Received: 3 February 2025 | Revised: 11 April 2025 | Accepted: 21 April 2025

DOI: 10.1002/alz.70259

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

REVIEW ARTICLE

The Down Alzheimer Barcelona Neuroimaging Initiative (DABNI) and its contributions to understanding Alzheimer's disease in Down syndrome: A decade of discovery

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Abstract

Down syndrome (DS) is a genetic form of Alzheimer's disease (AD) that offers crucial insights into AD pathogenesis. The Down Alzheimer Barcelona Neuroimaging Initiative (DABNI) is a population-based multimodal biomarker cohort studying AD's natural history and clinical trials in DS. DABNI included 1135 participants (mean age 42.82,

Funding information: Instituto de Salud Carlos III (Ministerio de Ciencia, Innovación y Universidades, Gobierno de España), Grant/Award Numbers: INT21/00073, PI20/01473, PI23/01786, PI20/00836, PI18/00335, PI22/00758, ICI23/00032, PI18/00435, PI22/00611, INT19/00016, INT23/00048, PI14/1561, PI20/01330, PI23/01767, PI22/00307, PI21/00791, PI24/00598; Fondo Europeo de Desarrollo Regional (FEDER), Unión Europea, Una Manera de Hacer Europa; National Institutes of Health, Grant/Award Numbers: R01 AG056850, R21 AG056974, R01 AG061566, R01 AG081394, R61AG066543, 1RF1AG080769-01; Global Brain Health Institute, Grant/Award Numbers: GBHI_ALZ-18-543740, GBHI_ALZ-23-971107; Fundación Tatiana Pérez de Guzmán el Bueno, Grant/Award Numbers: IIBSP-DOW-2020-151, PCN00180; Instituto de Salud Carlos III through the Sara Borrell Postdoctoral Fellowship, Grant/Award Numbers: CD23/00235, CD20/00133; Instituto de Salud Carlos III through the Río Hortega Fellowship, Grant/Award Numbers: CM22/00052, CM21/00243, CM22/00219, CM22/00291; Instituto de Salud Carlos III through the Miguel Servet, Grant/Award Numbers: CP20/00038, CP24/00112; Miguel Servet program; La Caixa Foundation and Ajuntament de Barcelona, Grant/Award Number: 23S06157-001; H2020 European Institute of Innovation and Technology, Grant/Award Number: H2020-SC1-BHC-2018-2020; Fondation Jérôme Lejeune, Grant/Award Numbers: PDC-2023-51, #1801Cycle2020, #1913cycle2019B, #2326–GRT-2024A; Alzheimer's Association, Grant/Award Numbers: AARFD-21-852492, AACSF-21-850193, AARF-22-924456, AARG-22-923680

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46.3% female). At baseline, 673 participants were cognitively stable, 113 had prodromal AD, 239 had AD dementia, and 110 were uncertain due to non-AD conditions. Over 10 years, > 10000 clinical visits were conducted; follow-up showed that progression to symptomatic AD before age 40 was rare, but rates increased after age 50 (> 50% within 5 years). Neuropsychological and biomarker assessments demonstrated excellent diagnostic performance and a predictable sequence of changes, similar to autosomal dominant AD. DABNI participates in AD clinical trials and produced approximately 100 publications. The 10-year DABNI study provided critical insights into DS-associated AD (DSAD) and serves as a key platform for DS clinical trials.

KEYWORDS
Alzheimer's disease, autosomal dominant Alzheimer's disease, biomarkers, clinical trials, cognition, DABNI, Down syndrome, health

Highlights

- Down Alzheimer Barcelona Neuroimaging Initiative (DABNI) is a population-based multimodal cohort studying Alzheimer's disease in Down syndrome.
- Over 10 years, 1135 participants contributed to more than 10000 clinical visits and extensive biomarker studies.
- DABNI findings have transformed the understanding of Alzheimer's disease in Down syndrome, reinforcing its classification as a genetic form of the disease.
- The cohort integrates clinical care and research, enhancing early detection and patient management.
- DABNI supports clinical trials and has produced over 100 publications advancing Down syndrome-related Alzheimer's research.

1 | BACKGROUND

Down syndrome (DS) is the most common genetic cause of intellectual disability (ID),[1] and in 95% of cases, it is caused by a complete triplication of chromosome 21.[2] DS affects about 6 million people worldwide[3] and life expectancy in this population has greatly increased in the last decades, mainly due to improved medical, social, and educational care, exceeding 60 years of age.[1] Consequently, age-related co-occurring conditions in this population have emerged, particularly Alzheimer's disease (AD).

In DS, the AD histopathological hallmarks are universal by age 40 years,[4] and the dementia prevalence increases exponentially thereafter,[5–7] with a cumulative incidence of more than 95% in the seventh decade and a lifetime risk of more than 90%.[6,7] Thus, AD is now the leading cause of death in this population.[8]

The strong association between DS and AD has a genetic basis, mainly due to an extra copy of the amyloid-β precursor protein gene, which is coded in chromosome 21.[9] Consequently, DS is now considered a genetic form of AD. It has a strikingly similar sequence of biomarker and clinical changes leading to AD dementia to autosomal dominant AD (ADAD).[7,10–12]

Given the extremely high risk of developing AD dementia in DS, it is crucial to further understand the pathophysiological mechanisms of AD, especially during the long preclinical phase. This knowledge could help optimize therapeutic intervention before symptom onset.[13] However, diagnosing AD dementia in DS is often confounded by other factors, including varying degrees of baseline ID[14] and the associated medical co-occurring conditions such as epilepsy, sleep apnea-hypopnea syndrome, sensory deficits, hypothyroidism, among others.[15,16]

The Down Alzheimer's Barcelona Neuroimaging Initiative (DABNI) was established as a population-based, multimodal AD biomarker study to comprehensively integrate clinical, cognitive, and biomarker data in adults with DS starting at the age of 18 years. This initiative builds on the first population-based screening program for neurological conditions in individuals with DS, and it was created by the Hospital of Sant Pau and the Catalan Down Syndrome Foundation, in Barcelona. DABNI is a longitudinal cohort with a comprehensive multimodal biomarker program to advance interventions and clinical research in DS-associated AD (DSAD). Additionally, DABNI actively contributes to the development of therapeutic strategies by participating in clinical trials targeting AD in adults with DS.

In this paper, we will review the structure of the health plan underpinning the DABNI initiative and its detailed protocol. Additionally, we will highlight the key contributions of the program to advancing knowledge and interventions in DSAD. With an extensive longitudinal dataset of more than 1100 individuals recruited, more than 10000 clinical visits and around 100 publications, DABNI stands as a global leader in population clinical research, driving forward the understanding and treatment of DSAD.

2 | METHODS

The DABNI cohort of adults with DS is recruited and followed at the Alzheimer-down Unit of the Hospital of Sant Pau and the Catalan Down Syndrome Foundation in Barcelona, Spain. It takes full advantage of the robust and multidisciplinary framework provided by the Sant Pau Initiative on Neurodegeneration (SPIN) cohort, a structured and longitudinal research platform specifically designed to support advanced studies in neurodegenerative diseases. This initiative integrates a wealth of clinical, biomarker, imaging, and genetic data, enabling high-quality research and fostering collaboration across various disciplines. The SPIN cohort has been instrumental in advancing our understanding of neurodegenerative diseases and therapeutic strategies, as comprehensively detailed by Alcolea et al.[17]

2.1 | The Alzheimer-down Unit

The Alzheimer-down Unit was founded in 2012 as a partnership between the Hospital of Sant Pau and the Catalan Down Syndrome Foundation and, in 2014, it was recognized by the Catalan government as the reference center for all neurological disorders in adults with DS in Catalonia. The main aim of the Alzheimer-down Unit is the prevention, early detection and treatment of AD in adults with DS.

To achieve this aim, we developed a pioneering health plan for adults with DS, which includes comprehensive medical and neuropsychological assessments conducted at least annually for routine screening. For individuals with symptomatic AD, assessments are conducted every 6 months or more frequently as clinically indicated. The DABNI cohort is seamlessly integrated into this health plan, comprising those individuals who provide informed consent and/or assent to participate in research studies. This integration ensures a dynamic cohort that enables the clinical longitudinal follow-up of participants and the research needs essential to advance in our understanding of DSAD.

The Alzheimer-down Unit is located in a less medicalized environment within the Hospital of Sant Pau in Barcelona. This unique setting aims to reduce the sense of pathology often associated with DS, creating a welcoming atmosphere for participants, many of whom undergo routine screening and have no underlying pathology. The unit is staffed by a multidisciplinary team including neurologists, neuropsychologists, nurses, social workers and administrative staff, with expertise in both ID and neurodegenerative diseases. Recruitment began with a pilot project in 2012, was fully launched in May 2014 and has been ongoing ever since.

2.2 | Participant recruitment

The DABNI cohort includes adults with DS of both sexes over the age of 18 years, recruited from the aforementioned population-based health plan, for the prevention, early detection, and treatment of AD and neurological co-occurring conditions. Individuals across all levels of ID (mild, moderate, severe, and profound), both with and without medical co-occurring conditions, are eligible.

Around 3500 adults with DS are estimated to live in Catalonia. To date, the Alzheimer-down Unit has evaluated more than 1100 individuals with DS. The health plan and the DABNI project have been disseminated in different foundations, residences, occupational centers, and special employment centers, firstly to offer specialized medical attention and, secondly, to expand recruitment and ensure a more representative population-based sample in our studies for the advancement of the knowledge of DS and related AD.

For those patients who were unable to physically attend our center, we developed the Domiciliary Alzheimer Visiting in Down Syndrome (DAVIS) program, initially funded by a competitive grant from the Global Brain Health Institute (GBHI) and the Alzheimer's Association, and then by the Catalan Society of Neurology. This program allowed us to reach different centers in Catalonia to evaluate individuals with difficulties in traveling to Barcelona. Additionally, telemedicine visits were implemented for patients with advanced dementia or severe medical problems who can no longer physically attend our center. For protocol details, see Supplementary Material Sections 1 and 2 (Figures S1 to S5).

