Received: 3 May 2023 | Revised: 8 September 2023 | Accepted: 19 September 2023

DOI: 10.1002/alz.13506

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

RESEARCH ARTICLE

Alzheimer's polygenic risk scores are associated with cognitive phenotypes in Down syndrome

Priyanka Gorijala[1,2] | M. Muaaz Aslam[3] | Lam-Ha T. Dang[4,5] | L. Xicota[5] | Maria V. Fernandez[1,2] | Yun Ju Sung[1,2,6] | Kang-Hsien Fan[3] | Eleanor Feingold[3] | Ezequiel I. Surace[7] | Jasmeer P Chhatwal[8] | Christy L. Hom[9] | Dominantly Inherited Alzheimer Network (DIAN), the Alzheimer's Disease Neuroimaging Initiative (ADNI)[a] | the NIA-LOAD family study, for the Alzheimer's Biomarkers Consortium–Down Syndrome (ABC-DS) Investigators | Sigan L. Hartley[10] | Jason Hassenstab[11] | Richard J. Perrin[12,13,14] | Mark Mapstone[15] | Shahid H Zaman[16,17] | Beau M Ances[14] | M. Ilyas Kamboh[3] | Joseph H Lee[4,5] | Carlos Cruchaga[1,2,12]

[1]Department of Psychiatry, Washington University School of Medicine, St. Louis, Missouri, USA

[2]Neurogenomics and Informatics Center, Washington University School of Medicine, St. Louis, Missouri, USA

[3]Department of Human Genetics, University of Pittsburgh, School of Public Health, Pittsburgh, Pennsylvania, USA

[4]Department of Epidemiology, Columbia University Irving Medical Center, New York, New York, USA

[5]Sergievsky Center, Taub Institute for Research on Alzheimer's Disease and the Aging Brain, and Department of Neurology, Columbia University Irving Medical Center, New York, New York, USA

[6]Division of Biostatistics, Washington University School of Medicine, St. Louis, Missouri, USA

[7]Laboratory of Neurodegenerative Diseases - Institute of Neurosciences (INEU-Fleni- CONICET), Buenos Aires, Argentina

[8]Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA

[9]Dept. of Psychiatry and Human Behavior, University of California, Irvine School of Medicine, California, USA

[10]Waisman Center and School of Human Ecology, University of Wisconsin- Madison, Madison, Wisconsin, USA

[11]Department of Neurology and Psychological & Brain Sciences, Washington University, St. Louis, Missouri, USA

[12]Hope Center for Neurologic Diseases, Washington University, St. Louis, Missouri, USA

[13]Department of Pathology and Immunology, Washington University School of Medicine, St. Louis, Missouri, USA

[14]Department of Neurology, Washington University School of Medicine, St. Louis, Missouri, USA

[15]Department of Neurology, University of California-Irvine, Irvine, California, USA

[16]Cambridge Intellectual and Developmental Disabilities Research Group, Department of Psychiatry, University of Cambridge, Douglas House, Cambridge, UK

[17]Cambridgeshire and Peterborough NHS Foundation Trust, Elizabeth House, Fulbourn Hospital, Fulbourn, Cambridge, UK

Funding information: NeuroGenomics and Informatics Center; Washington University School of Medicine; National Institutes of Health, Grant/Award Numbers: U01 AG024904, P01AG003991, RF1AG053303, RF1AG058501, U01AG058922, RF1AG074007, R01AG064877; Chan Zuckerberg Initiative; Michael J. Fox Foundation, Grant/Award Number: LI-W81XWH2010849; Alzheimer's Association Zenith, Grant/Award Number: ZEN-22-848604; Washington University; JCM, Grant/Award Number: P01AG03991; Dominantly Inherited Alzheimer Network, Grant/Award Number: U19AG032438; National Institute on Aging; Alzheimer's Association, Grant/Award Number: SG-20-690363-DIAN; German Center for Neurodegenerative Diseases; FLENI; Japan Agency for Medical Research and Development; KHIDI; ADNI, Grant/Award Numbers: U01 AG024904, W81XWH-12-2-0012; National Institute of Biomedical Imaging and Bioengineering; National Institute for Child Health and Human Development, Grant/Award Numbers: U01 AG051406, U01 AG051412, U19 AG068054; The Alzheimer's Disease Research Centers, Grant/Award Numbers: P50 AG008702, P30 AG062421, P50 AG16537, P50 AG005133, P50 AG005681, P30 AG062715, P30 AG066519; Eunice Kennedy Shriver Intellectual and Developmental Disabilities Research Centers, Grant/Award Numbers: U54 HD090256, U54 HD087011, P50 HD105353; National Center for Advancing Translational Sciences, Grant/Award Numbers: UL1 TR001873, UL1 TR002373, UL1 TR001414, UL1 TR001857, UL1 TR002345; Alzheimer's Disease and Related Dementias, Grant/Award Number: U24 AG21886; NICHD

Correspondence
Carlos Cruchaga, PhD, Department of Psychiatry, Washington University School of Medicine, St. Louis, Missouri, USA.
Email: cruchagac@wustl.edu

[a]A part of the data used in the preparation of this article was obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in the analysis or writing of this report. A complete listing of ADNI investigators can be found at: https://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

Abstract

INTRODUCTION: This study aimed to investigate the influence of the overall Alzheimer's disease (AD) genetic architecture on Down syndrome (DS) status, cognitive measures, and cerebrospinal fluid (CSF) biomarkers.

METHODS: AD polygenic risk scores (PRS) were tested for association with DS-related traits.

RESULTS: The AD risk PRS was associated with disease status in several cohorts of sporadic late- and early-onset and familial late-onset AD, but not in familial early-onset AD or DS. On the other hand, lower DS Mental Status Examination memory scores were associated with higher PRS, independent of intellectual disability and *APOE* (PRS including *APOE*, PRS_{APOE}, $p = 2.84 \times 10^{-4}$; PRS excluding *APOE*, $PRS_{nonAPOE}$, $p = 1.60 \times 10^{-2}$). PRS_{APOE} exhibited significant associations with Aβ42, tTau, pTau, and Aβ42/40 ratio in DS.

DISCUSSION: These data indicate that the AD genetic architecture influences cognitive and CSF phenotypes in DS adults, supporting common pathways that influence memory decline in both traits.

KEYWORDS
apoliprotein E *APOE*, amyloid precursor protein, area under the curve, cerebrospinal fluid biomarkers, cognitive batteries, Dominantly Inherited Alzheimer Network, Down syndrome, early-onset Alzheimer's disease, early-onset autosomal dominant, genetic architecture, genetic risk factor, late-onset Alzheimer's disease, polygenic risk score, *PSEN1*, *PSEN2*, sporadic late-onset Alzheimer's disease

Highlights

- Examination of the polygenic risk of AD in DS presented here is the first of its kind.
- AD PRS influences memory aspects in DS individuals, independently of *APOE genotype*.
- These results point to an overlap between the genes and pathways that leads to AD and those that influence dementia and memory decline in the DS population.
- APOE ε4 is linked to DS cognitive decline, expanding cognitive insights in adults.

1 | BACKGROUND

Down syndrome (DS), caused by the triplication of chromosome 21, is almost invariably complicated by Alzheimer's disease (AD)-like dementia.[1] Overexpression of the amyloid precursor protein (*APP*) gene, which resides on chromosome 21, leads to amyloid beta (Aβ) plaque formation,[2–4] triggering a pathophysiological cascade that includes tau hyperphosphorylation, neurofibrillary tangle formation, neuroinflammation, oxidative stress, and synaptic and neuronal loss; if sufficiently severe, this process causes dementia.[5,6] The density of hyper-phosphorylated tau in neurofibrillary tangles triples between 40 and 50 years of age in DS, in synchrony with dementia onset.[7] Indeed, about 30% of people with DS who are in their fifth decade of life have Alzheimer's dementia, and about 50% of people in their sixth decade develop dementia, indicating that age is a strong independent risk factor in the prevalence of dementia in DS. However, people with DS exhibit a wide range of age at onset (AAO) of dementia (< 40 to > 70 years),[8–10] and dementia prevalence does not reach 100% by 70 years of age, even among those with verified full trisomy of chromosome 21, suggesting that other genetic factors may influence AD penetrance and progression. Multiple studies suggest that the *apolipoprotein E* (*APOE*)*ε4* allele[11] also contributes to AD risk in DS, at least in part by increasing Aβ deposition.[11–13] However, the genetic contributions to AD dementia in DS remains unclear. Understanding the as yet unknown genetic contributions will be critical for the development of models that can predict the risk of dementia and for designing effective treatment strategies for people with DS.[9,10]

Several cognitive and functional measures to evaluate orientation, memory, language/communication, executive function, praxis, and instrumental activities of daily living have been developed

specifically for DS. These include the National Task Group—Early Detection Screen for Dementia (NTG-EDSD; http://www.the-ntg.org/ntg-edsd),[14,15] the Dementia questionnaire for people with learning disabilities (DLD),[16] and the Down Syndrome Mental Status Examination (DSMSE).[17]

No study has used genome-wide approaches to understand the relative burden of AD risk variants in adults with DS. Polygenic risk scores (PRSs) can be used to understand the overlap of genetic architecture between complex traits by studying the pleiotropic effects of markers associated with one trait on another trait. In recent years, this approach has been used to study the genetic contributions of congenital heart disease risk in infants with DS.[18] In our previous study, we used PRS to determine the genetic overlap between different forms of AD such as early and late onset in sporadic and familial presentations. We observed an association of AD PRS with late-onset AD (LOAD) risk in sporadic early-onset AD (sEOAD), sporadic late-onset AD (sLOAD), and familial late-onset AD (fLOAD), but not with familial early-onset AD (fEOAD) cases. However, in fEOAD, AD risk PRS is associated with the cerebrospinal fluid (CSF) ptau181-Aβ42 ratio, indicating genetic risk factors might modulate biological aspects of AD.[19]

This provides the basis for our current study, which explores the contribution of AD risk variants in AD/dementia in adults with DS. To achieve this, we calculated AD risk PRS based on the latest meta-analysis of AD risk summary statistics[20] in several cohorts of AD and DS and tested its association with status, cognitive measures, and CSF phenotypes in a large DS cohort (Figure 1).

