

# Effect of Cognitive Reserve on Age at Symptom Onset and Cognitive Decline in Individuals With Dominantly Inherited Alzheimer Disease

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## Abstract

### Background and Objectives

Cognitive reserve has been shown to modulate the onset and progression of Alzheimer disease (AD) symptoms. Although its role in sporadic AD is well-studied, how cognitive reserve influences the timing and progression of symptoms in dominantly inherited AD (DIAD) remains unclear. This study aimed to quantify cognitive reserve in DIAD carriers and test whether higher cognitive reserve is associated with later symptom onset and slower functional decline.

### Methods

We analyzed data from the Dominantly Inherited Alzheimer's Network study. Cognitive reserve was modeled using a residual-based latent variable approach, decomposing cognitive performance into demographic (CogD), biomarker (CogB), and reserve or residual (CogR) components. Primary outcomes were age at clinical symptom onset (CDR >0) and longitudinal change in the Clinical Dementia Rating–Sum of Boxes (CDR-SBs). Data were analyzed using Cox proportional hazards models and linear mixed-effects models, adjusting for estimated years from onset (EYO).

### Result

A total of 710 Dominantly Inherited Alzheimer Network (DIAN) participants were included in the analysis, comprising 271 non-DIAD carriers (nMC), 284 asymptomatic DIAD carriers (aMC), and 155 symptomatic DIAD carriers. In asymptomatic carriers, using a zero-inflation model adjusted for EYO showed that a 1 SD increase in the reserve component (CogR) was associated with a 4.06-fold increase in the odds of being clinically unimpaired (CDR-SB = 0;

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## Glossary

**AD** = Alzheimer disease; **CDR-SB** = clinical dementia rating–sum of box; **CogD** = cognitive performance into demographic; **DIAD** = dominantly inherited AD; **DIAN** = Dominantly Inherited Alzheimer Network; **DIAN-OBS** = Dominantly Inherited Alzheimer Network Observational Study; **EYO** = estimated years from onset; **FDG-PET** = fluorodeoxyglucose positron emission tomography; **MC** = DIAD carrier; **nMC** = non-DIAD carrier; **PiB-PET** = Pittsburgh compound B positron emission tomography; **ROI** = region of interest; **sAD** = sporadic AD; **SEM** = structural equation modeling; **SES** = social economic status; **sMC** = symptomatic DIAD carriers; **SUVr** = standardized uptake value ratio.

95% CI 1.84–8.95). Similarly, a 1 SD increase in the demographic (CogD) and biomarker (CogB) components increased the odds of being CDR-SB = 0 by 2.60 (95% CI 1.10–6.16) and 5.16 (95% CI 2.00–13.33), respectively. Among symptomatic carriers, only the reserve and the biomarker components were significant. A 1 SD increase in CogR was associated with a 0.81-fold reduction in baseline CDR-SB score (95% CI 0.72–0.92), and a 1 SD increase in CogB was associated with a 0.60-fold reduction in CDR-SB (95% CI 0.50–0.71).

## Discussion

Our findings indicate that higher cognitive reserve values are associated with delayed conversion to mild cognitive impairment and slower progression on clinical dementia rating scales. These findings suggest that cognitive reserve plays a protective role in modifying the clinical trajectory of genetically determined AD.

## Introduction

Alzheimer disease (AD) represents the leading etiology of dementia<sup>1</sup> and continues to rise as a major public health challenge.<sup>2</sup> Although the search for disease-modifying therapies continues, one of the most important priorities in AD research is identifying factors that prevent or delay AD.<sup>3</sup> Prevention of AD dementia comprises both avoiding the AD pathologic processes (resistance) and coping with AD pathology (resilience).<sup>4,5</sup> Increasing evidence implicates resistance and resilience factors occurring throughout life as potential modifiers of age at symptom onset and cognitive decline rate in dementia.<sup>6,7</sup> As a result, identifying and validating interactions between cognitive reserve factors and disease pathogenesis remains one of the most critical challenges in AD.

Efforts have been made to clarify the concepts of resistance, resilience, and cognitive reserve in relation to AD.<sup>8,9</sup> Resistance refers to the brain's ability to avoid or minimize the accumulation of AD-related pathologies, through genetic or environmental protective factors. By contrast, resilience refers to the ability to preserve cognitive performance even in the presence of underlying neuropathologic changes. Cognitive reserve, a form of resilience, reflects variability in how individuals tolerate or compensate for brain alterations such as those that occur in AD.<sup>4</sup> Cognitive reserve acts as a modifying factor that shapes the relationship between neuropathology and clinical expression, capturing the discrepancy between an individual's predicted cognitive status based on their biological burden and their observed performance.<sup>10</sup> Cognitive reserve is assumed to vary across people and to arise from a combination of neurobiological influences and accumulated life experiences,<sup>10</sup> such as education, cognitive engagement,

and physical activity, which enhance the brain's adaptability to age-related changes and pathology. Previous studies have explored the influence of cognitive reserve on dementia prevalence and disease progression.<sup>5,11–13</sup> However, there is limited evidence of the effect of cognitive reserve during asymptomatic phases of the disease and longitudinal studies exploring the effect of cognitive reserve on age at symptom onset and disease progression.