2.3 | DABNI cohort—General procedures

The health plan includes structured annual or semiannual (in participants with symptomatic AD) neurological and neuropsychological assessments by experienced clinicians, but the frequency of the visits is individually adapted according to the patient's specific needs.

All adults with DS attending the Alzheimer-down Unit are included in the health plan in the first instance and then invited to voluntarily participate in the DABNI cohort, which includes different assessments beyond routine healthcare visits. This initiative consists of a multimodal AD biomarker study to understand the AD natural history in this population. Specifically, DABNI includes clinical data from the yearly neurological, neuropsychological, and nursing assessments and optional neuroimaging, plasma, cerebrospinal fluid (CSF), neurophysiologic, and genetic biomarker assessments.

2.3.1 | Prebaseline phone call

When a person with DS is referred to the Alzheimer-down Unit for the first time, we begin by conducting a 30-min phone call to gather

preliminary information before the in-person assessment. During this initial contact, we obtain verbal consent to register the participant's medical history. Key details are collected, including the primary reason for referral, as well as relevant personal background information, such as educational level and the highest level of autonomy achieved. Additionally, we administer the Spanish version of the Cambridge Examination for Mental Disorders of the Elderly with Down Syndrome and Others with Disabilities Intellectual (CAMDEX-DS) interview[18] and assess for any neuropsychiatric symptoms with the Neuropsychiatric Inventory (NPI).[19] Based on the collected information, we determine the priority of the in-person visit and evaluate whether the participant is a suitable candidate for the full neuropsychological protocol.

Table 1 shows the clinical and cognitive protocols used at the Alzheimer-down Unit.

2.3.2 | Clinic medical evaluation

During the in-person visit, participants are asked to provide written informed consent to share their clinical data for research purposes. At this stage, they are also offered the option to take part in various biomarker-related procedures and studies. The process is intentionally designed to be participant-centered and highly adaptable, allowing individuals and their families to make informed decisions about their level of involvement. They can opt into one or more procedures based on their preferences, comfort, and interest. This flexible model supports participant autonomy and builds trust, while also ensuring that contributions to research are aligned with personal values and circumstances.

The routine medical/neurological visit consists of a structured anamnesis with the patient and a caregiver and a physical examination performed by expert neurologists. This visit includes CAMDEX-DS interview[18] in the follow-up visits and the NPI (except at baseline). We also collect demographic data, clinical and neurological history including epilepsy-associated risk factors, and detailed semiology of epileptic seizures and treatments. The physical evaluation includes a general and neurological exam, the Tinetti scale for balance and gait,[20] and the Scale for Outcomes in Parkinson's Disease (SCOPA).[21] We also administer a structured questionnaire for epilepsy, and we finally recommend performing an annual general blood test.

2.3.3 | ID assessment

At baseline, we establish the individuals' ID level following the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) criteria,[22] which rely on the best level of functioning assessed through a clinical interview and a semi-structured questionnaire. Additionally, we obtain the intelligence quotient (IQ) with the Kaufman Brief Intelligence Test (K-BIT) Spanish version[23] to further support the ID level classification. However, when there is suspicion of cognitive decline, the IQ is not considered, as this estimation is affected by the AD-related cognitive decline.

TABLE 1 Clinical and neuropsychological evaluation protocols.

Standard neuropsychological evaluation			
Test	**Domain**	**Baseline**	**FUPs**
KBIT	Intelligence quotient	X	
mCRT	Episodic memory	X	X
CAMCOG-DS	Global cognition	X	X
Cancellation task	Selective attention	X	X
Cats and Dogs	Flexibility, inhibition	X	X
Orientation TB	Person, time, and place orientation	X	X
Reading TB	Basic reading	X	
Writing TB	Basic writing	X	
DLD	Dementia scale	X	X
Standard neurological evaluation			
Test	**Domain/measure**	**Baseline**	**FUPs**
Informant Consent	Participation acceptance	X	
Pathological history	Personal	X	
Medical history	Health history	X	X
Treatment	Medication registry	X	X
CAMDEX-DS	Structured interview	X	X[a]
NPI	Neuropsychiatric symptoms	X	X
Physical evaluation	Neurological assessment	X	X
SCOPA	Motor assessment	X	X
TINETTI	Gait and balance	X	X
DABNI participation	NA	X[b]	X[c]
Brain donation	NA		X[d]
Standard nursing evaluation			
Test	**Measure**	**Baseline**	**FUPs**
Biometrics	Height[e], weight	X	X
Constants	BMI, pulse, blood pressure, oxygen saturation, cervical and abdominal perimeter	X	X
Audiometry	Hearing	X	X
Blood test[f]	Routine control and biomarkers	X	X

Abbreviations: BMI, body mass index; CAMCOG-DS, Cambridge Cognitive Examination for Older Adults with Down´s Syndrome; CAMDEX-DS, The Cambridge Examination for Mental Disorders of Older People with Down's Syndrome and Others with Intellectual Disabilities; DABNI, The Down Alzheimer Barcelona Neuroimaging Initiative; DLD, dementia questionnaire for people with intellectual disabilities; FUPs, follow-ups; KBIT, Kaufman brief intelligence test; mCRT, modified cued recall test; NA, not applicable; NPI, Neuropsychiatric Inventory; SCOPA, the scale for outcomes in Parkinson's disease; TB, test Barcelona; TINETTI, the Tinetti scale for balance and gait.

[a]Repeated annually only if the participant is older than 38 years old.

[b]Only if there are no critical medical conditions.

[c]Only if showed interest at baseline.

[d]Only if the participant is at an advanced age, if he/she has undergone biomarker study and family/caregivers are open-minded to receive the information.

[e]Height is only measured at baseline.

[f]Only if there is no recent blood test or if participating in the DABNI cohort.

2.3.4 | Neuropsychological evaluation

Our main neuropsychological protocol includes the Cambridge Cognitive Examination for Older Adults with Down's Syndrome (CAMCOG-DS) Spanish version[18] and the modified Cued Recall Test (mCRT).[24] The CAMCOG-DS is tailored for individuals with ID to evaluate cognitive function across 7 subscales, covering various cognitive domains including orientation, language, memory, attention, praxis, abstract thinking, and visoperception. Meanwhile, the mCRT is an adapted test to assess episodic memory in individuals with ID. It follows a two-phase paradigm, starting with a learning phase where participants memorize 12 stimuli. Subsequently, they are prompted to recall all items on the list, initially without cues, and then with cues provided for omitted items. This procedure is repeated three times with a delay of 20 min.

We complement our core protocol with additional assessments, including an expanded orientation task from the Barcelona Test,[25] a cancellation task to evaluate selective attention[26] and the Cats & Dogs task to assess cognitive flexibility and inhibitory control.[27] At baseline, we also evaluate basic reading and writing skills using components of the Barcelona Test. Finally, the Dementia Questionnaire for People with Learning Disabilities (DLD)[28] is administered to complement the information gathered by the neurologist. Of note, our center has participated in the validation of the CAMCOG-DS-2, and we plan to modify the protocol to incorporate this updated version in 2025.[29]

2.3.5 | Diagnostic process

The diagnostic classification of participants follows a systematic and structured process designed to ensure accuracy and minimize circularity in research studies. Neurologists and neuropsychologists independently classify subjects into one of four diagnostic categories without access to AD biomarker results but with access to basic neuroimaging and blood analytics. The categories are: (1) asymptomatic or cognitively stable, when there is no clinical or neuropsychological suspicion of symptomatic AD; (2) prodromal AD, when there is suspicion of cognitive deterioration due to AD, but symptoms do not fulfill the criteria for dementia; (3) AD dementia, characterized by full-blown AD dementia with cognitive decline and impaired activities of daily living (worsening from baseline level of independence); and (4) uncertain/nondegenerative neurocognitive disorder, where cognitive or daily living impairments are attributed to medical, pharmacological, or psychiatric conditions rather than a neurodegenerative origin. Importantly, some of these conditions are treatable and reversible, allowing individuals to transition into another diagnostic category upon resolution.

Neurologists and neuropsychologists initially conduct independent evaluations and establish separate preliminary diagnoses, remaining blind to each other's assessments and biomarker data. Subsequently, a consensus clinical meeting is conducted in which both professionals combine the full clinical information to establish a unified diagnosis, based solely on the complete data gathered during the clinical visits. Later, in some cases, this consensus diagnosis is further revisited and refined by incorporating biomarker data, if available, and/or longitudinal clinical follow-up information, ultimately establishing the definitive diagnosis for a given visit. For example, if CSF amyloid or positron emission tomography (PET) amyloid results are negative, the diagnosis should be reassessed or confirmed depending on the previous consensus decision.

As mentioned, this scheme was designed to avoid circularity in diagnostic and prognostic research studies, including cognitive and biomarker measures. For research purposes, the choice of diagnostic level depends on the specific objective. To evaluate neuropsychological test performance, clinical neurological diagnosis is used, while for biomarker performance, the consensus diagnosis is applied. This systematic approach ensures robust diagnostic validity while minimizing potential biases in diagnostic and prognostic studies involving cognitive and biomarker measures.

We define progression along the AD continuum when there is a change in the clinical and cognitive status after excluding other medical and psychosocial conditions that might justify the changes. We consider progression from asymptomatic to prodromal AD when there are relevant cognitive or behavioral changes, but there is no additional interference in daily living activities, and from prodromal to AD dementia when the cognitive and behavioral changes do interfere with the personal premorbid autonomy of patients.

2.3.6 | Nursing evaluation

During all clinical visits, a nurse assesses various vital signs and biometric measures of each individual, including weight and height at baseline, blood pressure, pulse rate, and abdominal and cervical circumference. The auditory function is also evaluated using an audiometer, while blood samples are collected as previously mentioned. Recently, we have been collecting lifestyle information, such as diet or leisure activities.