RESEARCH IN CONTEXT

1. **Systematic review**: Down syndrome (DS) is caused by chromosome 21 triplication. DS often presents Alzheimer's disease (AD)-like dementia later in life. More than 74 loci are associated with AD risk. However, no previous studies analyzed whether genetic AD risks were associated with memory and cognitive phenotypes in DS.
2. **Interpretation**: AD risk polygenic risk scores (PRSs) were associated with memory and cognitive phenotypes, as well as cerebrospinal fluid (CSF) biomarkers, beyond *APOE ε4*, indicating a shared biology in memory decline and dementia between AD and DS.
3. **Future directions**: Our study suggests research prospects in identifying genetic contributors to cognitive decline and dementia risk in DS. We recommend conducting more extensive studies to validate our findings and exploring approaches to incorporating chromosome 21 genes into PRS analysis.

2 | METHODS

2.1 | Samples

Participants included individuals from the Alzheimer Biomarkers Consortium – Down Syndrome (ABC–DS),[21] the Charles F. and Joanne Knight Alzheimer's Disease Research Center at Washington University (Knight-ADRC),[22] the National Institute on Aging Genetics Initiative for Late-Onset Alzheimer's Disease (NIA-LOAD),[23] the Alzheimer's Disease Neuroimaging Initiative (ADNI),[24] and the Dominantly Inherited Alzheimer Network Observational Study (DIAN-Obs).[25] Only unrelated participants that clustered with the non-Hispanic white population based on genetic principal component factors were included.

2.1.1 | Description of cohorts

Alzheimer's disease in Down syndrome (DS-AD): All participants with DS were part of the ABC-DS study, a multidisciplinary and multisite longitudinal study with the goal of identifying biomarkers associated with AD in adults with DS.[26] The inclusion criteria for the participants were age ≥ 35 years with mental age ≥ 30 months and with karyotyping information to confirm either full trisomy, partial trisomy, mosaic, or translocations. We included all the participants enrolled in the study as of April 30, 2022, as a part of the ABC-DS study. We examined 307 individuals where karyotyping confirmed full trisomy of chromosome 21. On average, participants were 45 years old at their baseline visit. The cohort was composed of 47.8% females and 23.13% *APOE ε4* carriers (Table 1, Figure S1). Dementia diagnosis at baseline was confirmed for 37 participants (12%; Table S1).

Familial early-onset AD (fEOAD): Clinical and genetic data were obtained from the Dominantly Inherited Alzheimer Network Observational Study (DIAN-Obs). DIAN-Obs utilizes a family-based long-term cohort study design to investigate autosomal-dominant Alzheimer's Disease (ADAD). Tissues collected (blood, CSF) were analyzed to detect changes in carriers of mutations causal to ADAD. The samples and data utilized in this study are from the 15th data freeze (DF15). For more information about DIAN-Obs, visit dian.wustl.edu. We included 196 unrelated mutation carriers from the DIAN-Obs study. They were defined as participants with mutations in the *Presenilin1*, *Presenilin2*, or *APP* genes.[27–30] The cohort had a mean AAO of 43 years, which is comparable to DS, and included 52% females and 26% *APOE ε4* carriers.

Familial late-onset AD (fLOAD): 1,413 fLOAD subjects were selected from the NIA-LOAD study. Individuals with definitive or probable LOAD with an AAO > 65 years in addition to a familial history of AD were included under the fLOAD cohort. One unrelated individual, based on genetic identity by descent (IBD), per family, was selected for inclusion in the study sample. The mean AAO of the group was 75 years, with 63% females and with highest percentage of *APOE ε4* carriers compared to other cohorts (70%).

Sporadic early-onset AD (sEOAD): We selected 395 unrelated participants from Knight ADRC and ADNI, including 49% females and 58% *APOE ε4* carriers. Those selected had received an AD diagnosis, exhibited an AAO < 65 years, and had no familial history of AD. The mean AAO of the group was 59 years old.

TABLE 1 Demographics of cohorts.

Cohort	*N*	Female (%)	Mean Age (SD)[a]	*APOE ε4+* (%)[b]	*APOE ε2* (%)[b]
Sporadic late onset AD (sLOAD)	2259	50.02	76.11 (6.81)	53.83	8.01
Familial late onset AD (fLOAD)	1413	63.13	75.33 (6.37)	69.99	5.94
Sporadic early onset AD (sEOAD)	395	49.87	59.59 (4.43)	58.48	7.08
Familial early-onset AD (fEOAD)	196	52.55	43.53 (7.95)	26.02	14.79
Down syndrome	307	47.88	45.25 (9.88)	23.13	14.98
Controls	2890	57.87	73.60 (11.78)	26.36	14.56

Abbreviations: APOE, apolipoprotein E; *N*, sample size; SD, standard deviation.
[a]Age at onset for cases and age at last assessment for controls.
[b]Percentage of participants, carriers of APOE ε4 and ε2 alleles.

Sporadic late-onset AD (sLOAD): We selected 2259 Knight ADRC and ADNI participants with an AD diagnosis, an AAO > 65 years, and no familial history of AD. The mean AAO of the group was 76 years, similar to that of the fLOAD group. Included were 50% females and 53% *APOE ε4* carriers.

Controls: Controls were all determined to be unaffected after neurological assessments. The age of all the controls ($n = 2890$) ranged from 20 to 90, with a mean of 74 years (Table 1 and Figure S1).

2.2 | Genetic data

The DS cohort was genotyped using the Illumina Infinium General Screening Array (GSA) versions 2 and 3 at the Center for Applied Genomics at the Childrens Hospital of Pennsylvania. Imputation was performed on all autosomes, excluding chromosome 21, using the TOPMed Imputation Server[31] employing the TOPMed reference panel. Variant imputation quality scores of Rsq > 0.30 were included in the analysis. As traditional tools cannot be applied for the imputation of trisomic variants, we excluded that region from the analysis. All the imputed variants were mapped to the GRCh38 assembly.

For the fLOAD cohort, which is a part of the NIA-LOAD study, genotyping was performed as described by Lee, 2008.[32] fEOAD, sEOAD, and sLOAD participants, derived from the DIAN-Obs, ADNI, and Knight ADRC studies, were genotyped using several Illumina arrays. Imputation was performed using the same pipeline as for the DS samples, for each array independently and merged after imputation.

We applied stringent quality control measures to each array separately before merging. To summarize, single nucleotide polymorphisms (SNPs) and individuals were filtered for a call rate of ≥98%, and autosomal SNPs not in the Hardy–Weinberg equilibrium ($P_{HWE} < 10^{-6}$) were filtered out. We split chromosome X to represent the X chromosome's pseudo-autosomal region as a separate "XY" chromosome and pruned SNPs to perform the sex check. Samples with discordance between phenotypic and genotypic sex were removed from the analysis after this check. We also identified duplicates and familial relatedness by having IBD estimates and selected only unrelated samples (IBD < 0.25) for further analysis. In the case of related subjects, we prioritized cases over controls and selected samples with high genotyping call rates when there were duplicates in cases. It is important to note that, for this study, only participants of European ancestry were included. The decision to focus on participants of European ancestry was made to minimize potential population stratification effects and to ensure homogeneity within the study cohort (Figure S2). We performed all quality control procedures using Plink1.9/Plink2 (http://www.cog-genomics.org/plink2).

