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RESEARCH ARTICLE

Generational effects in Down syndrome: Enriched environment enhances functionality without reducing Alzheimer's disease risk

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Abstract

INTRODUCTION: Down syndrome (DS) is the leading cause of intellectual disability (ID) and a genetic form of Alzheimer's disease (AD). We wanted to assess whether generational changes have induced (1) milder ID with greater independence and (2) delayed AD diagnosis.

METHODS: We analyzed 681 asymptomatic DS to test generational effects on ID, functionality, and cognition. In 353 DS individuals with AD, we compared clinical diagnosis age by ID using analysis of variance. In addition, dementia diagnosis age was examined through a published meta-analysis.

RESULTS: Our results indicate a generational shift toward a higher proportion of individuals with mild/moderate ID, greater intelligence, and autonomy. However, it was not paralleled by an ID-related delay in the age at AD onset in our cohort, or by generational delays reported over the past 35 years.

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DISCUSSION: The findings highlight notable generational improvements in DS, but no effects on the age at AD dementia diagnosis.

KEYWORDS
Alzheimer's disease (AD), Down syndrome (DS), functionality, intellectual disability (ID), intelligence

Highlights

- A generational effect has reduced the severity of intellectual disability in Down syndrome (DS).
- Individuals with DS have increased autonomy and improved intellectual milestones.
- The enriched environment has not delayed the age at Alzheimer's disease (AD) dementia in DS.
- Further studies should confirm if cognitive reserve might delay AD in DS.

1 | BACKGROUND

Down syndrome (DS) affects ≈6 million people worldwide.[1] It is the most common genetic cause of intellectual disability (ID), resulting from an extra copy of chromosome 21.[2] The full trisomy is present in more than 95% of cases, with this genetic imbalance[3] being the primary cause of neurodevelopmental alterations. Despite ID being the most prevalent phenotype of DS,[4] its degree and manifestation vary among individuals with the trisomy. Advancements in health care have significantly increased the life expectancy of individuals with DS, now averaging around 60 years.[5] As a result, addressing the challenges of aging in this population, particularly Alzheimer's disease (AD), has become increasingly urgent, being the proximate cause of death in 70%–80% of these individuals.[6] The triplication of chromosome 21, which results in an extra copy of the *amyloid precursor protein* (*APP*) gene,[3] is both sufficient and necessary to cause AD pathology in DS,[7] leading individuals with DS to have a >90% lifetime risk of AD.[8] The natural history of DS-associated AD (DSAD) follows a sequence of events (both biomarker alteration and clinical changes) that begins over two decades before the onset of dementia, mirroring the order observed in autosomal dominant AD (ADAD).[7,9,10] The age at symptom onset is as predictable in DS as in ADAD[6] and, on average, 20–30 years younger than in sporadic late-onset AD (LOAD). However, there remains considerable variability[11] in the age at onset of dementia diagnosis. Protective or risk factors could partially contribute to this variability but remain largely unexplored in this population.

The theoretical construct of "cognitive reserve" (CR) provides a framework for investigating the gap between pathological changes and clinical manifestations, and the significant heterogeneity increases in cognitive profiles that emerge across the lifespan. CR is defined as a "resilience" mechanism that allows a successful adaptation of cognitive resources to compensate for brain damage, resulting in a better-than-expected cognitive level given a degree of pathology. Within the broader concept of resilience, "brain reserve" captures the neurobiological status of the brain (i.e., its characteristics measured at any given time).[12] Complementing this, "resistance" denotes biological or environmental factors that slow or diminish the accumulation of AD pathology (i.e., modulation of amyloid beta or tau accumulation) in the presence of the disease.[12,13,14]

Thus, both "resistance" and "resilience" have been associated with high cognitive performance, reduced cognitive decline, and lower dementia risk in later life.[13,14] CR is typically measured through potential proxies, including educational attainment, estimated premorbid intelligence, occupational complexity, and engagement in cognitive-intellectual activities.[14] According to the Lancet Commission, extensive epidemiological evidence supports the association between various protective lifetime exposures and a reduced incidence of age-related dementia.[15,16]