2.3.7 | Postdiagnostic orientation visits

When the diagnosis of symptomatic AD is made, participants and caregivers are offered an orientation visit, led by a neuropsychologist, and a social worker. During these visits, families/caregivers receive information about the course of the disease and available legal, healthcare and social resources. The visit is tailored to each family according to the stage of the disease and their personal and familial needs. Additionally, families of patients with AD are invited to join mutual support groups and participate in a series of psychoeducational workshops specifically designed for them, offering emotional support and practical tools to navigate caregiving challenges.

2.3.8 | CSF and biomarker assessment

As described elsewhere,[17] we perform a lumbar puncture to collect 15- to 20-mL CSF samples. CSF samples are collected and processed in polypropylene tubes following international recommendations.[30] The

first 2 mL of CSF are transferred to the general biochemistry laboratory in Hospital de la Santa Creu i Sant Pau for cell count and analysis of glucose and protein levels. The remaining sample is transferred to the Sant Pau Memory Unit laboratory, where it is processed and aliquoted within the first 2 hours after collection. Aliquots are stored at −80°C and are not thawed before analyses.

CSF core AD biomarkers (Aβ1-42, Aβ1-40, t-Tau, and p-Tau181) are routinely measured in all participants. We use commercially available fully automated immunoassays to determine levels of CSF Aβ1-40, Aβ1-42, neurofilament light chain (NfL), total tau, and p-tau at threonine residue 181 (Lumipulse Aβ1-40, Aβ1-42, NfL, total tau, p-tau181, Fujirebio-Europe, NfL Simoa Quanterix, MA, USA). For further details on biofluid processing, see Supplementary Material Section 3 and Figure S6.

2.3.9 | Blood and DNA extraction

Blood extraction is performed at the time of lumbar puncture or during the routine clinical visit in participants who do not undergo a lumbar puncture. Samples are partly transferred to the general biochemistry laboratory in Hospital de la Santa Creu i Sant Pau for general blood analysis, including thyroid profile B12 vitamin and folic acid, and AD biomarkers, depending on the case (p-tau217). The remaining part is transferred to the Sant Pau Memory Unit laboratory where they are centrifuged and aliquoted within 2 hours after extraction and stored at −80°C until they are analyzed. Fasting is not mandatory before the blood extraction, but the time from the last meal to the blood extraction is recorded. Plasma markers associated with AD or neurodegeneration—such as Aβ1-40, Aβ1-42, pTau181, pTau217, and NfL, among others—are quantified locally using advanced technologies, including the ultrasensitive single-molecule assay (SIMOA) platform (Quanterix) and/or the fully automated Lumipulse system (Fujirebio-Europe).[31,32]

Regarding genetic analyses in the DABNI cohort, we perform whole-genome genotyping using single-nucleotide polymorphism (SNP) arrays. Leveraging SNP genotyping data, we determine the presence of trisomy 21 as well as other relevant genotypes across the genome. These analyses provide valuable insights into the genetic components that may contribute to the clinical features observed in our cohort. Details on the collection and processing of CSF, blood, and DNA collection are provided in Alcolea et al.[17]

2.3.10 | Structural, diffusion, and functional magnetic resonance imaging (MRI)

Participants undergo 3T-MRI scans, including structural, diffusion, and functional brain sequences. Data are preprocessed using standard and in-house pipelines using the Computational Anatomy Toolbox [CAT12][33] for Statistical Parametric Mapping 12 (SPM12; Welcome Center for Human Neuroimaging), Advanced Normalizations Tools ecosystem (ANTs),[34] FreeSurfer (v7.1.1),[35] FSL (v6.0.6), MRtrix3, and the T1 Automatic Segmentation of Hippocampal Subfields (T1-ASHS).[36] Specifically, gray matter integrity is quantified using the gray matter volume (CAT12 and ASHS), cortical thickness (FreeSurfer/ANTs), and cortical mean diffusivity extracted from an original surface-based pipeline (using both FSL and FreeSurfer).[37] White matter integrity is assessed using key diffusion measures [e.g., the fractional anisotropy (FA) and mean diffusion (MD)] extracted with the FMRIS's Diffusion Toolbox (FSL) and MRtrix3.[38] Regarding cerebrovascular lesions, white matter hyperintensities (WMH) are segmented on the FLAIR image using the lesion prediction algorithm (LPA) implemented in the Lesion Segmentation Toolbox (LST)[39] for SPM12. Regional WMH are further quantified using an in-house script and following a bullseye classification system.[40] In a subset of participants, microbleeds are manually segmented on the SWI sequence using ITK-SNAP[41] and microinfarct using the T1 image and MeVisLab (MeVis Medical Solutions AG; version 3.4.1). Finally, pseudo-continuous arterial spin labeling and resting-state functional MRI (rsfMRI) data are processed using the open-source and publicly available ASLPrep (version 7.2)[42] and fMRIPrep (version 23.2.1)[43] software, respectively. For further details on MRI processing, see Supplementary Material Section 4 (Tables S1 and S2).

2.3.11 | Nuclear medicine imaging

18-fluorodeoxyglucose ([^{18}F]FDG) PET, amyloid-PET, and tau-PET imaging are acquired at the Nuclear Medicine Department in the Hospital de la Santa Creu i Sant Pau, and images are processed by our neuroimaging team in the Memory Unit. The first [^{18}F]FDG-PET was performed in October 2014, amyloid-PET in January 2015, and Tau-PET in November 2021.

Amyloid PET is acquired using the [^{18}F]Florbetapir, [^{18}F]Flutemetamol, or [^{18}F]-Florbetaben compounds, and tau-PET using the PI-2620 tracer. Data are preprocessed using standard and in-house pipelines relying on SPM12, ANTs, and FreeSurfer. The main preprocessing steps include coregistration to the T1-image if available, intensity-scaling using a reference region, and normalization to a standardized space using either T1-derived normalization parameters or an MRI-independent approach relying on the automated adaptive template method.[44] Optimal reference regions to normalize the signal are still being explored, but we are currently using the pons for the [^{18}F]FDG-PET, the whole cerebellum for amyloid and tau-PET tracers. The standardized uptake value ratio is then extracted in regions of interest, including Landau's region for [^{18}F]FDG-PET and amyloid-PET.[45,46] For amyloid-PET, we further quantify amyloid burden using the AMYQ[44] and Centiloid[47] scores. For further details on PET processing, see Supplementary Material Section 5 (Table S3).

2.3.12 | Sleep evaluation

A subset of participants in the DABNI cohort undergo a comprehensive sleep evaluation, including subjective and objective measures of

sleep and circadian rhythm. This evaluation consists of an interview with a sleep specialist, nocturnal video-polysomnography (PSG), and actigraphy. Participants, in most cases with the support of a relative or caregiver, also track their sleep-wake patterns in sleep diaries and complete questionnaires assessing sleep quality (Pittsburgh Sleep Quality Index), somnolence (Epworth Sleepiness Scale), and sleep apnea risk (Berlin and Stop-Bang questionnaires). Nocturnal video-PSG is performed in a controlled sleep unit, monitoring 19 electroencephalogram (EEG) channels, two oculographic electrodes, four electromyography (EMG) channels, and respiratory parameters (oximetry, airflow, thoracoabdominal movements, and snoring). Actigraphy is worn the week before PSG to monitor daily activity and sleep patterns, providing data for comparison with sleep diaries and PSG.

2.3.13 | EEG

The waking EEG consists of a conventional 30-min resting-wake EEG using 19 EEG channels (FP1, FP2, F3, F4, F7, F8, C3, C4, O1, O2, P3, P4, T3, T4, T5, T6, CZ, CZ, and PZ) referenced to the average of both mastoid electrodes (A1–A2) according to the 10/20 system set-up. Stimulation maneuvers of photic intermittent stimulation and hyperventilation are performed.

2.3.14 | Neuropathology

Participants in the DABNI cohort are encouraged to consent to brain donation. During follow-up visits, especially in the end-of-life period, we emphasize the importance of neuropathological studies in advancing research on neurodegenerative diseases. Donors contact Barcelona's Neurological Tissue Bank (http://www.clinicbiobanc.org) for formal registration. We are part of the Down Syndrome Biobank Consortium (DSBC), an international collaboration of 11 biobanking sites across Europe, India, and the United States, focused on collecting and disseminating brain tissue with harmonized protocols from individuals with DS throughout their lifespan.[48] Of note, formalin fixed paraffin embedded samples are harvested from multiple neuroanatomic areas (see Supplementary Material Section 6 and Table S4), as well as frozen tissue and cryopreserved areas, and CSF if available.

2.3.15 | Data integration

Building on the methodology described in Alcolea et al.[17] we have integrated clinical, neuropsychological, biomarker, genetic, neuroimaging, and neuropathological information from all participants into a single unified database. Every participant receives a unique code, which links their data across all categories while maintaining confidentiality. Annual data freezes are performed after rigorous quality control, generating anonymized datasets with unique code, but without personal identifiers. Personal identification information is securely stored in a separate database. As all data are associated with specific time points for each participant, this structure allows seamless integration across categories and facilitates the generation of automated, ready-to-analyze datasets.

2.3.16 | Clinical trials and international studies

Alongside DABNI, we provide opportunities for participation in clinical trials focusing on AD in DS. Additionally, we facilitate participation in international studies and collaborations aimed at advancing our understanding of AD.

2.3.17 | Ethical aspects

All studies are conducted at the Alzheimer-down Unit in strict accordance with international ethical guidelines for medical research in humans following standards contained in the Declaration of Helsinki and Spanish law. Before the start of any study, all protocols, the information given to the subjects, as well as the informed consent model used, are approved by the Sant Pau Research Ethics Committees. Before including any subject in the study, the investigator gives detailed information to the participant and their legally authorized representative of the objectives, methods, potential risks, or any inconvenience it may cause. Moreover, all participants can ask for extra information or clarification whenever needed, and they can abandon the study at any point for any reason. All participants and their legally authorized representatives are asked for their assent and consent to the acquisition, analysis, and storage of biological samples. They are also informed about the possibility of sharing anonymized information and/or biological samples with other researchers. Confidentiality is guaranteed in accordance with the current Spanish legislation (LOPD 3/2018).