2.3 | Polygenic risk score calculation

We utilized PRSiceV2.3[33] to calculate the AD risk PRS. The latest publicly available summary statistics from the AD case-control Genome-Wide Associaiton studies (GWAS; $N = 111{,}326$ cases and 677,663 controls) were used as a base dataset.[20] All the AD and DS cohorts along with controls will be used as a target dataset. The polygenic risk was calculated as an additive effect of the risk alleles weighted by their effect sizes of the corresponding AD GWAS. We applied the standard clumping and thresholding approach to remove the variants in linkage disequilibrium (LD) with each other and retained the ones that were strongly associated with AD risk. We calculated PRS for the genome-wide threshold (5×10^{-8}) on the LD clumped SNPs after excluding the variants on chromosome 21. The thresholding approach allows only those variants with genome-wide significance ($p < 5 \times 10^{-8}$) to be included in the PRS calculation, and all variants 250 kb upstream and downstream of the top signal with $r2 < 0.1$ were removed. Finally, we standardized the risk scores to the mean of the population. The first set of PRS included the *APOE* region (PRS_{APOE}). As *APOE* has a strong effect on AD, we calculated the PRS by excluding the *APOE* region ($PRS_{nonAPOE}$; chromosome 19, coordinates GRCh38: 43907927 to 45908810) to identify associations not driven by *APOE*.

The PRS calculation is as follows:

$$PRS_j = \sum i\,(S_i \times G_{ij}) - Mean\,(PRS)\,/SD\,(PRS)$$

where S is the summary statistic (effect size) of the *i*th effect allele, and G is the number of effect alleles observed for jth individual

2.4 | Analyte measurement

CSF Aβ40, Aβ42, tTau, pTau, and neurofilament light (NFL) biomarkers of amyloid, neuronal injury, neurofibrillary tangles, and axonal injury respectively were measured in the DS cohort following a standard protocol: CSF was collected by lumbar puncture between 11:00 am and 4:00 pm after overnight fasting. Upon collection, samples were frozen on dry ice and sent to the Fluid Biomarker Core lab at Washington University in St. Louis (WUSTL).[26] Frozen samples were thawed, distributed in polypropylene tubes, and stored at −80°C. We further obtained CSF biomarker data for Aβ42, tTau, and pTau from the cohorts of the ADNI, DIAN, and Knight ADRC studies that included participants for the sLOAD, sEOAD, fEOAD, and control groups (Table S2).

Different platforms were employed for biomarker measurements within each study. Aβ40 levels were measured using the Lumipulse platform in Knight ADRC. In the DIAN and Knight ADRC studies, Aβ42, tTau, and pTau were measured with Lumipulse, while ADNI used the xMAP platform for these biomarkers. NFL levels were measured using the SomaLogic platform in all the studies (Table S2). To ensure comparability among the different cohorts and avoid introducing batch effects, we harmonized the CSF values across cohorts as reported previously.[27–30,34,35] Briefly, duplicate samples and those with missing biomarker levels were removed. Raw protein values were log-transformed, and outliers were identified using the interquartile range (IQR) approach and subsequently removed. Then Z-scores were calculated for each cohort and biomarker, ensuring the robustness and precision of the combined data (Figure S3).

2.5 | Cognitive and behavioral measures

Along with CSF biomarkers, we also analyzed the available cognitive and behavioral scores used for the assessment of AD-related cognitive impairments only in DS participants,[36] including NTG-EDSD memory score, DLD cognitive score, DSMSE memory score, and DSMSE total score. Descriptive statistics for each phenotype stratified by their diagnosis and intellectual disability (ID) status were presented in Table S3.

The NTG-EDSD is a caregiver screening of AD; the assessment includes 51 items distributed into six cognitive/functional domains, such as changes in daily living activities (seven items), language and communication (six items), sleep and wake cycles (eight items), ambulation (four items), cognition-related aspects (nine items), and behavior aspects (17 items).[36] Items are rated on a 4-point scale rating: (1) does not apply, (2) new symptom, (3) always but worse, and (4) always been the case. For the analysis, we binarized the scores of each item following the Dementia Screening Questionnaire for Individuals with Intellectual Disabilities (DSQIID) scoring.[16] Responses 1 and 4 were treated as "0" as they indicate the absence of dementia, and responses 2 and 3 as "1" as they indicate the presence of dementia or related concerns. Summing up all the items in each domain gives a single NTG-EDSD score, and we focused on the memory/cognition domain for this analysis. The higher the NTG-EDSD score, the greater the cognitive and behavioral changes from baseline (Table S3).

The DLD is a caregiver-reported screening assessment of dementia symptoms that consists of 50 items divided into two broad domains: cognition and social behavior. Memory-related abilities such as long-term and short-term memory and spatial orientation are summarized by the DLD-cognitive score (DLD-CS); behavior-related items such as mood, activity, behavioral disturbance, speech, and practical skills are summarized by the DLD-social score (DLS-SS).[37] We focused on cognitive scores for this study. Higher DLD scores indicate a higher degree of behavioral impairment, and the scores range from 0 to 42 depending on the ID severity (Table S3).

The DSMSE is a directly administered measure of orientation, memory, language, apraxia, and visuospatial skills developed for adults with DS. The test yields several scores, including memory (DSMSE-M) and non-memory (DSMSE-NM), with a maximum score of 24 and 79, respectively. The sum of both scores yields a DSMSE-Total score (DSMSE-T).[17] We used the DSMSE memory and the total scores for this analysis to test their association with AD risk PRS. In contrast to the NTG-EDSD and DLD, the lesser the DSMSE score, the greater the cognitive impairment (Table S3).

2.6 | Statistical analysis

We tested the association of AD risk PRS with case-control status as well as DS-related phenotypes. As *APOE* is the most significant locus on AD risk GWAS, two different models were run: PRS calculated by including (PRS_{APOE}) and excluding ($PRS_{nonAPOE}$) the *APOE* locus.

To test the association of AD risk PRS with disease status (AD or DS vs controls) we performed logistic regression correcting for sex. Age was not included as a covariate as the DS and fEOAD were significantly younger than the controls, which would lead to collinearity (Tables 1 and S1). We also performed logistic regression analysis by comparing the first versus the last tertile of the PRS to calculate the odds ratio (OR) for the effect of PRS on case-control status for each cohort.

Association of AD risk PRS with CSF biomarkers and cognitive scores was performed using regression models corrected for age on the test and sex. For the association with the cognitive scores, additional sensitivity analyses were performed where we included ID severity to the model as covariate, to confirm the analyses were not confounded by the baseline intellectual severity of the participants.

Receiver operating characteristic (ROC) analysis was performed to determine whether AD risk PRS could predict status in the different cohorts. ROC and area under the curve (AUC) analyses were run for each cohort using the R package pROC version 1.8. AUCs obtained for each cohort were compared using the "roc.test" function employing the Venkatraman method.[38]

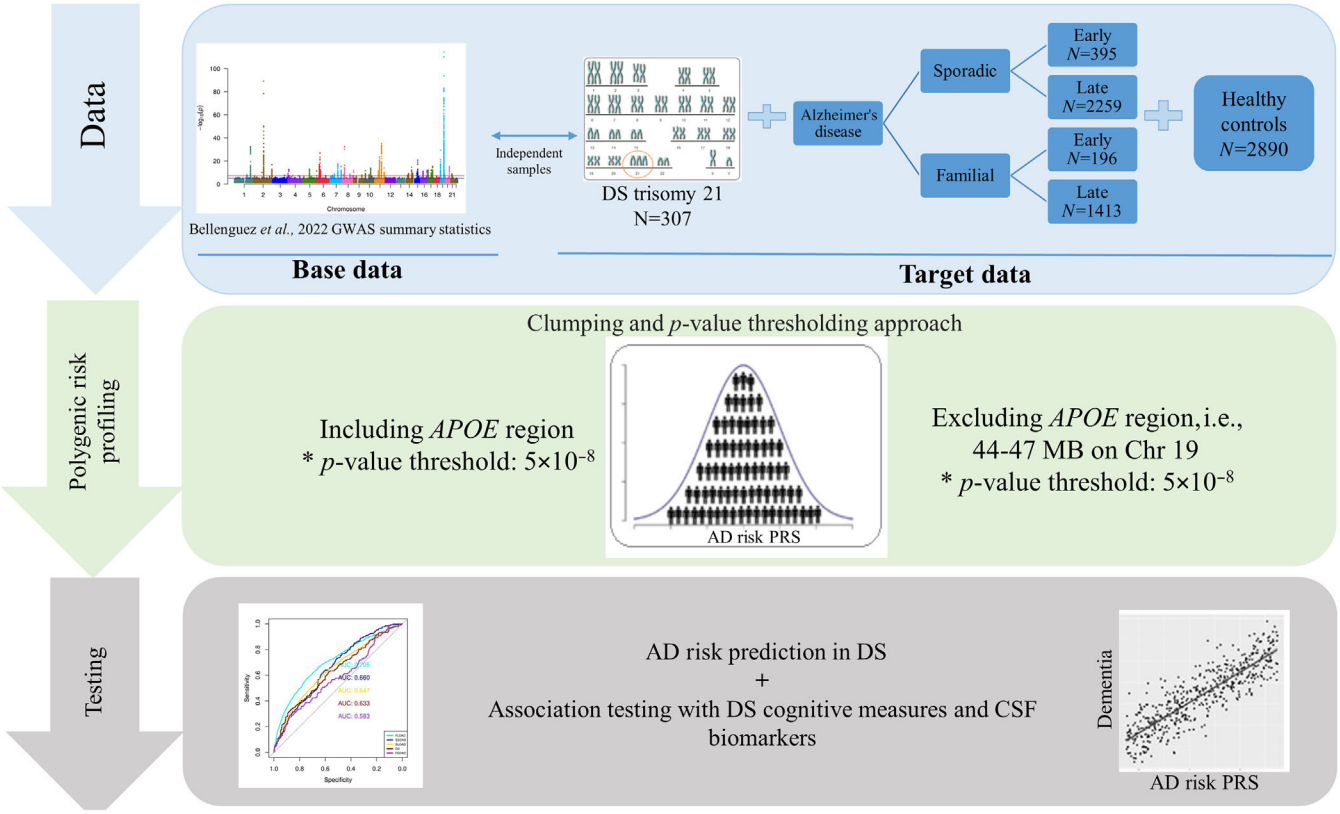

FIGURE 1 Schematic overview of study design.