In dominantly inherited AD (DIAD), similar to sporadic late-onset AD, there are differences in age at symptom onset and clinical heterogeneity, even within the same variant and family members. For example, families carrying an identical variant may demonstrate a 5- to 10-year difference in age at symptom onset.<sup>14,15</sup> Prior studies<sup>16</sup> showed that familial variant status explains only a portion of the marked heterogeneity seen across individuals with DIAD. Instead, the origin of the observed variability could lie in other factors (e.g., environmental, metabolic, or epigenetic). The study of cognitive reserve on AD using DIAD as a model may help to identify how individual levels of resistance and resilience influence the progression of AD pathophysiology, enhance resistance to pathology, delay age at symptom onset, and decrease cognitive decline rate. The model in DIAD also provides an opportunity to examine cognitive reserve during the asymptomatic phase, offering insights into how resilience and resistance factors operate before the onset of clinical symptoms. Using DIAD as a model to explore the effect of the cognitive reserve may help overcome significant challenges faced by similar studies in sporadic AD (sAD), including uncertainty about who will develop dementia, variation in onset age, and confounding age-related comorbidities; all factors are far more constrained in DIAD, where onset is highly predictable and individuals are

younger and healthier. As a result, DIAD provides a unique translational model in AD research to investigate the effect of resistance and resilience factors on age at onset and disease progression while controlling for late-life comorbidities and other confounders (e.g., vascular disease and medications) and genetic variants.<sup>17,18</sup>

Traditionally, cognitive reserve has been explored indirectly through static proxy variables (e.g., years of education and work complexity, among others).<sup>19</sup> However, these measures have several limitations, including the attempt to represent a dynamic construct that evolves over the lifespan as static,<sup>20,21</sup> vulnerable to confounding in correlational analysis,<sup>10</sup> and the same value of a proxy variable (e.g., 12 years of education) may reflect vastly different experiences across individuals and cultural contexts.<sup>19,22</sup> In response to these limitations, several studies have proposed estimating cognitive reserve more directly as the residual variance in cognitive performance after demographic influences and markers of brain pathology are taken into account.<sup>10,19,23,24</sup>

In this study, our measure of cognitive reserve followed the residual approach to quantify a continuous measure of reserve. This approach decomposes cognitive scores into components that are explained and unexplained by proxy measures of neuropathology (biomarker component), demographic component, and reserve component. This method is also more appropriate for longitudinal analysis.<sup>19</sup> We used cross-sectional and longitudinal data from a well-characterized DIAD cohort enrolled in the Dominantly Inherited Alzheimer Network (DIAN) to evaluate how cognitive reserve influences age at symptom onset and cognitive decline rate in DIAD. We hypothesized that 1-cognitive reserve modifies age at symptom onset and conversion to dementia; individuals with a higher cognitive reserve are more likely to remain asymptomatic than those with lower reserve, and 2-cognitive reserve modifies rates of clinical decline such that greater reserve is associated with less longitudinal decline.

## Methods

### Participants

Participants were recruited through the DIAN observational study, which enrolls individuals from families with confirmed pathogenic or likely pathogenic variants in the *APP*, *PSEN1*, or *PSEN2* genes.<sup>25</sup> The study includes both DIAD carriers and noncarriers who undergo standardized clinical, cognitive, imaging, and biomarker assessments at participating international sites. Non-DIAD carriers are biologically related family members from DIAD families who tested negative for the pathogenic variant segregating within their family. Participant enrollment and procedures have been previously described.<sup>25,26</sup> All individuals included in this analysis completed standardized clinical evaluations, comprehensive cognitive testing, multimodal neuroimaging, and CSF and blood collection for biomarker assays. Detailed descriptions of

DIAN study sites, recruitment procedures, and assessment protocols have been reported previously.<sup>25</sup> Measures relevant to this study are detailed below.

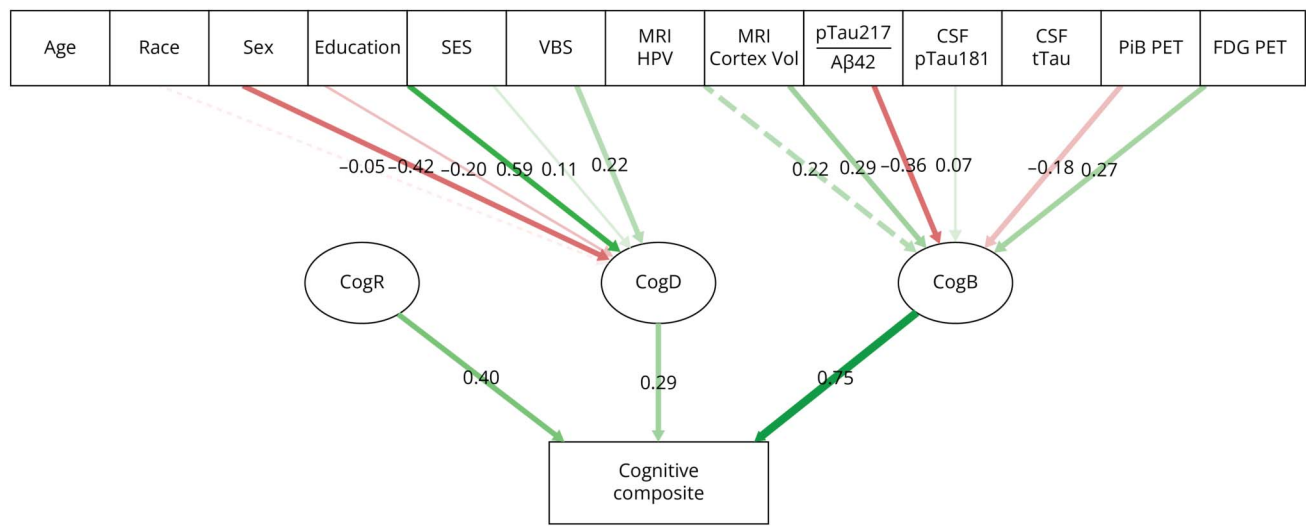
### Clinical and Neuropsychological Assessments