Return of individual research results to participants is handled with careful consideration of clinical relevance and ethical oversight. Biomarker results, including *APOE* genotyping, amyloid PET imaging, and fluid-based assays (e.g., plasma or CSF), are generally not returned when collected solely for research purposes, unless specifically requested and reviewed under ethics committee guidance. Apolipoprotein E (*APOE*) results are currently withheld due to the lack of clinical indication, although this approach is being re-evaluated in light of emerging anti-amyloid therapies and their implications for ARIA risk. When any of these biomarkers are obtained as part of clinical care, results are shared with the participant and their healthcare provider. This approach aims to respect participant autonomy while minimizing the potential for misunderstanding or undue concern in the absence of clear clinical benefit.

As shown in Figure 1, the health plan and the biomarker cohort are integrated to optimize data collection and the participant pathway. Supplementary Material Section 7 contains QR codes of the informative videos on some DABNI assessments.

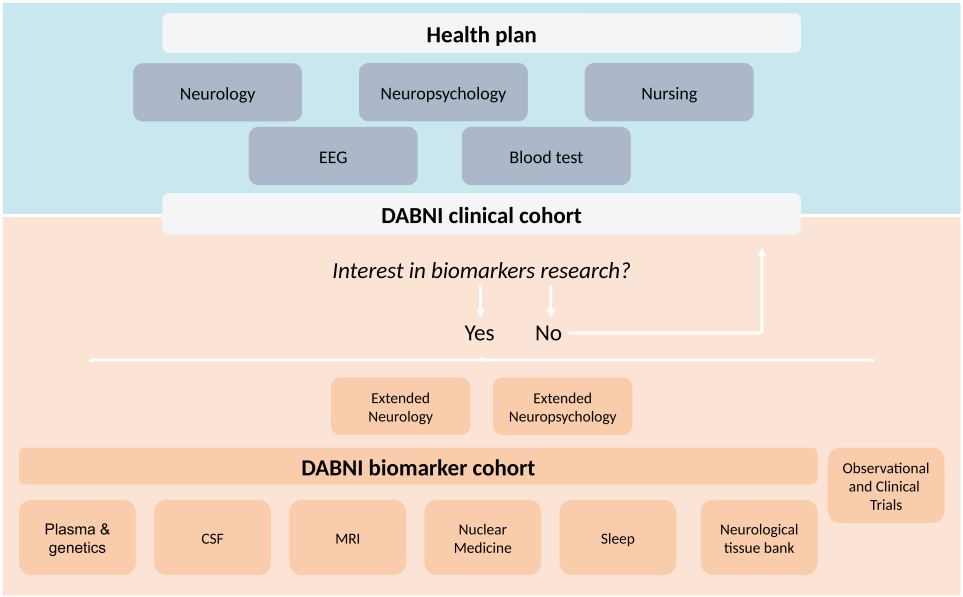

FIGURE 1 DABNI flowchart. The health plan run at the Alzheimer-down Unit and the biomarker cohort, are integrated to optimize data collection and the participant pathway. CSF, cerebrospinal fluid; DABNI, Down Alzheimer Barcelona Neuroimaging Initiative; EEG, electroencephalogram; MRI, magnetic resonance imaging.

3 | RESULTS

3.1 | Clinical studies

To date, the DABNI cohort represents one of the largest multimodal AD biomarker studies focusing on individuals with DS, comprising data from 1135 participants, 46.3% of whom are female. This extensive dataset was compiled over more than a decade and includes data from > 10000 clinical visits (6339 neurological and 4101 neuropsychological visits as of December 31, 2024). The first participant included in our cohort was recruited in October 2012.

The clinical diagnoses at baseline were 673 (59.3%) participants were classified as asymptomatic, 113 (10.0%) were diagnosed with prodromal AD, and 239 (21.1%) had AD dementia. An additional 110 (9.7%) participants were categorized as uncertain due to medical conditions unrelated to AD. There was a 92.9% diagnostic agreement between the neurologist and neuropsychologist based on blinded clinical assessments. The mean age of the cohort at baseline was 42.82 years (SD = 11.56). As expected, significant age differences were observed across clinical diagnostic groups, with the dementia group being the oldest. The cohort's ID distribution is as follows: 20% with mild ID, nearly 48% with moderate ID, 20% with severe ID, and 7% with profound ID. For 5% of participants, the premorbid ID level is unknown due to caregivers' inability to provide reliable information about their optimal level of functioning or because cognitive decline prevents the administration of an IQ test. The mean follow-up time is approximately 3 years (interquartile range [IQR] 0.4–4.58). Table 2 provides detailed demographic information, including follow-up time, ID levels, medication, and *APOE* distribution.

In the past decade, our understanding of AD in individuals with DS has evolved dramatically. Previously, it was believed that only a subset of individuals with DS would develop AD.[3,49] However, thanks to insights gained from the DABNI cohort and other international cohorts, we now know that over 95% of people with DS will develop AD if they live long enough.[7] This discovery has profoundly reshaped the clinical approach to AD in DS populations, emphasizing the necessity for early detection and tailored management strategies.

Our previous research with the DABNI cohort has shed light on the longitudinal progression of AD in adults with DS. We found a clear age dependency in asymptomatic individuals: progression is exceedingly rare before the age of 40 but increases significantly thereafter. After 5 years of follow-up, it occurs in 21.2% from age 40 to 45, 41.3% from age 45 to 50, and 57.5% of individuals aged over 50 years of age. Among individuals with prodromal AD, progression to AD dementia is nearly universal within 5 years.[50] Notably, the DABNI follow-up has enabled us to diagnose a significant number of cases, solidifying the importance of consistent longitudinal monitoring in this population. Specifically, we have diagnosed 496 symptomatic AD cases, 144 of whom were diagnosed during the follow-up. This represents 21.4% of those individuals who were asymptomatic for AD at baseline.

Our findings further suggest that the onset of AD in DS is as predictable as in ADAD, with a mean age for prodromal AD onset of 50.2 and AD dementia of 53.8 and near-full penetrance.[7,8,51] This highlights the pivotal role of AD in reducing life expectancy in DS, which remains more than 20 years shorter than in the general population.[8] Moreover, we observed that sex does not significantly influence AD clinical

TABLE 2 Demographics, mean follow-up time, and *APOE* genotype in the whole sample and stratified by clinical diagnoses.

Parameter	Whole sample *N* = 1135	Asymptomatic *n* = 673	Prodromal *n* = 113	Dementia *n* = 239	Uncertain *n* = 110	*p*-value
Sex (female %)	46.30 %	44.3%	48.6%	48.3%	52.4%	0.3523
Age mean (SD)	42.82 (11.56)	38.07 (10.40)	51.97 (5.16)	54.20 (5.64)	37.93 (9.61)	0.0001
ID *n* (%)						0.0000
Mild	220 (19.38%)	174 (25.85%)	16 (14.16%)	15 (6.28%)	15 (13.64%)	
Moderate	545 (48.02%)	298 (44.28%)	61 (53.98%)	119 (49.79%)	67 (60.91%)	
Severe	232 (20.44%)	124 (18.42%)	22 (19.47)	71 (29.71%)	15 (13.64%)	
Profound	82 (7.22%)	55 (8.17%)	7 (6.19%)	13 (5.44%)	7 (6.36%)	
Unknown	56 (4.93%)	22 (3.27%)	7 (6.19%)	21 (8.79%)	6 (5.45%)	
Time of FUP (years) (mean [IQR])	2.84 [0.4-4.58]	3.97 [0.2-6.9]	3.59 [0.5-5-7]	2.35 [0.04-3.7]	2.8 [0.4-4.3]	0.0000
APOE genotype *n* (%)						0.0000
22	3 (0.45%)	1 (0.26%)	1 (1.33%)	1 (0.63%)	0	
23	65 (9.70%)	40 (10.44%)	8 (5.70%)	8 (5.06%)	9 (16.67%)	
24	9 (1.34%)	5 (1.31%)	2 (6.96%)	2 (1.27%)	0	
33	470 (70.15%)	272 (71.02%)	46 (61.33%)	113 (71.52%)	39 (72.22%)	
34	116 (17.31%)	62 (16.19%)	16 (21.33%)	32 (20.25%)	6 (11.11%)	
44	7 (1.04%)	3 (0.78%)	2 (2.67%)	2 (1.27%)	0	
Drugs						
Anticholinesterases		0.15%	0.84%	5.93%	0%	
Memantine		0%	0.84%	1.27%	0%	
Anti-psychotics		11.21%	15.97%	22.46%	24,07%	
Antidepressants		10.18%	17.65%	25.42%	33,33%	
Benzodiazepines		6.19%	9.24%	13.98%	18.52%	

Abbreviations: *APOE*, apolipoprotein E; FUP, follow-up; GWAS, Genome-Wide Association Study; ID, intellectual disability; IQR, interquartile range; SD, standard deviation.

outcomes or most biomarker trajectories in adults with DS, except for its interaction with the *APOE* ε4 haplotype.[52,53] *APOE* ε4 carriers, irrespective of sex, had earlier clinical and biomarker changes of AD in adults with DS.[54]

The DABNI cohort has also played a pivotal role in redefining our understanding of AD presentation in DS. Contrary to earlier beliefs that claimed a frontal presentation and/or behavioral symptoms,[55] our cohort and others have demonstrated that the clinical presentation in DS is akin to that seen in the general population, with an early and progressive memory impairment as the most common presentation.[50,56] Atypical presentations are rare, as in ADAD, but do occur. For instance, we documented a case of posterior cortical atrophy (PCA) in a DS individual, highlighting the spectrum of possible manifestations.[53] These findings underscore the importance of nuanced clinical and neuropsychological assessments for accurate diagnosis and management of AD in DS populations.