3 | RESULTS

3.1 | Association of AD risk PRS with Down syndrome

We analyzed the overlap of the genetic architecture of sEOAD, sLOAD, fEOAD, fLOAD, and DS (Figure 1 and Figure S4) by determining whether the AD risk PRS was associated with status in each of those groups.

In the sLOAD cohort, the $PRS_{nonAPOE}$ was significantly associated with the clinical status ($PRS_{nonAPOE}$: OR = 1.67, $p = 1.28 \times 10^{-13}$, Table 2). The strength of the association was significantly higher when *APOE* was included in the PRS (sLOAD, PRS_{APOE}: OR = 3.06, $p = 3.28 \times 10^{-55}$; Table 2). This model led to an AUC of PRS_{APOE}: 0.643 (95% CI = 0.62–0.65, Figure 2), which increased to 0.655 when age and sex were included in the model (Figure S5 and S6), consistent with previous reports.[39]

Similar to sLOAD, PRS was also significantly associated with clinical status in the fLOAD cohort ($PRS_{nonAPOE}$: OR = 2.31, $p = 1.50 \times 10^{-24}$, PRS_{APOE}: OR = 4.74, $p = 5.20 \times 10^{-73}$; Table 2). The OR of fLOAD PRS_{APOE} was higher than that observed for sLOAD (OR_{sLOAD} = 3.06 vs OR_{fLOAD} = 4.74, $P = 3.75 \times 10^{-51}$) and the AUC for fLOAD = 0.70 (95% CI = 0.68–0.71, Figure 2) was significantly higher than that for sLOAD ($p = 2.2 \times 10^{-16}$; Venkatraman's test).

The OR of the sEOAD cohort with $PRS_{nonAPOE}$ was higher than those of all other cohorts ($PRS_{nonAPOE}$: OR = 2.56, $p = 2.59 \times 10^{-7}$, Table 2), and the OR increased further when *APOE* was included in the PRS (PRS_{APOE}: OR = 4.52 $p = 5.89 \times 10^{-23}$; Table 2). However, though the OR from the model with PRS_{APOE} for sEOAD was significantly higher than that of sLOAD, it was not higher than that of the fLOAD cohort (OR_{sLOAD} = 3.06, OR_{sEOAD} = 4.52, $P = 5.65 \times 10^{-18}$; OR_{fLOAD} = 4.74, OR_{sEOAD} = 4.52, $p = 0.21$). Consistent with these results, ROC analyses showed better performance in the case of sEOAD (PRS_{APOE}: AUC = 0.694 (95% CI = 0.66–0.72; Figure 2) compared to sLOAD (AUC = 0.64, Venkatraman's test $p = 2.00 \times 10^{-3}$; Figure 2).

In the fEOAD cohort that included carriers of the *APP*, *PSEN1*, or *PSEN2* gene mutations, our findings did not show any association of either $PRS_{nonAPOE}$ or PRS_{APOE} with clinical status. ($PRS_{nonAPOE}$: OR = 0.61 $p = 9.47 \times 10^{-1}$; PRS_{APOE}: OR = 1.05, $p = 7.89 \times 10^{-1}$; Table 2). These findings are in line with our previous studies.[19]

For DS, we observed that the $PRS_{nonAPOE}$ was not associated with clinical status in DS ($PRS_{nonAPOE}$: OR = 0.77, $p = 8.94 \times 10^{-2}$, Table 2). However, the effect becomes significant with the PRS_{APOE} with an OR of 0.64 (PRS_{APOE}: $p = 3.27 \times 10^{-3}$, Table 2). This association was driven by *APOE ε4*, as individuals with DS have a lower percentage of *APOE ε4* carries (23.13%; Tables 1 and S4) than controls (26.36%; Table 1) or even fEOAD (26.02%). These analyses included all controls, independent of age. However, older controls (age > 65) are less likely to include presymptomatic individuals, the *APOE ε4* frequency in older controls (23.63%) is similar and not significantly different to those of DS, suggesting that the association of PRS_{APOE} in DS driven by including presymptomatic individuals and not because the DS is depleted of

TABLE 2 Alzheimer's disease PRS association with AD and DS.

	Model 1 ($PRS_{nonAPOE}$)			Model 2 (PRS_{APOE})		
Cohort	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***
DS	0.77	[0.57, 1.03]	8.94×10^{-2}	0.64	[0.48, 0.86]	$\mathbf{3.27 \times 10^{-3}}$
Familial early-onset AD (fEOAD)	0.61	[0.42, 0.88]	9.47×10^{-1}	1.05	[0.73, 1.51]	7.89×10^{-1}
Sporadic early-onset AD (sEOAD)	2.56	[1.95, 3.39]	$\mathbf{2.59 \times 10^{-7}}$	4.52	[3.37, 6.15]	$\mathbf{5.89 \times 10^{-23}}$
Familial late-onset AD (fLOAD)	2.31	[1.97, 2.72]	$\mathbf{1.50 \times 10^{-24}}$	4.74	[4.01, 5.63]	$\mathbf{5.20 \times 10^{-73}}$
Sporadic late-onset AD (sLOAD)	1.67	[1.46, 1.91]	$\mathbf{1.28 \times 10^{-13}}$	3.06	[2.66, 3.52]	$\mathbf{3.28 \times 10^{-55}}$

Notes: Logistic regression results for extreme tertiles of the PRS derived for each cohort and compared to non-demented (control) participants. Both models correct for sex. Model 1 includes PRS calculated by excluding *APOE* loci. Model 2 consists of PRS calculated by including *APOE* loci. These results are the product of analyzing the tertiles with the lowest and highest PRS.

Numbers in bold denote significant associations.

Abbreviations: AD, Alzheimer's disease; *APOE*, apolipoprotein E; CI, confidence interval; DS, Down syndrome; OR, odds ratio; *P*, *p* value; PRS, polygenic risk score.

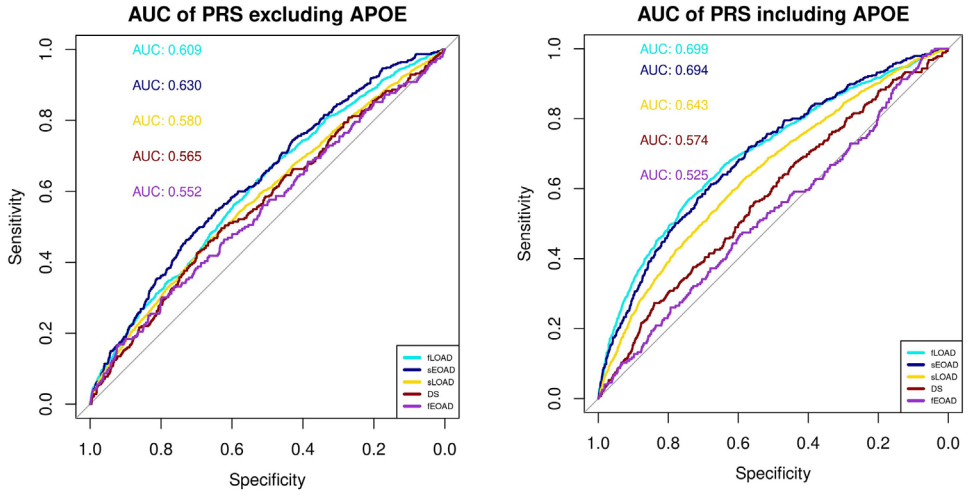

FIGURE 2 Receiver operating characteristic curves for the different cohorts predicting the disease status. The lines correspond to the accuracy obtained for the models. (A) Model including $PRS_{nonAPOE}$ corrected for sex. (B) Model including PRS_{APOE} corrected for sex. fLOAD, familial late-onset Alzheimer's disease; sEOAD, sporadic early-onset Alzheimer's disease; sLOAD, sporadic late-onset Alzheimer's disease; DS, Down syndrome; fEOAD, familial early-onset Alzheimer's disease; AUC, area under the curve.

APOE ε4 alleles. Consistent with these results, ROC analyses showed an AUC of 0.565, which is not statistically significant ($p = 6.18 \times 10^{-2}$) for $PRS_{nonAPOE}$ and a slightly higher AUC of 0.574 with a significant *p* value of 2.00×10^{-2} for the PRS_{APOE}.

