pilot	3220	942	29%	550	17%

Referral program	Referred	Responded	Response rate	Enrolled	Enrollment rate
Phase II RCT of High-dose Vitamin D Supplements in Older Adults	1434	374	26%	1	0%
Repetitive Transcranial Magnetic Stimulation and Dementia Study	290	62	21%	2	1%
Repetitive Transcranial Magnetic Stimulation for Mild Cognitive Impairment	633	103	16%	3	0%
Riluzoleat Rockefeller	21	6	29%	0	0%
Smell Study	3236	1841	57%	1164	36%
Study of Aging in Latinas/osfor Understanding Dementias	540	65	12%	17	3%
UC Irvine Alzheimer's Disease Research Center	140	25	18%	0	0%
UPenn Healthy Brain Aging Study	284	70	25%	0	0%
Total	259142	50249	19%	25997	10%

TABLE 5

Summary of coenrollments.

Study	Enrolled
Alzheimer's Disease Neuroimaging Initiative 3-Brain Health Registry (ADNI3-BHR)	114
Biomarker prediction study	864
Brain Health Registry-Affect: UCSF MAC Collaboration to Study Emotionality	10233
Brain Health Registry-GenePool Study	1690
Brain Health Registry-Imaging Dementia — Evidence for Amyloid Scanning	981
Buck Institute	76
Cognition After Surgery & Anesthesia-Brain Health Registry	22
Community Engaged Digital Alzheimer's Research (CEDAR)	384
Electric validation of online methods to predict and monitor cognitive decline	152
Head Impact&Trauma Surveillance Study (HITSS)	1000
Healthy Brain Initiative-Brain Health Registry (HBI-BHR)/ageHAPPY (Healthy Ageing Project Population Youth-senior)	4330
Memory assessment results initiative	380
Mobile toolbox study	7161
Online neuropsychological test validation project with imaging pilot	550
Striving together to prevent & treat Alzheimer's disease	169
Study to Evaluate Amyloid in Blood and Imaging Related to Dementia-Brain Health Registry	165
Veteran Brain Health Registry	7
Total	28,278