Participants received a standardized clinical evaluation based on the National Alzheimer's Coordinating Center Uniform Data Set.<sup>27-29</sup> This assessment included informant interviews, detailed medical and family history, neurologic and physical examinations, functional assessments, and a structured cognitive battery. Estimated years to symptom onset (EYO) was calculated as the participant's age at baseline minus the expected age at onset for their family's variant.<sup>15,30</sup> The age at symptom onset was calculated based on the average variant-specific expected age at first symptom onset or parental age at first symptom if the expected age at symptom onset for the variant was unknown. Clinical dementia severity was determined with the global CDR in accordance with standard protocols and criteria.<sup>31,32</sup> Clinical progression was assessed using consecutive scores on the Mini-Mental State Examination and Clinical Dementia Rating–Sum of Boxes ([CDR-SBs], higher values indicate greater clinical impairment). Cognitive performance and its rate of change were quantified using individual standardized neuropsychological test scores (e.g., digit symbol, category, and verbal fluency; trails A and B; and logical memory delayed recall) and a composite score comprised of the Mini-Mental State Examination total score, the Logical Memory delayed recall score from the Wechsler Memory Scale-Revised, the Digit Symbol Coding test total score from the Wechsler Adult Intelligence Scale-Revised, the animal fluency test, and the Boston Naming Test. Details of the DIAN cognitive composite and measurement properties have been published elsewhere.<sup>33</sup> Clinicians and neuropsychologists performing the assessments were blinded to the variant status of participants.

### Measures of Reserve

Reserve measures were quantified using a structural equation modeling (SEM) framework in which cognitive performance was decomposed into 3 orthogonal components: a demographic component (CogD), a biomarker component (CogB), and a reserve component (CogR). The 3 components were conceptualized as modifiers of the relationship between underlying pathology and clinical expression. CogD refers to variance in the cognitive composite explained by demographic factors (that is, age, education, sex, race, social economic status [SES], and vascular burden score). CogB refers to variance in the cognitive composite explained by pathology measures and markers of neurodegeneration variables (i.e., CSF pTau217/A  $\beta$  42, Pittsburgh compound B positron emission tomography (PiB-PET), fluorodeoxyglucose positron emission tomography (FDG-PET), MRI cortical volume, and MRI hippocampal volume). Both CogD and CogB were modeled as deterministic linear combinations of their corresponding predictors. CogR was modeled as a latent factor with unit variance, constrained to be orthogonal to CogD and CogB, and represents the residual variance in

**Figure 1** An Analytic Model for Decomposition of Cognitive Composite



Rectangles represent observed variables, and ovals represent latent variables. Dashed lines represent prefixed coefficients, and solid lines represent estimated coefficients. Red and green represent negative and positive associations, respectively.

the cognitive composite not explained by these determinants (Figure 1), reflecting cognitive reserve. Conceptually, CogR for participant  $i$  can be expressed as residual cognitive composite score, based on the estimated coefficients in Figure 1,

$$\text{CogR}_i \propto \text{Composite}_i - (0.29 \times \text{CogD}_i + 0.75 \times \text{CogB}_i)$$

Because CogR is modeled as a latent random variable, it is not computed as a raw residual. Instead, CogR is estimated from the SEM's factor-scoring procedure,<sup>34</sup> which infers the cognitive performance not attributable to CogD or CogB while accounting for measurement error, latent variances, and the model-imposed orthogonality constraints.

### Biochemical Analysis

DNA was isolated from peripheral blood using established laboratory procedures. Pathogenic variant status for APP, PSEN1, and PSEN2 was confirmed through PCR amplification of the relevant exon followed by Sanger sequencing.<sup>35</sup> CSF collection and handling followed procedures modeled on those used by the Alzheimer's Disease Neuroimaging Initiative. After collection, biospecimens were transported on dry ice to the DIAN Biomarker Core at Washington University for centralized analysis. Concentrations of Aβ<sub>1-42</sub>, total tau, and phosphorylated tau (p-tau181) were quantified using the INNO-BIA AlzBio3 xMAP Luminex assay with uniform analytical protocols.<sup>36</sup>

### Neuroimaging

As part of the international Dominantly Inherited Alzheimer Network Observational Study (DIAN-OBS) involving more than 20 imaging centers, standardized harmonization procedures are implemented to ensure cross-site data comparability. Below, we describe key elements of image acquisition and processing; additional details of the DIAN imaging protocol have been published elsewhere.<sup>37</sup>

### FDG and Amyloid PET

Acquisition and processing followed standardized DIAN protocols, described in detail elsewhere.<sup>37</sup> In summary, for amyloid PET, [11C]PiB data were processed to obtain standardized uptake value ratios (SUVRs) across 34 cortical and 6 subcortical FreeSurfer-defined regions of interest (ROIs) using cerebellar gray matter as the reference region; all regional values were corrected for partial volume effects. A PiB composite was derived by averaging SUVRs from the precuneus, prefrontal (superior and rostral middle frontal), orbitofrontal (lateral and medial), and lateral temporal (superior and middle temporal) cortices. FDG-PET scans were acquired using a harmonized DIAN protocol: participants received ~5 mCi of [18F] FDG through bolus injection. FDG uptake was quantified as SUVRs in FreeSurfer-defined ROIs, normalized to pons uptake, and processed using the same cross-site harmonization and partial-volume-corrected pipelines used for amyloid PET to ensure consistency across scanners and sites.