The OR of the PRS_{APOE} for the DS was significantly lower than the OR calculated for the sEOAD, sLOAD, and fLOAD ($OR_{DS} = 0.62$ vs $OR_{sEOAD} = 4.52$, $p = 8.46 \times 10^{-73}$; $OR_{DS} = 0.62$ vs $OR_{sLOAD} = 3.06$, $p = 2.01 \times 10^{-47}$; $OR_{DS} = 0.62$ vs $OR_{fLOAD} = 4.74$; $p = 3.24 \times 10^{-122}$). ROC analysis for the PRS_{APOE} revealed weaker performance for the DS cohort with an AUC of 0.57 (95% CI = 0.53–0.60; Figure 2) compared with the sEOAD, sLOAD, and fLOAD ($sEOAD_{AUC} = 0.694$, $p < 2.2 \times 10^{-16}$; $sLOAD_{AUC} = 0.643$, $p = 1.00 \times 10^{-3}$; $fLOAD_{AUC} = 0.699$, $p < 2.2 \times 10^{-16}$; Figure 2). No significant difference was observed between DS and fEOAD cohorts ($fEOAD_{AUC} = 0.525$, Venkatraman's test $p = 6.5 \times 10^{-2}$). The inclusion of *APOE* in the PRS does not significantly affect the predictive accuracy of the disease risk for DS and fEOAD cohorts.

3.2 | AD risk PRS shows a significant association with cognitive, and biochemical biomarkers in DS

We further explored whether the AD risk PRS was associated with cognition and behavioral functioning in DS by evaluating its association with DSMSE, NTG-EDSD, and DLD scores, which were available from the ABC-DS study (Table S3). The AD risk PRSs were negatively associated with DSMSE ($PRS_{nonAPOE}$: $\beta = -0.59$, $p = 1.35 \times 10^{-2}$; PRS_{APOE}: $\beta = -0.91$, $p = 9.01 \times 10^{-5}$; Table 3), independent of *APOE ε4*. NTG-EDSD memory score ($PRS_{nonAPOE}$: $\beta = 0.39$, $p = 6.48 \times 10^{-2}$; PRS_{APOE}: $\beta = 0.63$, $p = 8.28 \times 10^{-3}$; Table 3), DLD cognitive score ($PRS_{nonAPOE}$: $\beta = 2.28$, $p = 5.03 \times 10^{-2}$; PRS_{APOE}: $\beta = 3.22$, $p = 2.67 \times 10^{-3}$), and

TABLE 3 Linear regression models comparing AD PRS with cognitive phenotypes in adults with DS.

Phenotype, $N = 307$	Variables adjusted for	Model 1 ($PRS_{nonAPOE}$)		Model 2 (PRS_{APOE})		Model 3 (*APOEε4* carrier status)	
		Coefficient	*P*	Coefficient	*P*	Coefficient	*P*
NTG-EDSD memory	Age at testing, sex	0.39	6.48×10^{-2}	0.63	$\mathbf{8.28 \times 10^{-3}}$	0.46	5.12×10^{-2}
	Age at testing, sex, ID severity status	0.38	7.48×10^{-2}	0.64	$\mathbf{8.38 \times 10^{-3}}$	0.47	5.10×10^{-2}
DLD cognitive score	Age at testing, sex	2.28	5.03×10^{-2}	3.22	$\mathbf{2.67 \times 10^{-3}}$	1.57	1.51×10^{-1}
	Age at testing, sex, ID severity status	1.68	9.33×10^{-2}	2.19	$\mathbf{2.93 \times 10^{-2}}$	1.05	2.85×10^{-1}
DSMSE memory score	Age at testing, sex	−0.59	$\mathbf{1.35 \times 10^{-2}}$	−0.91	$\mathbf{9.01 \times 10^{-5}}$	−0.68	$\mathbf{1.87 \times 10^{-3}}$
	Age at testing, sex, ID severity status	−0.58	$\mathbf{1.60 \times 10^{-2}}$	−0.85	$\mathbf{2.84 \times 10^{-4}}$	−0.66	$\mathbf{2.53 \times 10^{-3}}$
DSMSE total score	Age at testing, sex	−1.87	2.05×10^{-1}	−4.68	$\mathbf{1.06 \times 10^{-3}}$	−1.76	2.07×10^{-1}
	Age at testing, sex, ID severity status	−1.4	2.43×10^{-1}	−2.74	$\mathbf{2.48 \times 10^{-2}}$	−1.11	3.52×10^{-1}

Notes: Model 1 consists of PRS calculated by excluding *APOE* loci. Model 2 includes PRS calculated by including *APOE* loci. Model 3 consists of *APOEε4* carrier status (0 = non-carrier, 1 = carrier). These results are the product of analyzing the tertiles with the lowest and highest PRS.
Numbers in bold denote significant associations.
Abbreviations: AD, Alzheimer's disease; DLD, Dementia Questionnaire for People with Learning Disabilities; DSMSE, Down Syndrome Mental Status Examination; ID, intellectual disability; *N*, sample size; NTG-EDSD, National Task Group-Early Detection Screen for Dementia; *P*, *p* value; PRS, polygenic risk score.

DSMSE total scores ($PRS_{nonAPOE}$: $\beta = -1.87$, $p = 2.05 \times 10^{-1}$; PRS_{APOE}: $\beta = -4.68$, $p = 1.06 \times 10^{-3}$) were associated with PRS_{APOE} but not with $PRS_{nonAPOE}$. NTG-EDSD, DLD, and DSMSE total scores showed a trend for association with both *APOE ε4* carrier status and $PRS_{nonAPOE}$, suggesting that both *APOE* and the other AD risk variants contributed to this association. Furthermore, we conducted an additional sensitivity analysis to rule out the possibility of PRS being associated with ID severity status rather than dementia symptoms. Notably, the PRS_{APOE} and $PRS_{nonAPOE}$ associations remained consistent even after adjusting for the ID severity status (Table 3).

We further analyzed the association of the PRS with CSF biomarkers Aβ40, Aβ42, Aβ42/40, tTau, pTau, and NFL. As reported previously,[19,40] we found a very strong association of PRS_{APOE}, $PRS_{nonAPOE}$, and *APOE ε4* with CSF biomarkers Aβ42, tTau, and pTau in both sLOAD and sEOAD. For fEOAD, PRS_{APOE} and *APOE ε4*. On the other hand, $PRS_{nonAPOE}$ were not associated with Aβ42, tTau, and pTau (Tables 4 and S5). In the case of DS, significant associations were found between Aβ42 (PRS_{APOE}, $\beta = -0.18$, $p = 9.99 \times 10^{-11}$), tTau (PRS_{APOE}, $\beta = 0.09$, $p = 2.75 \times 10^{-4}$), pTau (PRS_{APOE}, $\beta = 0.12$, $p = 5.95 \times 10^{-6}$), and Aβ42/40 ratio (PRS_{APOE}, $\beta = -0.28$, $p = 2.51 \times 10^{-12}$) for the AD risk PRS that included the *APOE* region, while $PRS_{nonAPOE}$ did not show significant associations (Table 4). The effect sizes observed for Aβ42, tTau, and pTau with both $PRS_{nonAPOE}$ and PRS_{APOE} were consistent across the various cohorts, including DS, sEOAD, and fEOAD (PRS_{APOE}—Aβ42: $\beta_{DS} = -0.18$, $\beta_{fEOAD} = -0.16$, $\beta_{SEOAD} = -0.28$; tTau: $\beta_{DS} = 0.09$, $\beta_{fEOAD} = 0.09$, $\beta_{SEOAD} = 0.20$; pTau $\beta_{DS} = 0.12$, $\beta_{fEOAD} = 0.11$, $\beta_{SEOAD} = 0.21$; Table 4). In additional analyses performed only in cases, excluding controls, we found that PRS_{APOE} and *APOE ε4* were associated with tTau and NFL in DS (Table S5) reinforcing the notion that *APOE* and AD risk variants influence neurodegeneration in adults with DS.

4 | DISCUSSION

We analyzed the association of AD risk PRS with five well-defined cohorts covering different presentations of AD (late vs early, and sporadic vs familial) and DS to determine whether the genetic variants and genes associated with AD also influenced DS-related phenotypes. PRSs were derived from the latest GWAS meta-analysis for AD risk.[20] To the best of our knowledge, the analysis of the potential overlap of the genetic architecture of AD with that of DS is the first of its kind. As reported previously,[19] we found that sEOAD, fLOAD, and sLOAD individuals had significantly higher PRS_{APOE} and $PRS_{nonAPOE}$ than controls (Table 2), but no association was found for fEOAD, as the disease in these individuals is explained by mutations in *APP*, *PSEN1*, and *PSEN2* genes. Similar findings to those for fEOAD were found for the DS cohort, where the $PRS_{nonAPOE}$ was not associated with status. However, in our analyses, we found that DS individuals had significantly lower PRS_{APOE} scores than controls. This was driven by *APOE ε4* alone, and initial analyses suggested that DS individuals had lower *APOE ε4+* frequency (23.13%) than the general population (*APOE ε4+* frequency: 26.36%). However, our analyses indicated that this was due to the inclusion of younger controls, which included presymptomatic individuals, resulting in a higher proportion of *APOE ε4* (*APOE ε4+* frequency: 38.10%) than older individuals (age > 65; *APOE ε4+* frequency: 23.63%). Another reason for finding no association of AD risk PRS in DS could be due to a lack of power, as the sample size for DS is still limited.