Our neuropsychological studies using the DABNI dataset have further challenged prior diagnostic paradigms. In contrast to recommendations from earlier frameworks,[57] we demonstrated that neuropsychological tests, particularly the CAMCOG-DS and mCRT, show excellent diagnostic performance for AD dementia and moderate performance for prodromal AD when stratified by the level of ID.[50,58,59] Additionally, we found significant variability in neuropsychological measures over 1 year, underscoring that baseline assessments are more reliable for diagnostic accuracy than 1- or 2-year intraindividual longitudinal changes.[59] These findings advocate for a revision of diagnostic frameworks to prioritize the utility of baseline neuropsychological assessments stratified by the level of ID in this population.

These works from the DABNI cohort have enabled the development and update of clinical guidelines to improve care for individuals with DS and AD. These include the 2018 guidelines of the Spanish Neurology Society,[60] international contributions such as those by Lumind,[61] the Clinical Guidelines for Monterrey in Mexico[62] and the recommendations for postdiagnostic support.[63] We also collaborated in the elaboration of book chapters regarding AD and AD biomarkers in DS.[16,64,65]

Together, these advancements reflect the profound impact of research efforts on shaping both the clinical management and the quality of life for individuals with DS facing the challenges of AD. Table 3 provides an overview of baseline and longitudinal clinical and biomarker data across the different clinical groups.

TABLE 3 DABNI clinical visits and biomarker studies in the whole sample and stratified by clinical diagnosis.

Parameter	Whole sample	Asymptomatic	Prodromal	Dementia	Uncertain
Clinical Visits					
Neurology visits (total)	6339	2860	662	2218	434
Baseline (*n*)	1135	673	113	239	110
Longitudinal (*n*, mean time between visits [SD] in years)	5204 [0.76 (0.80)]	2187 [1.02 (0.85)]	549 [0.66 (0.74)]	1979 [0.54 (0.66)]	324 [0.81 (0.86)]
Neuropsychology visits (total)	4101	2529	420	852	296
Baseline (*n*)	1078	656	103	211	108
Longitudinal (*n*, mean FUP time [SD] in years)	3023 [1.09 (0.75)]	1873 [1.2 (0.66)]	317 [0.98 (0.88)]	641 [0.88 (0.77)]	188 [1.18 (1.07)]
Fluid Biomarkers					
CSF total samples (n)	383	157	83	113	30
Baseline	316	123	68	100	25
Longitudinal	67	34	15	13	5
Blood total samples (*n*)	1956	1109	217	509	121
Baseline	753	427	85	177	64
Longitudinal	1203	682	132	332	57
Neuroimaging and nuclear medicine biomarkers					
MRI total (*n*)	486	261	70	115	40
Baseline	334	170	53	83	28
Longitudinal	152	91	17	32	12
FDG-PET total (*n*)	235	111	39	67	18
Baseline	190	85	32	57	16
Longitudinal	45	26	7	10	2
Amyloid-PET total (*n*)	204	114	30	48	12
Baseline	182	104	24	42	12
Longitudinal	22	10	6	6	0
Tau-PET total (*n*) baseline	83	41	13	25	4
Baseline	65	33	8	20	4
Longitudinal	18	8	5	5	0
Sleep studies and EEG					
PSG	279	173	30	76	0
Baseline	254	154	25	75	0
Longitudinal	25	19	5	1	0
EEG	163	67	25	46	25
Baseline	152	65	22	41	24
Longitudinal	11	2	3	5	1

Abbreviations: CSF, cerebrospinal fluid; EEG, electroencephalogram.; FDG-PET, fluorodesoxyglucose positron emission tomography; MRI, magnetic resonance imaging; PSG, polysomnography; SD, standard deviation.

3.2 | Sleep and EEG studies

Sleep evaluations in the DABNI cohort (including PSG studies; $n = 254$) have yielded clinically significant findings, including distinct alterations in sleep architecture. Adults with DS exhibit markedly reduced rapid eye movement (REM) sleep and increased slow-wave sleep (SWS) compared to the general population.[66] These differences in sleep structure are further exacerbated along the AD continuum, with an increased prevalence of obstructive sleep apnea (OSA) and progressive reductions in REM sleep alongside decreases in SWS.[67] These changes underscore the impact of AD-related neurodegeneration on sleep regulation in this population.[68]

Adults with DS frequently experience severe sleep disturbances[69] and a high prevalence of OSA, often undetected through self-reported

or caregiver-reported measures,[68] but reliably identified via actigraphy and PSG.[66] Importantly, DABNI has shown that OSA can be effectively managed with continuous positive airway pressure (CPAP) therapy, as in the general population, as demonstrated by the high long-term adherence among OSA patients with DS.[70]

Individuals with DS also face an elevated risk of epilepsy throughout their lives, with a particularly increased risk after the age of 40. This late-onset epilepsy is associated with the development of symptomatic AD. We described that more than 50% of adults with DS and AD dementia will develop epilepsy, which in this population typically presents as generalized myoclonic epilepsy. Known as late-onset myoclonic epilepsy in DS (LOMEDS), this condition significantly impacts quality of life, may worsen cognitive and functional outcomes in AD dementia patients, and affects mortality rates.[15] Moreover, in collaboration with investigators from New York University, we have shown that high-frequency oscillations (HFOs) during slow-wave sleep in PSG occur prior to the onset of AD dementia and LOMEDS, suggesting that HFOs may serve as an early, noninvasive biomarker for symptomatic AD in DS.[71]

3.3 | Blood, CSF, genetics, and *post mortem* studies

CSF (n = 383) and blood (n = 1956) samples from the DABNI cohort form the largest biorepository of CSF and plasma from adults with DS, significantly advancing the understanding of AD in this population.[7,31,72] DABNI enabled the first study to demonstrate the diagnostic performance of core AD biomarkers in CSF, establishing their reliability in this context.[73]

In addition to CSF biomarkers, plasma biomarkers have shown great promise. Plasma p-tau181 and plasma p-tau217 were shown to be reliable screening tools for AD in this population,[74] while plasma p-tau212, NfL, and glial fibrillary acidic protein (GFAP) concentrations demonstrate strong diagnostic performance, showing a progressive increase along the AD continuum without plateauing in the dementia stage.[7,31,75–77]

Emerging CSF and plasma biomarkers, neuropathological and biochemical studies are advancing the understanding of AD pathology in DS as well. We demonstrated in synaptosomes isolated from *post mortem* tissue that β-C-terminal fragment (βCTF) accumulates in synapses in sporadic AD, ADAD, and DS, suggesting a role of βCTF in synapse degeneration in AD.[78] Using array tomography, we also report that APP is located in pre and postsynaptic compartments in different AD forms, including DS. Changes in nerve growth factor (NGF) metabolism, detectable in plasma, CSF, and neuron-derived extracellular vesicles, highlight its role in AD progression.[79,80] Reduced CSF NPTX2 levels, observed in DS before symptom onset, correlated with decreased CSF GluA4, suggesting impaired inhibitory interneuronal activity, and positioning NPTX2 as a potential biomarker of circuit dysfunction.[81] A study evaluating biochemical and hematological parameters in adults with DS has provided additional insights into the complex biomarker landscape of AD in this population.[82] Additionally, synaptic proteins such as Calsyntenin-1, GluR4, and Thy-1, detectable via targeted proteomics, show promise for early disease detection and monitoring drug efficacy. Another study focused on fluid biomarkers of peripheral and central nervous system inflammation across the AD continuum in adults with DS and has shown common and specific inflammatory alterations associated with DS and DSAD.[83]

In summary, these findings lay the groundwork for precision medicine for DSAD, although longitudinal studies are needed to validate their prognostic value.[74]

3.4 | Neuroimaging studies

Imaging studies using MRI from the DABNI cohort have provided critical insights into the neuroanatomical and pathological changes associated with DS and AD. These studies have revealed a characteristic pattern of atrophy in individuals with DS and symptomatic AD, characterized by a reduced cortical thickness[7] and volume in temporoparietal,[84] precuneus-posterior cingulate, and frontal areas. Importantly, the first study investigating the neuroanatomical correlates of episodic memory processes in adults with DS demonstrated that distinct subscores of the mCRT correlate with cortical thickness in symptomatic AD. This highlights the involvement of specific brain regions in different stages of episodic memory processing in DS.[85]

Additionally, all adults with DS exhibit smaller hippocampal volumes across the lifespan compared to controls, reflecting both lifelong neurodevelopmental changes inherent to DS and AD-related changes that emerge over time.[7] Detailed analyses of medial temporal lobe structures identified the entorhinal cortex, posterior hippocampus, and Brodmann area 35 as the regions showing the earliest thickness/volume loss in DS, starting 13–15 years before AD symptom onset.[86] The medial temporal lobe structures also present a significantly higher probability of showing gray matter volume loss before any other brain regions.[84] This pattern and timing are largely in line with prior studies in ADAD, underscoring a shared temporality in medial temporal lobe vulnerability associated with AD. This serves as a crucial reminder that, as with any biomarker, it is essential to first disentangle neurodevelopmental alterations associated with DS from AD-related pathological changes to fully understand the biomarker's trajectory and implications.

Cerebral amyloid angiopathy (CAA) is more frequently found in DSAD than in sporadic AD.[87] We have performed several studies showing distinct vascular patterns associated with DSAD. We demonstrated that the modified Boston criteria for CAA are more frequently met in DSAD (and ADAD) than in sporadic AD.[87,88] WMH emerge approximately a decade before AD symptom onset, correlating strongly with AD biomarkers and neurodegeneration, thus indicating a direct link to AD pathophysiology, independent of traditional vascular risk factors.[40] Microbleeds in DS predominantly affect posterior lobar regions and correlate with disease severity, although they do not clearly influence cognitive performance.[84] Notably, we reported the first case of CAA-related inflammation in a person with DSAD in the absence of amyloid-related treatments.[89] Cortical microinfarcts are primarily located in posterior regions and are associated with ischemic, but not

hemorrhagic, findings, suggesting a specific ischemic CAA phenotype.[89,90] Altogether, these findings suggest that CAA is frequently observed as individuals with DS age and develop DSAD, highlighting its role as part of the broader AD continuum. This underscores the need for further research, particularly given the cerebrovascular implications of anti-amyloid immunotherapies.