### MRI

Structural MRI acquisition was performed using the AD Neuroimaging Initiative protocol. Structural MRI data were obtained using acquisition parameters modeled on the Alzheimer's Disease Neuroimaging Initiative protocol. All centers used 3T scanners and were required to meet quality assurance benchmarks to ensure acquisition uniformity. Images were preprocessed using the FreeSurfer software suite (version 5.3-HCP-patch) for cortical reconstruction and volumetric segmentation. Subsequently, all volumetric ROI T1 measures were normalized to each participant's intracranial volume. To assess global cortical atrophy, a signature map of cortical ROI preferentially affected by DIAD was used, including precuneus, lateral and mesial orbitofrontal,



rostral mesial and superior frontal, and superior and mesial temporal regions.<sup>38</sup>

## Statistical Analysis

We adopted a 2-step analytic approach using the Clinical Dementia Rating–Sum of Boxes (CDR-SBs) as the primary clinical outcome, where higher scores indicate greater cognitive and functional impairment. In the first step, we fitted a latent variable model to decompose the variance in baseline cognitive composite into 3 uncorrelated components: demographic component (CogD), biomarker component (CogB), and reserve component (CogR). In the second step, we examined the associations of baseline and longitudinal CDR-SB with the obtained latent variables to test the hypothesis that cognitive reserve is associated with both clinical status and disease progression.

**Latent variable model:** The baseline cognitive composite was calculated as the average of normalized Z-scores of 5 tests, including the Mini-Mental State Examination, Logical Memory, Digit Symbol, Boston naming, and animal fluency tests. A structural equation model (SEM) was used to decompose the baseline cognitive composite into latent components representing demographics, biomarkers, and a residual. The model is depicted in Figure 1 in which rectangles and ovals represent observed and latent variables, respectively.

CDR-SB at baseline and longitudinal follow-up was modeled using generalized linear mixed-effects models with the baseline latent cognitive components (CogR, CogD, and CogB) as predictors. As CDR-SB is characterized by a high proportion of zero values and right-skewed non-zero values, a hurdle lognormal distribution was specified. Under this formulation, the probability of zero CDR-SB is modeled using a logistic regression with a logit link, and conditional on being non-zero, and CDR-SB is modeled on the log scale with Gaussian errors. Both cross-sectional and longitudinal models included fixed effects of EYO, the 3 cognitive components, and their interaction with EYO. To account for correlated observations induced by the family-based design, the cross-sectional model incorporated family-level random intercepts, whereas the longitudinal model included individual-level random intercepts to account for within-participant correlation across repeated measures of CDR-SB over time. The latent variable model was implemented using lavaan, and the hurdle lognormal mixed-effects model was implemented using GLMMadaptive, both in R 4.4.0.

To examine longitudinal changes in the reserve component, the fitted latent variable model was applied to follow-up data to estimate CogR at each visit. These longitudinal CogR values were modeled using a linear mixed-effects model with fixed effects of mutation group, EYO, and their interaction. EYO was parameterized using 2 variables that separately capture time before and after EYO = 0. Specifically, negative EYO values were coded in one variable and positive values in

the other, allowing distinct time effects on CogR before and after EYO = 0. Random intercepts were included to account for within-participant variability. The model was implemented using the lme4 package in R version 4.4.0.

All analyses evaluating the association between cognitive reserve (CogR) and clinical outcomes (symptom onset and disease progression) were restricted to DIAD carriers to capture the effects of cognitive reserve within the AD trajectory. Non-DIAD carriers (nMC) were included only in assessing longitudinal changes in CogR as a function of estimated years to onset (EYO), serving as a familial reference group to characterize the expected trajectory of CogR in the absence of variant-related pathology. This comparison provided context for interpreting reserve depletion patterns in DIAD carriers before and after symptom onset.

## Data Availability

Data supporting the findings of this study are available on request. Data are not publicly available to preserve the privacy of research participants. The analytic code used for decomposing CogD, biomarker, and reserve components is publicly available at GitHub DIAD Cognitive Reserve.

## Standard Protocol Approvals, Registrations, and Patient Consents

Written informed consent was obtained from patients or their legal representatives. The institutional review boards at DIAN participating sites approved all aspects of the study. DIAN-OBS study is registered at ClinicalTrials.gov (NCT00869817).

## Results

Across the DIAN cohort, 710 individuals (nMC n = 271; aMC n = 284, symptomatic DIAD carriers [sMC] n = 155) were included in the analysis. Among DIAD carriers, 77.0% had *PSEN1*, 6.6% had *PSEN2*, and 16.4% had *APP* pathogenic variants. Participants' characteristics are presented in Table 1. In summary, the EYO for the entire cohort ranged from −37.09 (years before the variants age at symptom onset) to 18.11 (years after the variant age at symptom onset). CDR scores in the sMC group ranged from 0.5 (very mild) to 3 (severe) (Table 1). Longitudinal assessments were available for most of the cohort (n = 468), with a mean follow-up of approximately 2.24 years.