There is growing interest in understanding how CR influences brain and cognitive development across the lifespan.[17] Notably, in 2023, a working group was established under the umbrella of the Alzheimer's Association International Society to Advance Alzheimer's Research and Treatment (ISTAART) to advance research on "resistance" and "resilience" to DSAD, culminating in a consensus publication.[18] However, the study of protective factors in terms of their impact on a developmental disorder like DS and their effect on AD development in this population remains largely underexplored.[19] In this context, it is well known that in recent decades, individuals with DS have experienced improvements in access to and quality of stimulating cognitive and social activities, driven by increased employment opportunities[20] and greater investment in community support resources.[21] Moreover, concurrent advances in medical care (i.e., earlier detection and surgical correction of congenital heart defects[22]) expanded early intervention and parent-mediated therapies and inclusive education policies.[23] Therefore, we hypothesize that this enriched environment has contributed to generational improvements, resulting in individuals from

more recent birth exhibiting lower ID levels and better cognitive profiles. In addition, we propose that ID, as a proxy for CR analogous to premorbid intelligence quotient (IQ), may influence the age at symptom onset of AD in DS. Our primary objectives are to (1) examine whether an enriched environment has led to generational improvements in ID levels and (2) investigate whether ID might influence the clinical onset of AD. We also studied generational changes in the age at AD dementia diagnosis in the literature in the last 35 years.

RESEARCH IN CONTEXT

1. **Systematic review**: In recent decades, individuals with Down syndrome (DS) have gained access to enhanced cognitive and social opportunities, including increased employment and community support resources, enriching their life experiences. A literature search was conducted using PubMed, and the extent to which these generational improvements reduce the degree of intellectual disability (ID) and increase autonomy in individuals with DS remains unknown.
2. **Interpretation**: We corroborated a generational effect in individuals with DS with major changes in the degree of ID, the independence in activities of daily living, and the intelligence quotient but not the penetrance of symptomatic Alzheimer's disease (AD) diagnosis.
3. **Future directions**: Longitudinal studies including biomarkers are needed to better understand the putative resilience and resistance mechanisms against AD in DS, assessing the interplay of biological, cognitive, and environmental factors, leading to a significant advancement in primary prevention strategies.

2 | METHODS

2.1 | Study design

This study included a subset of participants from the longitudinal, prospective cohort of adults with DS recruited through the Down Alzheimer Barcelona Neuroimaging Initiative (DABNI) in Barcelona, Spain, which began in 2014.[10] The DABNI cohort integrates a population-based health plan designed for screening neurological complications in the DS population (notably AD). In this cohort, participants are referred for semiannual or annual visits. Inclusion criteria were (1) having DS (including all levels of ID) and (2) age ≥18 years.

To address our first aim—assessing the generational effect—we analyzed the initial visits of DS individuals without AD symptoms. For the second objective—trying to detect an effect on AD clinical manifestation—we used the first visit with an AD dementia diagnosis for each patient, based on all diagnoses during the 10-year DABNI study. It is important to note that we excluded all those visits in which participants had an uncertain diagnosis or non–AD-related neurocognitive disorder (i.e., a medical, pharmacological, or psychiatric condition interfering with cognition and/or activities of daily living, but no suspicion of AD). Figure S1 shows the sample flowchart.

The study was approved by the Sant Pau Research Ethics Committees, following the standards for medical research in humans recommended by the Declaration of Helsinki. All participants or their legally authorized representatives provided written informed consent before enrollment.

2.2 | Clinical assessment

The study procedures included medical/neurological and neuropsychological visits. The medical visit consists of a structured anamnesis with the patient and his caregiver, performed by expert neurologists, including The Cambridge Examination for Mental Disorders of Older People with Down Syndrome and Others with Intellectual Disabilities (CAMDEX-DS) interview,[24,25] a physical examination, and the collection of demographic data, and clinical and neurological history. The data collected from the informant's structured interview, encompassing questions about intellectual milestones achieved and daily life activities, were utilized to assess the intellectual profile and functional level in the present study. In addition, variables such as type of school, occupation, and bilingualism were analyzed as proxies for CR.