Additionally, basal forebrain (BF) atrophy has been identified as a promising neuroimaging biomarker of cholinergic neurodegeneration related to AD in DS.[91] Finally, we described how magnetic resonance spectroscopy detects AD-related inflammation and neurodegeneration, and could be a good noninvasive disease-stage biomarker in this population.[92] These findings point to a complex interaction between AD pathology and brain structure in DS, providing important insights for therapeutic approaches.

Brain perfusion decreases before clinical symptoms in adults with DS, particularly in the medial parietal lobe, as shown using pseudo-continuos arterial spin labeling (pCASL).[93] At the symptomatic stage, hypoperfusion extends to temporoparietal and frontal regions, resembling the pattern in sporadic AD. These findings highlight the potential of pCASL for early AD detection and monitoring in DS. Consistently, FDG-PET also reveals medial parietal hypometabolism in prodromal stages, which later spreads to temporoparietal and frontal regions during dementia.[94,95]

In terms of amyloid deposition, symptomatic participants exhibited increased global cerebral Aβ deposition, with relatively spared sensory and motor areas. Notably, amyloid PET uptake began to rise in the late, around 12 years before the expected onset of symptoms.[7] Regarding tau PET, tau was accumulated in the medial and basal temporal lobe regions (Braak stages III to V) following amyloid-β (Aβ) deposition, and was significantly correlated with cortical atrophy.[96] This is supported by a recent unpublished work showing that tau deposition in DSAD follows a similar pattern to that of ADAD and increases along the disease continuum.[97] These findings underscore the early onset of both metabolic and amyloid changes in DS, marking a critical aspect of AD progression in this cohort.

Figure 2 shows DABNI participants in different clinical and research assessments.

3.5 | Natural history

The natural history of AD in DS has been significantly elucidated through the contributions of the DABNI cohort. In collaboration with the University of Cambridge, we performed the first comprehensive description of the clinical and biomarker changes that precede and accompany symptomatic AD in DS.[7] Remarkably, these findings revealed a strikingly similar temporality to the progression described in ADAD,[98] underscoring shared mechanistic pathways despite differing etiologies. This trajectory also closely mirrors the progression of AD in the general population.

Intraneuronal accumulation of Aβ and β-CTFs/C-99 within endosomes, considered as the earliest neuropathological hallmark of AD, is seen in the fetal brain of individuals with DS as early as 21 weeks of gestation. This is followed by the emergence of diffuse amyloid plaques during adolescence and neuritic plaques in the 30s. By the time individuals reach their 40s, full-blown AD neuropathology is almost universal.[16]

The earliest abnormality in DSAD is a decrease in CSF Aβ levels beginning in the late 20s, likely following a pseudonormal phase, as children with DS have been reported to exhibit increased Aβ levels consistent with APP gene dose.[99] Plasma GFAP and NfL levels start to rise in the early 30s, followed by increases in phospho-tau in plasma and CSF in the mid-30s shortly before amyloid build-up in amyloid PET in the late 30s.[7,31,76] Neuroimaging studies reveal that AD-related entorhinal and hippocampal.[7,40,86] and temporoparietal metabolic loss,[94] start in the late 30s. As mentioned, WMH, indicative of cerebrovascular changes, appears in the early 40s and worsens with age[40] and microbleeds appear later and are more frequent in symptomatic AD.[84,87] In addition, the recently developed alpha-synuclein Seed Amplification Assay (αSyn-SAA) has enabled the determination of a 9.2% prevalence of alpha-synuclein copathology in DSAD, regardless of age or clinical status. αSyn-SAA positivity was associated with neocortical Lewy body deposits, as confirmed by neuropathological studies.[100]

Finally, cognitive decline typically begins by age 35–40 in memory tests and in the mid-40s in CAMCOG-DS measures, with over 90% of individuals showing AD dementia by their 60s, occurring later than ADAD but more than 20 years earlier than sporadic AD.[7,50]

This sequence of events with a long preclinical phase offers a unique opportunity for intervention with primary and secondary prevention in clinical trials. A deeper understanding of the natural history of the disease in DS will enable personalized medicine and improved designs for disease-modifying therapies aimed at slowing or halting the progression of AD, thus accelerating the path toward effective therapies for AD in both DS and the general population.[10,51,101]

3.6 | International collaborations

There are numerous reasons to be optimistic about the future of DSAD. Over the past decade, significant strides have been made, largely driven by the growing number of international collaborations across disciplines and institutions. DABNI has been a main contributor to these global efforts that have advanced our understanding of DSAD. Some examples include a European multicenter study highlighting the early AD-related cognitive markers in DS.[101–103] Furthermore, DABNI's work has underscored the need for specialized care due to the complex medical and intellectual needs.[6,104,105] The cohort has also contributed to research on behavioral, psychological, and cognitive symptoms of dementia, such as the Behavioral and Psychological Symptoms of Dementia (BPSD-DS) scale, which provides critical insights into the psychopathology of AD in DS[106,107] or the discrepancies between sites in assessing ID levels and its implications for diagnosis of dementia.[108] Additionally, through DABNI's international collaborations, healthcare disparities, such as racial inequalities in access to care and research, have gained attention, emphasizing the

FIGURE 2 DABNI participants in different clinical and research assessments. The volunteers in the pictures have signed their consent to appear in them and have given permission for their dissemination. DABNI, Down Alzheimer Barcelona Neuroimaging Initiative.

need to address these disparities to improve care for individuals with DS and AD.[109–111]

DABNI's collaborators have significantly advanced AD biomarker research in individuals with DS.[112,113] Research on NGF pathway biomarkers has provided insights into early changes in CSF and plasma, improving understanding of AD progression in DS.[79] Studies on the kynurenine pathway due to trisomy 21 have identified unique metabolic pathways contributing to the higher AD risk in DS.[114] Furthermore, DABNI has contributed to the identification of biomarkers like amyloid plaque proteomes, CSF proteome, and tau-related extracellular vesicles, distinguishing DS-related AD from other forms,[115–118] while exosome release in DS has shown potential as a diagnostic tool for disease monitoring.[119] Recently the DABNI cohort was included in the Head-to-Head Harmonization of Tau Tracers in Alzheimer's Disease (HEAD) study, whose aim is to harmonize tau tangle measurements obtained with different tau PET radiopharmaceuticals to elucidate the advantages and caveats of their use in clinical trials/practice and provide parameters to integrate their estimates.

Beyond clinical and biomarker research, DABNI has been a key player in several international consortia, including the Horizon 21 consortium, which now includes 11 centers across Europe, and the Down Syndrome Biobank Consortium, which is enhancing the collection and use of biological samples, enabling more tailored research and treatment approaches in DS.[48] DABNI is also part of the Trial Ready Cohort—Down syndrome (TRC-DS), detailed below. Additionally, DABNI investigators have actively contributed to various international organizations, such as the Alzheimer's Association Professional Interest Area in Down syndrome, the Lumind Foundation, and many other global organizations, including Down España, the Alzheimer Biomarkers Consortium—Down Syndrome (ABC-DS), National Institute of Health—INvestigation of Co-occurring conditions across the Lifespan to Understand Down syndrome (NIH-INCLUDE), the Trisomy 21 Research Society (T21RS), the National Down Syndrome Society (NDSS), the Global Down Syndrome Foundation, and the Jérôme Lejeune Foundation, all of which are working to improve the quality of life for individuals with DS.

These collective efforts have been instrumental in establishing a robust foundation of clinical, cognitive, and genetic data, along with biomarkers, to better understand AD in DS. DABNI's active involvement in these consortia has helped solidify the framework for future clinical trials in DS and AD, fostering the development of standardized protocols for research and scientific dissemination.

3.7 | Clinical trials

There is an urgent need for prevention and clinical trials focused on DSAD. Despite the near full penetrance of AD dementia, individuals with DS have often been overlooked in prevention trials.[10,51,120] The unique genetic and clinical characteristics of DS demand tailored interventions and early detection strategies.[51,121] To address these challenges, the NIH INCLUDE Down syndrome clinical trials the Readiness Working Group has refined clinical trial methodologies to ensure the inclusion of individuals with DS in research aimed at improving health outcomes.[122] This effort underscores the importance of understanding AD pathophysiology in DS for advancing interventions that can address the complex needs of this population.

A key initiative in this area is the Alzheimer's Clinical Trial Consortium—Down Syndrome (ACTC-DS), funded by the National Institute on Aging (NIA). ACTC-DS is leading the TRC-DS, with DABNI serving as one of the European sites. TRC-DS is preparing participants for upcoming randomized, placebo-controlled clinical trials targeting AD in DS.[123] These foundational efforts are essential for enabling secondary preventive trials and hold the promise of significant progress in AD research for individuals with DS.

DABNI is actively participating in pioneering clinical trials targeting AD in individuals with DS, contributing significantly to the development of therapeutic options for this at-risk population. Among these, there is the ABATE trial (NCT05462106), which investigates ACI-24.060, an anti-amyloid vaccine developed by AC Immune. This phase 1b/2, multicenter, adaptive, double-blind, randomized, placebo-controlled study evaluates the safety, tolerability, immunogenicity, and pharmacodynamic effects of ACI-24.060 in individuals with prodromal AD and adults with DS without dementia. DABNI is also involved in the HERO trial (NCT06673069), which focuses on an antisense oligonucleotide drug targeting the APP gene, developed by Ionis Pharmaceuticals. This innovative approach aims to reduce the production of amyloid precursor protein, thereby decreasing amyloid plaque formation.[124] Another key initiative is the ALADDIN trial (NCT05508789), testing Donanemab, an anti-amyloid monoclonal antibody developed by Eli Lilly, designed to bind to and clear existing beta-amyloid plaques in the brain. These three trials, the ABATE (NCT05462106), HERO (NCT06673069), and ALADDIN (NCT05508789), are ACTC-DS affiliated clinical trials. Finally, it is worth noting the Levetiracetam to prevent seizures in Symptomatic Alzheimer's Disease in adults with Down syndrome trial (the LESS-AD trial), which is led by DABNI investigators. This is the first trial studying the efficacy and safety of levetiracetam in DS and aims to potentially prevent epileptic seizures and delay or mitigate AD-related cognitive decline. This pivotal research seeks to explore the crucial link between AD and epilepsy in this at-risk group.