We also identified a significant association of AD risk PRS with cognition and behavior in DS. We found that AD risk PRSs were associated with memory (NTG-EDSD Memory, DSMSE memory), cognition (DLD cognition), and general mental status (DSMSE-Total score; Table 3). This association was found in the PRS that included *APOE* ($PRS_{nonAPOE}$), but this association was not driven by *APOE ε4* alone, as *APOE ε4* was

TABLE 4 Comparison of Alzheimer's disease PRS with CSF biomarkers across DS, sLOAD, sEOAD, fEOAD, and control cohorts, adjusted for study.

		Biomarker	Aβ40	Aβ42	tTau	pTau	NFL	Aβ42 /40
DS	$PRS_{nonAPOE}$	Coefficient	0.01	−0.01	0.03	0.05	−0.01	−0.03
		P	7.43×10^{-1}	7.58×10^{-1}	2.69×10^{-1}	9.15×10^{-2}	8.22×10^{-1}	5.36×10^{-1}
	PRS_{APOE}	Coefficient	−0.03	−0.18	0.09	0.12	−0.03	−0.28
		P	4.35×10^{-1}	$\mathbf{9.99 \times 10^{-11}}$	$\mathbf{2.75 \times 10^{-4}}$	$\mathbf{5.95 \times 10^{-6}}$	1.58×10^{-1}	$\mathbf{2.51 \times 10^{-12}}$
	APOEε4 carrier status	Coefficient	−0.08	−0.56	0.28	0.30	−0.14	−0.80
		P	3.48×10^{-1}	$\mathbf{1.68 \times 10^{-20}}$	$\mathbf{4.85 \times 10^{-7}}$	$\mathbf{2.34 \times 10^{-7}}$	$\mathbf{7.55 \times 10^{-3}}$	$\mathbf{5.55 \times 10^{-22}}$
sLOAD	$PRS_{nonAPOE}$	Coefficient	−0.03	−0.11	0.13	0.13	0.04	−0.03
		P	4.36×10^{-1}	$\mathbf{1.58 \times 10^{-6}}$	$\mathbf{3.35 \times 10^{-9}}$	$\mathbf{3.69 \times 10^{-9}}$	$\mathbf{3.90 \times 10^{-2}}$	4.61×10^{-1}
	PRS_{APOE}	Coefficient	−0.08	−0.33	0.24	0.24	−0.001	−0.24
		P	$\mathbf{2.08 \times 10^{-2}}$	$\mathbf{4.98 \times 10^{-60}}$	$\mathbf{6.73 \times 10^{-32}}$	$\mathbf{3.66 \times 10^{-31}}$	9.43×10^{-1}	$\mathbf{1.75 \times 10^{-12}}$
	APOEε4 carrier status	Coefficient	−0.16	−0.87	0.55	0.54	−0.05	−0.66
		P	$\mathbf{2.36 \times 10^{-2}}$	$\mathbf{7.07 \times 10^{-85}}$	$\mathbf{2.74 \times 10^{-35}}$	$\mathbf{5.58 \times 10^{-33}}$	2.35×10^{-1}	$\mathbf{4.13 \times 10^{-20}}$
sEOAD	$PRS_{nonAPOE}$	Coefficient	0.01	−0.08	0.09	0.09	0.03	−0.04
		P	8.56×10^{-1}	$\mathbf{9.94 \times 10^{-3}}$	$\mathbf{3.30 \times 10^{-3}}$	$\mathbf{5.76 \times 10^{-3}}$	3.01×10^{-1}	3.87×10^{-1}
	PRS_{APOE}	Coefficient	−0.06	−0.28	0.20	0.21	0.02	−0.27
		P	1.39×10^{-1}	$\mathbf{9.50 \times 10^{-25}}$	$\mathbf{1.87 \times 10^{-12}}$	$\mathbf{1.06 \times 10^{-13}}$	5.26×10^{-1}	$\mathbf{1.54 \times 10^{-12}}$
	APOEε4 carrier status	Coefficient	−0.13	−0.75	0.48	0.50	−0.07	−0.80
		P	1.30×10^{-1}	$\mathbf{3.88 \times 10^{-34}}$	$\mathbf{1.28 \times 10^{-14}}$	$\mathbf{3.50 \times 10^{-15}}$	1.83×10^{-1}	$\mathbf{9.42 \times 10^{-23}}$
fEOAD	$PRS_{nonAPOE}$	Coefficient		0.02	0.04	0.05		
		P		4.84×10^{-1}	1.59×10^{-1}	6.44×10^{-2}		
	PRS_{APOE}	Coefficient		−0.16	0.09	0.12		
		P		$\mathbf{1.43 \times 10^{-9}}$	$\mathbf{3.87 \times 10^{-4}}$	$\mathbf{9.54 \times 10^{-6}}$		
	APOEε4 carrier status	Coefficient		−0.53	0.24	0.28		
		P		$\mathbf{3.46 \times 10^{-19}}$	$\mathbf{1.40 \times 10^{-5}}$	$\mathbf{9.50 \times 10^{-7}}$		

Notes: All models were corrected for sex, age at testing, and study. Model: $PRS_{nonAPOE}$ consists of PRS calculated by excluding *APOE* loci. Model PRS_{APOE} includes *APOE* in the PRS calculation. Model *APOEε4* carrier status tests for *APOEε4* (0 = non-carrier, 1 = carrier). These results are the product of analyzing the continuous PRS. Numbers in bold denote significant associations.

Abbreviations: *APOE*, apolipoprotein E; Aβ, amyloid beta; CSF, cerebrospinal fluid; DS, Down syndrome; fEOAD, familial early-onset Alzheimer's disease; NFL, neurofilament light chain; *P*, *p* value; PRS, polygenic risk scores; pTau, phosphorylated tau; sEOAD, sporadic early-onset Alzheimer's disease; sLOAD, sporadic late-onset Alzheimer's disease; tTau, total tau.

not associated with these phenotypes, with the exception of DSMSE memory, indicating that *APOE* and the AD risk variants contributed to memory in DS. The same pattern held true for DSMSE memory. Additionally, in this case, the PRSs that did not include *APOE* ($PRS_{nonAPOE}$) were also associated with this phenotype (Table 3). However, these findings may have been influenced by the baseline severity of intellectual disability of each participant. We conducted sensitivity analyses, which confirmed that the associations between the PRS and cognitive phenotypes remained largely unchanged after adjusting for ID status. The association of PRS with these cognitive phenotypes is independent of the severity of intellectual disability, although larger studies are required to replicate these findings.

In the context of previous research that emphasized a potential link between *APOE ε4* carriers and attentional deficits in adults with DS,[41] our study broadens the comprehension of cognitive impairments associated with *APOE ε4*. Our study consisted of cognitive data from a cohort of 307 adults with DS (Table S1), ranging in age from 25 to 70 years, which is a slightly larger dataset than was used in previous studies.[41] As mentioned previously, individuals carrying the *APOE ε4* allele have lower DSMSE memory scores (Table 3). This observation is in line with previous studies,[41–43] as lower DSMSE scores indicate greater cognitive impairment. Given the increased sample size in our study, we believe that our findings contribute to the understanding of the relationship between *APOE ε4* and cognitive phenotypes in adults with DS. This and previous studies collectively provide essential insights into the role of *APOE ε4* in cognitive function and its potential impact on attentional and memory abilities in adults with DS. While further investigations are necessary, our findings offer a foundation for future interventions and research aimed at addressing the risk of AD in individuals with DS.

It is well known and recognized in the field that DS is caused by a trisomy of chromosome 21, which includes *APP*, one of the three

genes that cause ADAD.[27–30,44–46] In addition, there is considerable heterogeneity among the DS population in ID and the onset of memory decline and cognition, suggesting that other genetic factors beyond the *APP* may be involved. The latest GWAS for LOAD identified more than 74 loci associated with AD, and the genomics and pathway analyses indicate that those loci are enriched for immune and inflammatory genes.[47] The association of PRS with cognitive and behavioral functioning suggests that other AD risk genetic loci outside of chromosome 21 contribute to cognition and potentially dementia. PRS is a very powerful tool to analyze the overlap of complex traits, as in this case. However, we cannot point to specific loci or genes, but we can hypothesize that genes, cell types, and pathways similar to those altered in AD (astrocytes, microglia, and vasculature[48]) are also involved in memory decline in DS.