The CogD, CogB, and CogR were moderately positively related to the cognitive composite score. The correlation between cognitive composite and the demographic, reserve, and biomarker components was 0.39, 0.58, and 0.80, respectively. Higher values in the components are related to better cognitive function. The demographic component was of higher value when the participant was young and male, had higher education, and had higher SES. The biomarker component was of higher value when the participant had higher FDG SUVR, higher hippocampus volume, higher cortical volume, lower CSF pTau217/A  $\beta$  42, and lower PiB-PET SUVR.

**Table 1** Baseline Demographic and Clinical Characteristics of DIAD Carriers and Noncarriers in the DIAN Cohort

| N                                          | Non-DIAD carriers<br>N = 271 | DIAD carriers<br>(asymptomatic, CDR = 0)<br>N = 284 | DIAD carriers<br>(symptomatic, CDR >0)<br>N = 155 |
|--------------------------------------------|------------------------------|-----------------------------------------------------|---------------------------------------------------|
| Sex n (%) female                           | 116 (42.80)                  | 120 (42.25)                                         | 74 (47.74)                                        |
| Education (y) mean (SD)                    | 14.55 (2.96)                 | 14.77 (2.91)                                        | 13.48 (3.43)                                      |
| Age (y) mean (SD)                          | 36.55 (11.02)                | 33.56 (9.17)                                        | 45.86 (9.57)                                      |
| Race n (%)                                 |                              |                                                     |                                                   |
| White                                      | 230 (84.87)                  | 246 (86.62)                                         | 135 (87.10)                                       |
| African American                           | 13 (4.80)                    | 8 (2.82)                                            | 2 (1.29)                                          |
| Other/unknown                              | 28 (10.33)                   | 30 (10.56)                                          | 18 (11.61)                                        |
| Follow-up time (y) mean (SD)               | 2.53 (1.14)                  | 2.51 (1.38)                                         | 1.24 (0.46)                                       |
| Number of evaluations n (%) 2 evaluations  | 74 (27.31)                   | 77 (27.11)                                          | 45 (29.03)                                        |
| n (%) 3 evaluations                        | 39 (14.39)                   | 44 (15.49)                                          | 24 (15.48)                                        |
| n (%) 4 evaluations                        | 25 (9.23)                    | 28 (9.86)                                           | 13 (8.39)                                         |
| n (%) >4 evaluations                       | 39 (14.39)                   | 41 (14.44)                                          | 19 (12.26)                                        |
| Conversion to MCI, n (%) <sup>a</sup>      | 12 (4.72)                    | 33 (11.62)                                          | —                                                 |
| Conversion to dementia, n (%) <sup>b</sup> | 0 (0)                        | 6 (2.11)                                            | 33 (34.38)                                        |

Abbreviations: CDR = Clinical Dementia Rating; DIAD = dominantly inherited Alzheimer disease; MCI = mild cognitive impairment.  
<sup>a</sup> CDR = 0 to CDR = 0.5.  
<sup>b</sup> CDR < 1 to CDR ≥ 1.

**Cognitive Reserve, Clinical Status, and Disease Progression**

To explore the effect of brain resilience (as measured by CogR) on clinical status and progression, we sought to explore the association between the components, baseline clinical status, and clinical progression. For the asymptomatic DIAD carrier, using the zero-inflation model and after adjusting by EYO, 1 SD increase in the reserve component would multiply the odds of being CDR-SB = 0 by 3.66 (95% CI 2.11–6.38), while 1 SD increase in demographic component and biomarker component will multiple the odds by 1.24 (95% CI 0.76–2.02) and 7.77 (95% CI 3.40–17.80), respectively (Table 2). Once symptomatic, only the reserve and the biomarker components were significant. One SD increase in reserve and in biomarker corresponds to a 0.83-fold (95% CI 0.75–0.92) and 0.60-fold (95% CI 0.52–0.69) decrease in baseline CDR-SB, respectively (Table 2).

Longitudinally, higher values of all 3 components were related to lower odds of converting to mild cognitive impairment or dementia (Table 3). All components increase the odds of CDR-SB staying at 0 significantly. One SD increase in reserve, demographic, and biomarker components corresponds to a 3.29-fold (95% CI 2.06–5.26), 1.52-fold (95% CI 1.04–2.23), and 11.82-fold (95% CI 5.67–24.63) increase in odds, respectively. After symptom onset, all components were associated with lower CDR-SB (Table 3), while only CogB is significant. One SD increase in CogB corresponds to

a 0.73-fold (95% CI 0.64–0.83) decrease in the overall CDR-SB score.

**Cognitive Reserve Modifies the Expected Age at Symptom Onset**

To explore whether cognitive reserve explains variability in expected age at symptom onset, 3 groups were defined based on the baseline CogR component by tertile cutoffs (high CogR, medium CogR, vs low CogR). Independent of the biomarker and demographic component, higher baseline CogR was significantly associated with higher odds of remaining asymptomatic (CDR-SB = 0), regardless of the variant expected age at symptom onset (Figure 2, top panel). Although not statistically significant, after symptom onset (CDR-SB>0), the high CogR group showed lower odds of progression. Corresponding plots for CogB and CogD tertile groups are also provided in eFigures 1 and 2.