These groundbreaking trials represent a major step forward in developing targeted treatments for individuals with DS at risk of AD, offering hope for improved clinical outcomes and quality of life in this vulnerable population.

Figure 3 synthesizes the main contributions of DABNI to the advance in the knowledge of DSAD.

4 | DISCUSSION

The DABNI study is a groundbreaking research cohort within the first population-based health plan dedicated to screening for neurological conditions in adults with DS. This health plan is free for patients, ensuring equitable access to care. DABNI represents the largest worldwide single-center cohort of adults with DS, combining multimodal clinical and biomarker studies focused on AD. Since its inception more than 10 years ago, DABNI has resulted in the publication of over 100 scientific articles, has influenced changes in clinical guidelines, and has contributed to the reconceptualization of DS as a genetically determined form of AD.

Improved medical care has significantly increased the life expectancy of individuals with DS, with some reaching their seventh decade. However, this longer lifespan has brought a rise in age-related co-occurring conditions, particularly AD, for which specific health plans for adults with DS have been lacking. In response, the health plan developed at the Alzheimer-down Unit represents a novel and comprehensive model of care. Successfully integrated into the public health system, this program has directly enhanced medical attention for adults with DS, improving individualized care while raising awareness among families about the high risk of AD dementia in this population. This innovative model seamlessly incorporates research into routine clinical visits, enriching the quality of care by enabling early detection and intervention. A notable achievement has been the diagnosis of numerous new patients ($n = 144$) who, without this program, would likely have been undiagnosed or experienced significant delays in diagnosis. DABNI investigators are also healthcare providers. This has been a key success factor, enabling us not only to monitor, detect, and treat AD and co-occurring conditions at an early stage, but also to integrate research with patient care. This has fostered trust and commitment among participants and their families, significantly enhancing participation and retention in research studies. This dual approach not only improves clinical outcomes but also strengthens the ability to advance knowledge through research. An example of the program's impact is the development of updated clinical guidelines for dementia in DS, such as those published by the Spanish Society of Neurology.[60] This unique model sets a benchmark for integrating care and research, ensuring better outcomes for individuals with DS, and advancing the field of neurodegenerative disease.

Over the past decade, there has been a profound transformation in the understanding and diagnosis of AD in individuals with DS. Previously, AD in DS was often considered atypical, likely due to referral bias and limited data. Similarly, the penetrance was estimated to be around 50% of individuals exhibiting symptoms by the age of 60.[55] However, longitudinal studies, including those from the DABNI cohort, have now provided a clearer picture of the natural history of the disease. These studies have demonstrated that AD in DS is better understood as a typical form of early-onset AD, characterized by virtually full penetrance, meaning that nearly all individuals with DS will develop AD if they live long enough. Memory and executive function deficits are the most frequent early cognitive changes, mirroring the presentation seen in other forms of early-onset AD.

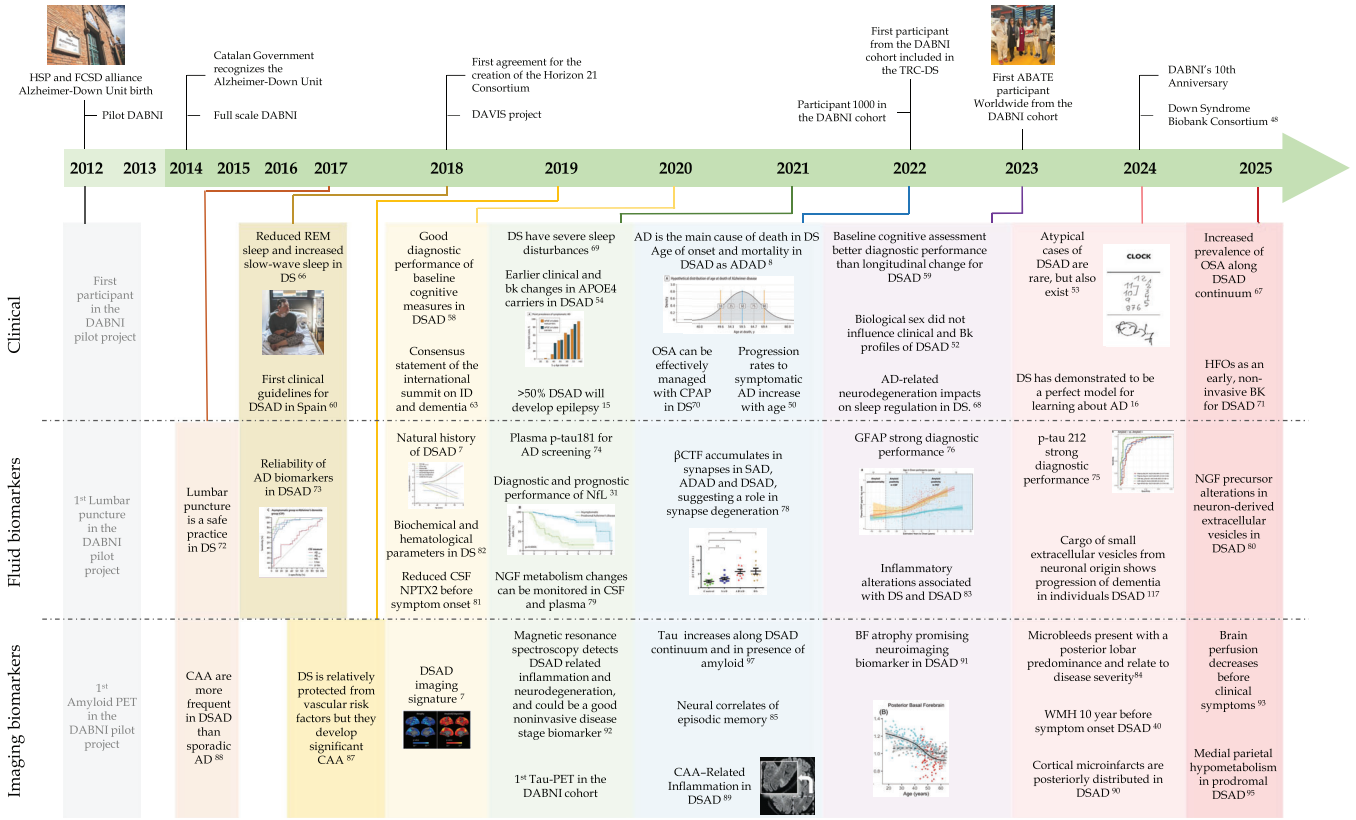

FIGURE 3 DABNI's chronogram including milestones and contributions to DSAD. ABATE, autoimmunity-blocking antibody for tolerance; AD, Alzheimer's disease; ADAD, autosomal dominant Alzheimer's disease; *APOE*, apolipoprotein E; βCTF, β-C-terminal fragment; BF, basal forebrain; CAA, cerebral amyloid angiopathy; CSF, cerebrospinal fluid; GFAP, glial fibrillary acidic protein; DABNI, Down Alzheimer Barcelona Neuroimaging Initiative; DAVIS: domiciliary Alzheimer visiting in Down syndrome; DS, Down syndrome; DSAD, Down syndrome Alzheimer's disease; FCSD, Fundació Catalana Síndrome de Down; HSP, Hospital de Sant Pau; HFO, hight frequency oscillations; ID, intellectual disability; NGF, nerve growth factor; NfL, neurofilament light polypeptide; NPTX2, CPAP, continuous positive airway pressure; neuronal pentraxin 2; OSA, obstructive sleep apnea; PET, positron emission tomography; REM, rapid eye movement; SAD, sporadic Alzheimer's disease; TRC-DS, Trial Ready Cohort – Down syndrome; WMH, white matter hyperintensities.

At the same time, the approach to diagnosing AD in DS has undergone a dramatic evolution in the past 15 years. Historically, diagnostic criteria commonly used in the general population were not directly applicable to individuals with DS due to the challenges posed by ID. This required reliance on intra-individual changes rather than population-based norms in neuropsychological evaluations, which, while useful, limited the ability to make timely and accurate diagnoses. The work in DABNI is leading to the recognition that neuropsychological assessments can be very useful in diagnosing AD in DS, providing valuable insights into early cognitive decline and supporting more timely and accurate diagnoses. Additionally, the lack of accessible biomarkers further complicated the identification of prodromal AD and AD dementia in this population. Our work in DABNI and other international groups has transformed this landscape. Biomarkers, which have revolutionized the diagnosis of AD in the general population, are now increasingly applied to individuals with DS.[10,125] These tools are particularly valuable in DS given the challenges of clinical diagnosis due to the overshadowing of ID. DABNI and other cohorts have focused on AD biomarkers in DS, leading to its integration into routine clinical practice.[7,10,13,73,126] The integration of biomarkers and neuropsychological assessments has improved clinical care and enabled earlier, more accurate diagnoses, which are critical for timely interventions and improving quality of life for individuals with DS.

The DABNI cohort has led the characterization of the natural history of AD in DS,[7] revealing a predictable progression of biomarkers similar to that observed in ADAD. This work has been key in reconceptualizing DS as a genetically determined form of AD in both the Alzheimer´s Association and the International Working Group criteria[55] and has demonstrated the feasibility of biomarker research in DS, paving the way for ongoing and future clinical trials. Like sporadic AD and ADAD, individuals with DS exhibit a long preclinical phase in which biomarkers follow a predictable sequence of changes over two decades before a clinical diagnosis of prodromal AD. Further longitudinal studies are essential to deepen our understanding of the natural history of DSAD and the impact of lifestyle and co-occurring conditions that may predispose individuals to either risk or resilience against AD. While the DABNI cohort represents the largest group dedicated to studying the natural history of AD in DS, it is still a relatively new cohort with a relatively short follow-up period. Therefore, the inclusion and continued follow-up of participants in DABNI remain a priority, and over the com-

ing years, this cohort will provide more accurate and comprehensive data.