However, there are several limitations to the current study. The sample size for the DS cohort remains modest, which may limit the ability to detect smaller genetic effects. As with any genetic study, replication in larger independent cohorts is crucial to validate our findings and draw definitive conclusions. Another limitation is the exclusion of genes located on chromosome 21 from the PRS calculation. While chromosome 21 contains genes relevant to various traits and diseases, including AD, we made this deliberate decision to mitigate the potential influence of trisomy 21. There are several reasons for excluding chromosome 21. The first one is that the current imputation pipelines cannot handle trisomic SNPs, so only genotype SNPs are available for chromosome 21. This will lead to very sparse SNP data in this chromosome, which will affect PRS calculations. Second, the current PRS calculation is not designed to deal with trisomic variants. However, we recognize that this exclusion may limit the comprehensive assessment of genetic risk factors associated with AD on chromosome 21. Future studies could explore tailored approaches to incorporating chromosome 21 genes into PRS analysis for DS populations, taking into account the unique genetic landscape. Additionally, obtaining CSF samples from a consenting subset of participants may introduce potential bias in the representativeness of the DS population. While these samples provide valuable biomarker data, caution is needed when generalizing the findings to the broader DS population. Future studies with larger and more diverse cohorts are needed to better assess the representativeness of CSF samples and validate the observed biomarker associations.

Furthermore, we acknowledge the challenge of comparing clinical diagnoses between individuals with intellectual disabilities and the general population. Clinical criteria for AD may differ slightly between these groups, warranting caution when making cross-comparisons. To mitigate this limitation, we advocate employing standardized assessments and taking into account the specific clinical characterization of individuals with DS. Despite these limitations, our study contributes valuable insights into the genetic factors influencing AD risk and their implications for DS-related phenotypes.

ACKNOWLEDGMENTS

We thank all participants and their families for their commitment and dedication to helping advance the research into the early detection of AD and DS and support staff at each of the participating sites for their contributions to this study. This work was also supported by access to equipment made possible by the Hope Center for Neurological Disorders, the NeuroGenomics and Informatics Center (NGI: https://neurogenomics.wustl.edu/), and the Departments of Neurology and Psychiatry at Washington University School of Medicine. This work was supported by grants from the National Institutes of Health (R01AG044546 (CC), P01AG003991(CC, JCM), RF1AG053303 (CC), RF1AG058501 (CC), U01AG058922 (CC), RF1AG074007 (YJS), R01AG064877 (MIK, CC), the Chan Zuckerberg Initiative (CZI), the Michael J. Fox Foundation (CC), the Department of Defense (LI-W81XWH2010849), and the Alzheimer's Association Zenith Fellows Award (ZEN-22-848604, awarded to CC). The recruitment and clinical characterization of research participants at Washington University were supported by NIH P30AG066444 (JCM), P01AG03991 (JCM), and P01AG026276 (JCM). DIAN: Data collection and sharing for this project were supported by the Dominantly Inherited Alzheimer Network (DIAN, U19AG032438) funded by the National Institute on Aging (NIA), the Alzheimer's Association (SG-20-690363-DIAN), the German Center for Neurodegenerative Diseases (DZNE), Raul Carrea Institute for Neurological Research (FLENI), partial support by the Research and Development Grants for Dementia from Japan Agency for Medical Research and Development, AMED, the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), Spanish Institute of Health Carlos III (ISCIII), Canadian Institutes of Health Research (CIHR), Canadian Consortium of Neurodegeneration and Aging, Brain Canada Foundation, and Fonds de Recherche du Québec Santé. This manuscript was reviewed by DIAN Study investigators for scientific content and consistency of data interpretation with previous DIAN Study publications. We acknowledge the altruism of the participants and their families and the contributions of the DIAN research and support staff at each of the participating sites for their contributions to this study. ADNI: Data collection and sharing for this project was also funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging and the National Institute of Biomedical Imaging and Bioengineering and through generous contributions from the following: AbbVie; Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; Bristol-Myers Squibb Company; CereSpir, Inc.; Cogstate; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd. and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Lumosity; Lundbeck; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research provides funds to support ADNI clinical sites in Canada. Private-sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study was coordinated

by the Alzheimer's Therapeutic Research Institute at the University of Southern California. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California. ABC-DS: The Alzheimer's Biomarkers Consortium–DS (ABC-DS) is funded by the National Institute on Aging and the National Institute for Child Health and Human Development (U01 AG051406, U01 AG051412, U19 AG068054). The work contained in this publication was also supported through the following National Institutes of Health Programs: The Alzheimer's Disease Research Centers Program (P50 AG008702, P30 AG062421, P50 AG16537, P50 AG005133, P50 AG005681, P30 AG062715, and P30 AG066519), the Eunice Kennedy Shriver Intellectual and Developmental Disabilities Research Centers Program (U54 HD090256, U54 HD087011, and P50 HD105353), the National Center for Advancing Translational Sciences (UL1 TR001873, UL1 TR002373, UL1 TR001414, UL1 TR001857, UL1 TR002345), the National Centralized Repository for Alzheimer's Disease and Related Dementias (U24 AG21886), and DS-Connect® (The DS Registry) supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD). The authors are grateful to the ABC-DS study participants, their families and care providers, and the ABC-DS research and support staff for their contributions to this study. This manuscript has been reviewed by ABC-DS investigators for scientific content and consistency of data interpretation with previous ABC-DS study publications. The content is the sole responsibility of the authors and does not necessarily represent the official views of the NIH.

CONFLICT OF INTEREST STATEMENT

CC received research support from GSK and EISAI. The funders of the study had no role in the collection, analysis, or interpretation of data, in the writing of the report, or in the decision to submit the paper for publication. He is a member of the advisory board of Vivid Genomics and Circular Genomics and owns stock in those companies. Authors PG, MA, LTD, LX, KHF, EIS, and CLH have nothing to disclose. JPC has served on the medical advisory board of Humana Healthcare; there are no conflicts with the current work. MM is listed as an inventor on issued and pending patents not related to the material in this manuscript, and he receives royalty payments from the University of Rochester. He has served on scientific advisory boards of Brain Neurotherapy Bio, Inc.; Davis Phinney Foundation for Parkinson's; and Alzheon, Inc. He was chair of the NIH/NIA Data and Safety Monitoring Board. JH is a paid consultant for Parabon Nanolabs, AlzPath, Roche, and Prothena, outside the scope of this work. JHL receives funding from NIH/NIA U01 AG051412 and U19 AG068054, mentioned in the funding sources. EF, BMA, MIK, RJP, SLH, SHZ, MVF, and YJS declare no conflicts with the current work. Author disclosures are available in the supporting information.

CONSENT STATEMENT

Ethics approval for every individual cohort was obtained from the respective institutional review boards, and research was carried out in accordance with the approved protocols (WUSTL IRB approval 201109148). Written informed consent was obtained from participants or their family members, and all participating institutions approved the study design.

ORCID

Carlos Cruchaga https://orcid.org/0000-0002-0276-2899

REFERENCES

1. Salehi A, Wesson Ashford J, Mufson EJ. Editorial (Thematic issue: the link between alzheimer's disease and Down syndrome. A historical perspective). *Curr Alzheimer Res*. 2015;13(1):2-6. doi:10.2174/1567205012999151021102914
2. Lott IT, Head E. Dementia in Down syndrome: unique insights for Alzheimer disease research. *Nat Rev Neurol*. 2019;15(3):135-147. doi:10.1038/s41582-018-0132-6
3. Hardy J. The discovery of Alzheimer-causing mutations in the <scp>APP</scp>gene and the formulation of the "amyloid cascade hypothesis.". *FEBS J*. 2017;284(7):1040-1044. doi:10.1111/febs.14004
4. Strydom A, Coppus A, Blesa R, et al. Alzheimer's disease in Down syndrome: an overlooked population for prevention trials. *Alzheimer's Dement*. 2018;4(1):703-713. doi:10.1016/j.trci.2018.10.006
5. Patel A, Rees SD, Kelly MA, et al. Association of variants within APOE, SORL1, RUNX1, BACE1 and ALDH18A1 with dementia in Alzheimer's disease in subjects with Down syndrome. *Neurosci Lett*. 2011;487(2):144-148. doi:10.1016/j.neulet.2010.10.010
6. Schupf N, Lee JH, Kapell D, et al. Onset of dementia is associated with apolipoprotein E ?4 in Down's syndrome. *Ann Neurol*. 1996;40(5):799-801. doi:10.1002/ana.410400518
7. Liu CC, Kanekiyo T, Xu H, Bu G. Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy. *Nat Rev Neurol*. 2013;9(2):106-118. doi:10.1038/nrneurol.2012.263
8. Wiseman FK, Al-Janabi T, Hardy J, et al. A genetic cause of Alzheimer disease: mechanistic insights from Down syndrome. *Nat Rev Neurosci*. 2015;16(9):564-574. doi:10.1038/nrn3983
9. Sinai A, Mokrysz C, Bernal J, et al. Predictors of age of diagnosis and survival of Alzheimer's disease in Down syndrome. *J Alzheimer's Dis*. 2017;61(2):717-728. doi:10.3233/JAD-170624
10. Hithersay R, Startin CM, Hamburg S, et al. Association of dementia with mortality among adults with Down syndrome older than 35 years. *JAMA Neurol*. 2019;76(2):152. doi:10.1001/jamaneurol.2018.3616
11. Deb S, Braganza J, Norton N, et al. *APOE ε*4 influences the manifestation of Alzheimer's disease in adults with down's syndrome. *The British Journal of Psychiatry*. 2000;176(5):468-472. doi:10.1192/bjp.176.5.468
12. Prasher VP, Sajith SG, Rees SD, et al. Significant effect of APOE epsilon 4 genotype on the risk of dementia in Alzheimer's disease and mortality in persons with Down syndrome. *Int J Geriatr Psychiatry*. 2008;23(11):1134-1140. doi:10.1002/gps.2039
13. Hyman BT, West HL, Rebeck GW, et al. Quantitative analysis of senile plaques in Alzheimer disease: observation of log-normal size distribution and molecular epidemiology of differences associated with apolipoprotein E genotype and trisomy 21 (Down syndrome). *Proc Natl Acad Sci*. 1995;92(8):3586-3590. doi:10.1073/pnas.92.8.3586
14. Esralew L, Janicki MP, Keller SM. National Task Group Early Detection Screen for Dementia (NTG-EDSD). *Neuropsychological Assessments of Dementia in Down Syndrome and Intellectual Disabilities*. Springer International Publishing; 2018:197-213. doi:10.1007/978-3-319-61720-6_11
15. Esralew L, *National Task Group Early Detection Screen for Dementia (NTG-EDSD)*; 2013. Accessed March 22, 2023. https://www.caunj.org/wp-content/uploads/2019/07/Natl_Task_Force-Early_Detection_Dementia_PPT-1.pdf