**Longitudinal Changes in Cognitive Reserve**

In the linear mixed-effect model using a piecewise coefficient function centered at estimated age at onset (EYO = 0), DIAD carriers (MC) demonstrated significantly lower cognitive reserve at EYO = 0 compared with noncarriers (nMC). At EYO = 0, the estimated mean CogR is 0.75 for nMC and 0.49 for MC, reflecting a significant group difference of –0.26 (*p* = 0.0028). Before estimated age at onset (EYO <0), nMC showed an increase in CogR over time (0.033 per year, *p* < 0.001), which MC exhibited a significantly attenuated increase (slope difference = –0.017. *p* =

**Table 2** Relationships of Cognitive Components With Baseline Clinical Diagnosis in DIAD Carriers

| CDR-SB = 0                   |            |            |
|------------------------------|------------|------------|
| Characteristic               | Odds ratio | 95% CI     |
| Intercept                    | 0.52       | 0.30–0.91  |
| DIAN EYO                     | 0.85       | 0.79–0.91  |
| Reserve component (cogR)     | 3.66       | 2.11–6.38  |
| Demographic component (cogD) | 1.24       | 0.76–2.02  |
| Biomarker component (cogB)   | 7.77       | 3.40–17.80 |
| cogR:EYO                     | 1.07       | 1.02–1.13  |
| cogD:EYO                     | 0.99       | 0.95–1.04  |
| cogB:EYO                     | 1.06       | 0.98–1.14  |
| Cognition decline            |            |            |
| Characteristic               | Odds ratio | 95% CI     |
| Intercept                    | 1.04       | 0.90–1.21  |
| DIAN EYO                     | 1.05       | 1.03–1.07  |
| Reserve component (cogR)     | 0.83       | 0.75–0.92  |
| Demographic component (cogD) | 0.94       | 0.86–1.04  |
| Biomarker component (cogB)   | 0.60       | 0.52–0.69  |
| cogR:EYO                     | 1.00       | 0.98–1.01  |
| cogD:EYO                     | 0.99       | 0.98–1.01  |
| cogB:EYO                     | 0.97       | 0.96–0.99  |

Abbreviations: CDR-SB = Clinical Dementia Rating–Sum of Boxes; CogB = biomarker component; CogD = demographic component; CogR = cognitive reserve component; EYO = estimated years to symptom onset; OR = odds ratio; SE = standard error.  
CDR-SB was modeled using a 2-part hurdle log-normal mixed-effects model, with a logistic regression for zero scores and a linear mixed-effects model for log-transformed non-zero scores. In the first part, odds ratios >1 indicate higher likelihood of remaining unimpaired; odds ratios <1 in the decline model indicate slower progression. Models are adjusted for estimated years to symptom onset (EYO) and interaction terms between EYO and each cognitive component.

0.0011). After EYO = 0, nMC showed no significant change in CogR (slope =  $-0.009$ ,  $p = 0.504$ ), whereas MC demonstrated a significantly steeper decline (slope difference =  $-0.070$ ,  $p < 0.001$ ), suggesting a depletion of reserve mechanisms as the disease progresses and pathologic burden increases. Additional post hoc analyses examining longitudinal associations of CogB and CogD with CogR are provided in eTable 1.

## Discussion

This study presents novel evidence that cognitive reserve significantly modulates age at symptom onset and the rate of cognitive decline in individuals with DIAD. Our findings indicate that higher cognitive reserve values are associated with delayed conversion to mild cognitive impairment and slower progression on clinical dementia rating scales. These results

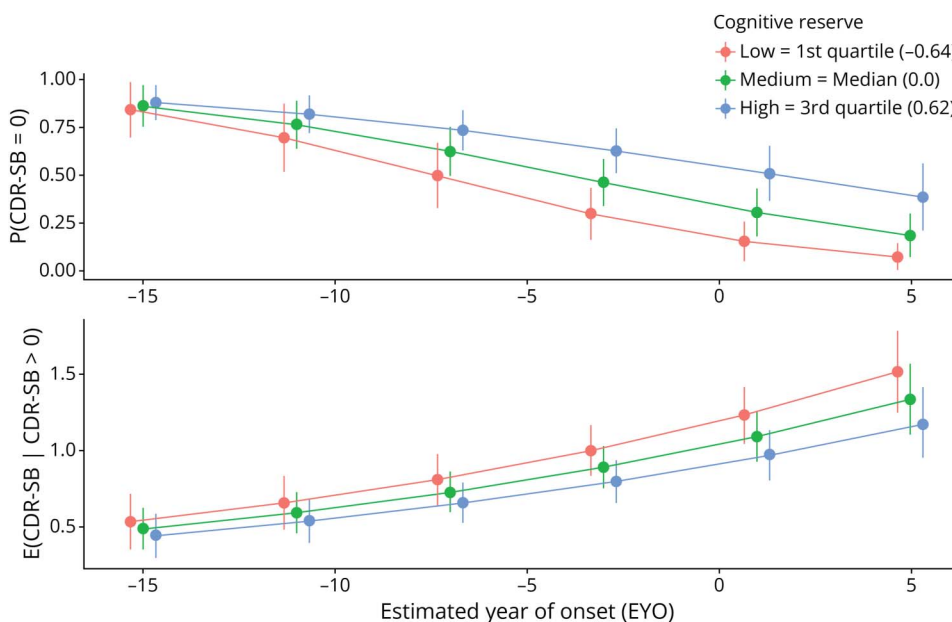
**Table 3** Relationships of Cognitive Components, Symptom Onset, and Longitudinal Decline in DIAD Carriers