DS represents the largest population with genetically determined AD, significantly larger than ADAD, offering a unique opportunity to study AD in a genetically homogeneous group. Moreover, adults with DS present particularities in their co-occurring conditions, including a lower prevalence of vascular risk factors such as hypertension and atherosclerosis, which could affect the course of AD. Additionally, there is a wealth of neuropathological data available in the DS population, making DS the most suitable model for studying AD and developing preventive or disease-modifying strategies. The increasing availability of biomarkers in this population not only enhances diagnostic accuracy but also supports early interventions and the development of targeted therapies, highlighting the importance of continuing to gather and analyze biomarkers from large cohorts to advance both research and clinical applications. Historically, individuals with DS have been excluded from clinical trials. To date, few randomized pharmacological clinical trials have been performed in this population. Fortunately, this scenario is changing rapidly with now several ongoing clinical trials for AD in DS, in which DABNI participants are actively enrolling. The results from the Abate, HERO, ALADDIN, and LESS-AD trials hold the promise to delay or prevent this disease in DS.

The recent approval of disease-modifying therapies targeting amyloid-beta for early symptomatic AD in the general population, including Lecanemab[127] and onanemab[128] has created a challenging situation for individuals with DS. Current appropriate-use recommendations advise against the use of these therapies in DS due to safety concerns related to the increased risk of CAA,[129] which is more prevalent in this population. We have actively participated in ongoing discussions and advocate for balancing these safety concerns with the urgent need for effective treatments.[105,121] Increasing participation in clinical trials is essential to address the unique challenges of this population and to reconcile these opposing priorities. Fortunately, the ALADDIN trial will provide critical safety data and help establish optimal treatment protocols for DS. Collaborative efforts are underway to adapt prescribing criteria for amyloid-targeted antibodies in DS.[130]

International collaboration is essential for accelerating progress in AD research in individuals with DS. Harmonizing protocols across research groups is a critical step to ensure consistency and comparability in findings, while expanding the scope of clinical trials from Phase 1 to Phase 4 studies is vital for developing effective therapies and interventions tailored to this population. These coordinated international efforts, combined with increasing funding for DSAD research, offer a promising outlook for the future. DABNI plays an active role in such international consortia aimed at harmonizing data collection and clinical evaluations. However, a key challenge remains the lack of diversity in research populations. Individuals with DS are particularly vulnerable to inequalities, both in healthcare and research, as highlighted by McGlinchey et al.[131] To address this, we and others, including initiatives like the ADDORE project of ABC-DS, are working to increase diversity within the Global North while simultaneously fostering projects in the Global South. In Africa,[109] collaborative efforts with GBHI aim to establish new research networks, and in Latin America, initiatives such as the soon-to-be-launched Buriti project in Brazil are expanding opportunities for inclusive research. These efforts strive to ensure that advances in AD research in DS benefit diverse populations worldwide. The growth of these collaborative initiatives, coupled with the scaling up of clinical trials and the integration of DS into broader AD research, marks a pivotal moment in the field. By fostering global partnerships and addressing inequalities, we are paving the way for improved outcomes and quality of life for individuals with DS, while significantly advancing our understanding of AD in this population.

In conclusion, the DABNI cohort serves as a comprehensive multimodal biomarker platform, integrating clinical, cognitive, neurophysiological, genetic, biochemical, imaging, and neuropathological data. This integrated approach offers a unique opportunity to deepen our understanding of AD in DS and can significantly enhance diagnostic accuracy and prognostic evaluations, ultimately leading to more targeted interventions and improved outcomes for individuals affected by this dual condition.

AFFILIATIONS

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ACKNOWLEDGMENTS

The authors express their sincere gratitude to all study participants, their families, and caregivers in the DABNI cohort for their invaluable support and commitment to this research. We also extend our heartfelt thanks to the administrative staff of the Alzheimer-Down Unit: Alex Ibáñez, Marta Salinas, Tania Martínez, Cristina Pastor, and Ana Santisteban, for their essential contributions. Additionally, we would like to acknowledge the Fundació Catalana Síndrome de Down (https://fcsd.org/) for their ongoing support. Finally, we are deeply grateful for all the collaborative initiatives worldwide, and we make a special mention of the investigators who have contributed to the achievements of the DABNI cohort: Dr. Wisniewski, Dr. Raffi, Dr. Cuello, Dr. Busciglio, Dr. Blessing, Dr. Osorio, Dr. Hassenstab, Dr. Espinosa, Dr. Levin, Dr. Strydom, Dr. Head, Dr. Zaman, Dr. Rebillat, Dr. Schöll, Dr. Tsolaki, Dr. McCarron, Dr. Coppus and Dr. Larsen. This study was also funded by the Instituto de Salud Carlos III (Ministerio de Ciencia, Innovacion y Universidades, Gobierno de España) through the projects INT21/00073, PI20/01473 and PI23/01786 to JF; PI20/00836 to SG; PI18/00335, PI22/00758, ICI23/00032 to MCI; PI18/00435, PI22/00611, INT19/00016, INT23/00048 to DA; PI14/1561, PI20/01330 to AL; PI23/01767 to AL and SS:PI22/00307 to AB; PI21/00791, PI24/00598 to IIG. The Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas CIBERNED Program 1, partly jointly funded by Fondo Europeo de Desarrollo Regional (FEDER), Unión Europea, Una Manera de Hacer Europa. This work was also supported by the National Institutes of Health grants (R01 AG056850, R21 AG056974, R01 AG061566, R01 AG081394, R61AG066543 and 1RF1AG080769-01 to JF. It was also supported by the Alzheimer's Association (AARG-22-973966 to MCI; AACSF-21-850193 to IIG and AARF-22-924456 to UDI), the Global Brain Health Institute (GBHI_ALZ-18-543740 to MCI and GBHI_ALZ-23-971107 to SG), the Jérôme Lejeune Foundation (#1801 Cycle 2020 to SG; #1913 cycle 2019B to MCI; #2326–GRT-2024A to LDHS and PDC-2023-51 to UDI). Fundación Tatiana Pérez de Guzmán el Bueno (IIBSP-DOW-2020-151 to JF and SG, and PCN00180 to AL and SS) and Horizon 2020–Research and Innovation Framework Programme from the European Union (H2020-SC1-BHC-2018-2020 to JF). LVA was supported by Instituto de Salud Carlos III through the Sara Borrell Postdoctoral Fellowship, CD23/00235″. IRB, JA, JEAI and LMB were supported by Instituto de Salud Carlos III through the Río Hortega Fellowship (CM22/00052 to IRB; CM21/00243 to JA; CM22/00219 to JEAI and CM22/00291 to LMB) and co-funded by the European Union. AB acknowledges support from Instituto de Salud Carlos III through the Miguel Servet grant "CP20/00038"" and co-funded by the European Union, and the Alzheimer's Association "AARG-22-923680″ and the" Ajuntament de Barcelona, in collaboration with Fundació La Caixa (23S06157-001). CP was funded by the Sara Borrell Postdoctoral Fellowship (CD20/00133). LDHS is supported by the Miguel Servet program co-funded by the European Union CP24/00112. MRA acknowledges funding from the Alzheimer's Association Research Fellowship to Promote Diversity (AARF-D) Program (AARFD-21-852492).

CONFLICT OF INTEREST STATEMENT

Juan Fortea reported receiving personal fees for service on the advisory boards, adjudication committees or speaker honoraria from AC Immune, Adamed, Alzheon, Biogen, Eisai, Esteve, Fujirebio, Ionis, Laboratorios Carnot, Life Molecular Imaging, Lilly, Lundbeck, Novo Nordisk, Perha, Roche, Zambón and outside the submitted work. Daniel Alcolea, Alberto Lleó, and Juan Fortea reports holding a patent for markers of synaptopathy in neurodegenerative disease (licensed to ADx, EPI8382175.0). Sandra Giménez reported receiving personal fees for service on the advisory boards, speaker honoraria or educational activities from Esteve, Indorsia and Biojen. María Carmona-Iragui reported receiving personal fees for service on the advisory boards, speaker honoraria or educational activities from Esteve, Lilly, Neuraxpharm, Adium, and Roche. JA reported receiving personal fees for service on the speaker honoraria or educational activities from Esteve, Lilly and Roche, outside the submitted work. DA reported receiving personal fees for advisory board services and/or speaker honoraria from Fujirebio-Europe, Roche, Nutricia, Krka Farmacéutica, Lilly, Zambon S. A. U., Grifols, and Esteve, outside the submitted work. AL has served as a consultant or on advisory boards for Almirall, Fujirebio-Europe, Roche, Biogen, Grifols, Novartis, Eisai, Lilly, and Nutricia, outside the submitted work. Valle Camacho reported receiving personal fees for service on the advisory boards, speaker honoraria or educational activities from General Electric, Life Molecular Imaging, Lilly and Novartis. Mateus Rozalem Aranha has provided paid consultancy for Veranex. Mateus Rozalem Aranha is a partner and director of production at Masima—Soluções em Imagens Médicas LTDA. María Carmona-Iragui reported receiving personal fees for service on the advisory boards, speaker honoraria or educational activities from Esteve, Lilly, Neuraxpharm, Adium and Roche. Isabel Barroeta reported receiving personal fees for speaker honoraria from Adium. No other competing interests were reported. Author disclosures are available in the supporting information.

ETHICS STATEMENT

All human subjects provided informed consent.

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SUPPORTING INFORMATION

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

How to cite this article: Videla L, Benejam B, Barroeta I, et al. The Down Alzheimer Barcelona Neuroimaging Initiative (DABNI) and its contributions to understanding Alzheimer's disease in Down syndrome: A decade of discovery. *Alzheimer's Dement*. 2025;21:e70259. https://doi.org/10.1002/alz.70259