16. Deb S, Hare M, Prior L, Bhaumik S. Dementia screening questionnaire for individuals with intellectual disabilities. *The British Journal of Psychiatry*. 2007;190(5):440-444. doi:10.1192/bjp.bp.106.024984
17. Krinsky-McHale SJ, Zigman WB, Lee JH, et al. Promising outcome measures of early Alzheimer's dementia in adults with Down syndrome. *Alzheimer's Dement (Amst)*. 2020;12(1):e12044. doi:10.1002/dad2.12044
18. Trevino CE, Holleman AM, Corbitt H, et al. Identifying genetic factors that contribute to the increased risk of congenital heart defects in infants with Down syndrome. *Sci Rep*. 2020;10(1):18051. doi:10.1038/s41598-020-74650-4
19. Cruchaga C, Del-Aguila JL, Saef B, et al. Polygenic risk score of sporadic late-onset Alzheimer's disease reveals a shared architecture with the familial and early-onset forms. *Alzheimer's Dement*. 2018;14(2):205-214. doi:10.1016/j.jalz.2017.08.013
20. Bellenguez C, Küçükali F, Jansen IE, et al. New insights into the genetic etiology of Alzheimer's disease and related dementias. *Nat Genet*. 2022;54(4):412-436. doi:10.1038/s41588-022-01024-z
21. Accessed August, 2022. https://www.nia.nih.gov/research/abc-ds#data
22. Accessed July, 2022. https://knightadrc.wustl.edu/
23. Accessed July, 2022. https://www.nia.nih.gov/research/dn/alzheimers-disease-genetics-initiative
24. Accessed July, 2022. http://www.adni-info.org
25. Accessed July, 2022. https://dian.wustl.edu/
26. Handen BL, Lott IT, Christian BT, et al. The Alzheimer's biomarker consortium-Down syndrome: rationale and methodology. *Alzheimer's Dement*. 2020;12(1). doi:10.1002/dad2.12065
27. Yang C, Farias FHG, Ibanez L, et al. Genomic atlas of the proteome from brain, CSF and plasma prioritizes proteins implicated in neurological disorders. *Nat Neurosci*. 2021;24(9):1302-1312. doi:10.1038/s41593-021-00886-6
28. Yang C, Fagan AM, Perrin RJ, Rhinn H, Harari O, Cruchaga C. Mendelian randomization and genetic colocalization infer the effects of the multi-tissue proteome on 211 complex disease-related phenotypes. *Genome Med*. 2022;14(1):140. doi:10.1186/s13073-022-01140-9
29. Sung YJ, Yang C, Norton J, et al. Proteomics of brain, CSF, and plasma identifies molecular signatures for distinguishing sporadic and genetic Alzheimer's disease. *Sci Transl Med*. 2023;15(703). doi:10.1126/scitranslmed.abq5923
30. Timsina J, Ali M, Do A, Wang L, Sung YJ, Cruchaga C. Harmonization of CSF and imaging biomarkers for Alzheimer's disease biomarkers: need and practical applications for genetics studies and preclinical classification. *bioRxiv*. 2023. doi:10.1101/2023.05.24.542118. Published online May 24.
31. Taliun D, Harris DN, Kessler MD, et al. Sequencing of 53,831 diverse genomes from the NHLBI TOPMed program. *Nature*. 2021;590(7845):290-299. doi:10.1038/s41586-021-03205-y
32. Lee JH. Analyses of the National Institute on Aging late-onset Alzheimer's disease family study. *Arch Neurol*. 2008;65(11):1518. doi:10.1001/archneur.65.11.1518
33. Choi SW, Mak TSH, O'Reilly PF. Tutorial: a guide to performing polygenic risk score analyses. *Nat Protoc*. 2020;15(9):2759-2772. doi:10.1038/s41596-020-0353-1
34. Deming Y, Filipello F, Cignarella F, et al. The *MS4A* gene cluster is a key modulator of soluble TREM2 and Alzheimer's disease risk. *Sci Transl Med*. 2019;11(505). doi:10.1126/scitranslmed.aau2291
35. Phillips B, Western D, Wang L, et al. Proteome wide association studies of LRRK2 variants identify novel causal and druggable proteins for Parkinson's disease. *NPJ Parkinsons Dis*. 2023;9(1):107. doi:10.1038/s41531-023-00555-4
36. Silverman W, Krinsky-McHale SJ, Lai F, et al. Evaluation of the National Task Group-Early Detection Screen for Dementia: sensitivity to 'mild cognitive impairment' in adults with Down syndrome. *J Appl Res Intellect Disabil*. 2021;34(3):905-915. doi:10.1111/jar.12849
37. Koehl L, Harp J, Van Pelt KL, Head E, Schmitt FA. Longitudinal assessment of dementia measures in Down syndrome. *Alzheimer's Dement*. 2020;12(1). doi:10.1002/dad2.12075
38. Robin X, Turck N, Hainard A, et al. pROC: an open-source package for R and S+ to analyze and compare ROC curves. *BMC Bioinformatics*. 2011;12(1):77. doi:10.1186/1471-2105-12-77
39. Escott-Price V, Sims R, Bannister C, et al. Common polygenic variation enhances risk prediction for Alzheimer's disease. *Brain*. 2015;138(12):3673-3684. doi:10.1093/brain/awv268
40. Deming Y, Li Z, Kapoor M, et al. Genome-wide association study identifies four novel loci associated with Alzheimer's endophenotypes and disease modifiers. *Acta Neuropathol*. 2017;133(5):839-856. doi:10.1007/s00401-017-1685-y
41. D'Souza H, Mason L, Mok KY, et al. Differential associations of apolipoprotein E ε4 genotype with attentional abilities across the life span of individuals with Down syndrome. *JAMA Netw Open*. 2020;3(9):e2018221. doi:10.1001/jamanetworkopen.2020.18221
42. Bejanin A, Iulita MF, Vilaplana E, et al. Association of apolipoprotein E ε4 allele with clinical and multimodal biomarker changes of Alzheimer disease in adults with Down syndrome. *JAMA Neurol*. 2021;78(8):937. doi:10.1001/jamaneurol.2021.1893
43. Forte GI, Piccione M, Scola L, et al. Apolipoprotein E genotypic frequencies among Down syndrome patients imply early unsuccessful aging for ApoE4 carriers. *Rejuvenation Res*. 2007;10(3):293-300. doi:10.1089/rej.2006.0525
44. Sawa M, Overk C, Becker A, et al. Impact of increased *APP* gene dose in Down syndrome and the Dp16 mouse model. *Alzheimer's Dement*. 2022;18(6):1203-1234. doi:10.1002/alz.12463
45. Prasher VP, Farrer MJ, Kessling AM, et al. Molecular mapping of alzheimer-type dementia in Down's syndrome. *Ann Neurol*. 1998;43(3):380-383. doi:10.1002/ana.410430316
46. Doran E, Keator D, Head E, et al. Down syndrome, partial trisomy 21, and absence of Alzheimer's disease: the role of APP. *J Alzheimer Dis*. 2017;56(2):459-470. doi:10.3233/JAD-160836
47. Romero-Molina C, Garretti F, Andrews SJ, Marcora E, Goate AM. Microglial efferocytosis: diving into the Alzheimer's disease gene pool. *Neuron*. 2022;110(21):3513-3533. doi:10.1016/j.neuron.2022.10.015
48. De Strooper B, Karran E. The cellular phase of Alzheimer's disease. *Cell*. 2016;164(4):603-615. doi:10.1016/j.cell.2015.12.056

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: Gorijala P, Aslam MM, Dang LH, et al. Alzheimer's polygenic risk scores are associated with cognitive phenotypes in Down syndrome. *Alzheimer's Dement*. 2023;1-12. https://doi.org/10.1002/alz.13506