| CDR-SB = 0                   |            |            |
|------------------------------|------------|------------|
| Characteristic               | Odds ratio | 95% CI     |
| Intercept                    | 0.39       | 0.26–0.59  |
| DIAN EYO                     | 0.78       | 0.73–0.83  |
| Reserve component (cogR)     | 3.29       | 2.06–5.26  |
| Demographic component (cogD) | 1.52       | 1.04–2.23  |
| Biomarker component (cogB)   | 11.82      | 5.67–24.63 |
| cogR:EYO                     | 1.07       | 1.02–1.12  |
| cogD:EYO                     | 0.97       | 0.94–1.01  |
| cogB:EYO                     | 1.12       | 1.04–1.21  |
| Longitudinal decline         |            |            |
| Characteristic               | Odds ratio | 95% CI     |
| Intercept                    | 1.15       | 1.01–1.30  |
| DIAN EYO                     | 1.11       | 1.09–1.12  |
| Reserve component (cogR)     | 0.92       | 0.85–1.01  |
| Demographic component (cogD) | 0.94       | 0.87–1.03  |
| Biomarker component (cogB)   | 0.73       | 0.64–0.83  |
| cogR:EYO                     | 1.00       | 0.98–1.01  |
| cogD:EYO                     | 0.99       | 0.97–1.00  |
| cogB:EYO                     | 0.95       | 0.94–0.97  |

Abbreviations: CDR-SB = Clinical Dementia Rating–Sum of Boxes; CogB = biomarker component; CogD = demographic component; CogR = cognitive reserve component; EYO = estimated years to symptom onset; OR = odds ratio; SE = standard error.  
CDR-SB was modeled using a 2-part hurdle log-normal mixed-effects model, with a logistic regression for zero scores and a linear mixed-effects model for log-transformed non-zero scores. In the first part, odds ratios >1 indicate higher likelihood of remaining unimpaired; odds ratios <1 in the decline model indicate slower progression. Models are adjusted for estimated years to symptom onset (EYO) and interaction terms between EYO and each cognitive component.

validate the hypothesis that cognitive reserve acts as a buffer against Alzheimer pathology, particularly when considering differences in age at symptom onset and the variability of disease progression among DIAD carriers and underscores the potential of cognitive reserve as a protective factor in AD. Our study supports and extends previous research, which has demonstrated similar protective effects of cognitive reserve in sporadic forms of AD but with the unique advantage of using DIAD that supports the study of cognitive reserve during symptomatic and asymptomatic phases of the disease. Moreover, consistent with our second hypothesis, we found that higher cognitive reserve was associated with slower rates of cognitive decline over time, indicating that even after the onset of symptoms, cognitive reserve continues to play a protective role by decelerating the progression of cognitive decline.

**Figure 2** Cognitive Reserve Levels and Clinical Progression Changes in DIAD



The top panel shows the probability of being unimpaired ( $P(\text{CDR-SB} = 0)$ ), and the bottom panel shows expected CDR-SB scores among impaired participants, plotted against estimated years to onset (EYO). Participants were divided into tertiles of cognitive reserve (low = red, medium = green, high = blue). Higher cognitive reserve was associated with an increased probability of remaining unimpaired and lower expected clinical severity across the disease continuum. Error bars represent 95% CIs. CDR-SB = Clinical Dementia Rating-Sum of Boxes; DIAD = DIAD = dominantly inherited Alzheimer disease.

Our study uses a residual-based quantification method for measuring cognitive reserve, an approach that offers several distinct advantages compared with traditional proxy variables such as education or occupational complexity.<sup>10,19,23</sup> By defining cognitive reserve as the variance in cognitive performance that remains unexplained after accounting for factors such as biomarker burden and demographic characteristics, we avoid the use of static proxies, which do not account for the influence of dynamic change ongoing behaviors or environmental factors across the life course. Using this approach, we were also able to capture changes in cognitive reserve, probably due to the effect of modifiable variables, which can change over time. At the same time, we recognize the potential disadvantages of the method. Particularly, the complexity involved in its measurement introduces a degree of uncertainty regarding what exactly is captured by the cognitive reserve estimate and its interpretation.

The delay in the age at symptom onset of symptoms in DIAD individuals with high-cognitive reserve can be attributed to several mechanisms, including compensatory brain networks, higher neural efficiency, enhanced synaptic density and plasticity, and improved vascular health.<sup>5,23,39</sup> It is hypothesized that these factors will contribute to mitigating the spread and progression of neuropathologic markers such as A $\beta$  and tau even in genetically predisposed populations such as DIAD carriers, contributing to a longer preclinical phase. Differences in the use of compensatory mechanisms in the context of cognitive reserve across individuals are likely the result of differences in genetic and lifestyle factors. Previous studies using the DIAN cohort have shown that ongoing lifestyle factors such as physical activity, education, and complex cognitive activities have been shown to enhance cognitive

reserve, even in the presence of early pathologic changes.<sup>40-42</sup> Similarly, genetic variants have been shown to significantly modify expected age at symptom onset, even in the context of this deterministic population.<sup>43-45</sup> Lifestyle and genetic factors are likely to facilitate the recruitment of compensatory mechanisms and vascular health optimization, preventing pathology spread, facilitating clearance, and compensating neurodegeneration. Overall, by leveraging this compensatory mechanism, individuals with higher cognitive reserve can tolerate accumulating AD pathology longer before reaching the threshold for clinical expression.

Our study also indicates that demographic factors, for example, age, sex, education, and SES, play a significant role in maintaining asymptomatic status in individuals with DIAD. This aligns with previous research that suggests that demographic factors contribute to resilience against brain aging. Notably, sex differences have also been found to influence cognitive resilience in DIAD, with female carriers demonstrating better cognitive performance compared with male carriers, hinting at a role for sex in cognitive reserve mechanisms.<sup>46</sup> However, after symptom onset, the demographic component's effect diminishes, with only the reserve (CogR) and biomarker (CogB) components remaining significantly associated with disease progression. This suggests that following symptom onset, the primary determinants of clinical progression are biological factors and cognitive reserve, not demographic factors. Thus, although demographic components may initially provide compensatory support against emerging pathology, once symptomatic thresholds are reached, the course of disease progression becomes more strongly tied to neuropathology and reserve capacities. Similarly, the effect of the reserve mechanism is attenuated after



symptom onset, coinciding with a decline in the cognitive reserve score. These findings suggest that as pathologic burden increases, reserve mechanisms become progressively depleted, triggering symptom onset in those with high-cognitive reserve.

The consistency of our findings with studies in sAD suggests that cognitive reserve acts universally across different AD forms, thus bridging an important gap in our understanding of resilience to neurodegeneration. In both DIAD and sAD, higher cognitive reserve delays age at symptom onset, even in the presence of significant pathology.<sup>5,24</sup> This provides a framework to link interventions targeting these modifiable factors to potentially impactful outcomes in both sAD and DIAD settings. Despite these similarities, our findings differ from research in sAD, where groups with proxies for higher cognitive reserve exhibit faster cognitive decline after symptom onset compared with their counterparts with lower cognitive reserve. Studies in sAD show that although cognitive reserve delays initial symptom onset, once symptoms emerge, individuals with high-cognitive reserve experience a steeper decline.<sup>47,48</sup> This pattern is believed to reflect the fact that these individuals reach a critical threshold of neuropathology later but decline more rapidly once compensatory mechanisms are exhausted. The key difference in our study of DIAD is related to the ability to predict the age at onset due to known family variants. This predictability allows for capturing the transition from presymptomatic phase to early symptomatic phase, which is difficult to do in sAD. In DIAD, we can study the transition from asymptomatic to symptomatic more precisely, observing the phase where compensatory mechanisms are still effective, even in the early symptomatic stages.

Although our findings provide valuable insights, there are limitations worth noting. One primary limitation is the relatively small sample size, especially in subgroups with distinct cognitive reserve characteristics (high vs low), which limits the power of subgroup analyses. The DIAD cohort, while providing an excellent model for studying resilience in AD, consists of individuals with a rare genetic form of AD, which limit the generalizability of our findings to sAD cases. In addition, residual-based approaches to quantifying cognitive reserve are influenced by the specific predictors and outcomes included in the model, which may limit comparability across studies. Future work should seek to replicate these findings using harmonized methods across sAD cohorts to better delineate shared and distinct effects of reserve on disease progression. Finally, because higher cognitive reserve delayed symptom onset and slowed progression despite similar biomarker burden, our model likely reflects both resistance and resilience mechanisms, and future work should disentangle these processes to clarify how cognitive reserve operates in AD.

Despite these limitations, this study presents several key strengths. One of the main strengths is the ability to study

presymptomatic and early symptomatic phases due to the predictability of variant-specific age at onset, which allows capturing a critical window where compensatory mechanisms are still active. Unlike sAD, where the timing of onset is variable and often studied only after significant pathology has accumulated, this predictability provides unique insights into the early dynamics of cognitive reserve and disease progression. Another advantage is the use of a residual-based approach to quantify cognitive reserve, allowing for the assessment of individual differences beyond traditional demographic proxies. This approach provided a more nuanced understanding of how cognitive reserve interacts with biomarkers and demographic factors across different stages of DIAD.

In conclusion, the study significantly advances our understanding of the role of cognitive reserve in AD. It reinforces the concept that cognitive reserve is an influential factor in modulating the clinical course of AD. Future studies should elucidate the mechanisms through which cognitive reserve affects disease progression and better understand the potential for cognitive reserve-focused interventions to alter the course of AD across different populations. Future directions should explore the molecular and genetic pathways contributing to cognitive reserve in this cohort. Understanding how certain lifestyle factors translate to neuroprotection on a molecular level might yield biomarkers that are useful in identifying individuals at risk and tracking the effects of interventions.

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## Author Contributions

J.J. Llibre-Guerra: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. R. Lu: analysis or interpretation of data. M.F. Clarens: drafting/revision of the manuscript for content, including medical writing for content. I. Liu: analysis or interpretation of data. A. Renton: drafting/revision of the manuscript for content, including medical writing for content. N.S. Ryan: drafting/revision of the manuscript for content, including medical writing for content. A.M. Goate: drafting/revision of the manuscript for content, including medical writing for content. D. Aguillón: drafting/revision of the manuscript for content, including medical writing for content. R.F. Allegri: drafting/revision of the manuscript for content, including medical writing for content. T.L.S. Benzinger: drafting/revision of the manuscript for content, including medical writing for content. S. Berman: drafting/revision of the manuscript for content, including medical writing for

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