The ID level was categorized as mild, moderate, severe, or profound, based on caregivers' reports of the individuals' best-ever level of functioning across the conceptual, social, and practical domains, following criteria outlined in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5).[26] This classification was informed by clinician judgment through caregiver interview. The score of the Kaufman Brief Intelligence Test (KBIT) Spanish version,[27] which was evaluated in the first neuropsychological visit, provided additional insight into cognitive functioning, particularly in the conceptual domain, and served as a proxy for premorbid cognitive level in our clinical context (for further details regarding ID level assessment see ref. [28]). In addition, in our analyses, KBIT measures were analyzed through two subscales: vocabulary and matrices. The vocabulary evaluates verbal intelligence and the breadth of word knowledge, assessing language comprehension, lexical knowledge, and verbal expression abilities. In contrast, the matrix reasoning subscale assesses nonverbal problem-solving and abstract reasoning, evaluating skills such as pattern recognition, logical reasoning, and the ability to understand relationships between shapes and designs without relying on language. Together these subscales provide a balanced overview of an individual's verbal and non-verbal cognitive strengths.

The clinical classification along the AD continuum was first performed independently by the neurologist and neuropsychologist followed by a consensus meeting to determine the final diagnosis. Global cognition was assessed, using a Spanish version of the Cambridge Cognitive Examination for Older Adults with Down syndrome (CAMCOG-DS) Spanish version, which is an adapted cognitive battery.[29] Thus, at each visit, the participants were clinically classified into three

groups along the AD continuum: (1) asymptomatic: no clinical or neuropsychological suspicion of symptomatic AD (absence of cognitive impairment beyond the ID or functional decline compared to previous functioning); (2) prodromal AD: suspicion of AD-related cognitive impairment, but symptoms did not fulfill criteria for dementia (no additional functional impairment); and (3) AD dementia: full-blown AD dementia (evidence of cognitive impairment that interfered with everyday activities beyond the basal functioning).

2.3 | Statistical analyses

All statistical analyses were performed with R version 4.3.3 (R foundation for statistical computing). To assess the descriptive statistics for the baseline data, we performed analyses of variance (ANOVAs) for numerical variables and chi-square test (χ^2) for categorical variables. Density plots were created as a visual tool to display frequency differences across birth years in relation to ID level, intellectual milestone acquisition, and the maximum level of autonomous functionality reached. In addition, a stacked bar chart was used to represent the distribution of ID levels by decades of birth. To test the association between decade of birth and ID, χ^2 test was conducted. To investigate the relationship between the birth year and subscales of the KBIT raw scores, locally estimated scatterplot smoothing (LOESS) curves—with a tricubic weight function and a span parameter of 0.75—and linear models were conducted. ANOVA was conducted to compare the age at AD clinical diagnosis across the four ID levels. Finally, we created a LOESS plot to illustrate the relationship between the mean age at symptom onset of DSAD and the publication year of the studies included in a previous meta-analysis conducted by our group.[6] All statistical analyses were performed using two-sided tests with a level of significance at $p < 0.05$.

3 | RESULTS

3.1 | Population

A total of 1002 participants with DS were included in our study (see Tables 1 and S1 for further details regarding comorbidities in our sample). For the first aim, a cross-sectional subset was selected, consisting of the first visit of 681 individuals with DS who showed no clinical symptoms of AD (excluding prodromal AD and AD dementia diagnosis; see Table 1).

This sample of DS asymptomatic for AD (see Tables 1 and S2) had a mean age of 37.47 ± 10.31 years and an approximately equal distribution of sexes (45.08% female, 54.92% male). The participants were divided into ID groups with the following distribution: 25.25% mild ($N = 172$), 46.55% moderate ($N = 317$), 18.50% severe ($N = 126$), and 9.70% profound ($N = 66$). Regarding age, there were significant differences across ID levels ($t = 45.289$, $p < 0.001$), with mild ID individuals being younger (mean age: 35.18 ± 9.61 years) and the severe ID group being older (mean age: 40.55 ± 11.13 years). In addition, the distribution of sex varied ($\chi^2 = 16.579$, $p < 0.001$), driven by an imbalance in the profound ID group, where males comprised 74.2%. The proportion of apolipoprotein E (*APOE*) ε4 carriers and non-carriers was equal across groups ($p = 0.376$).

TABLE 1 Study participants.

	Asymptomatic $N = 681$	Prodromal AD $N = 105$	AD dementia $N = 216$	*p*-value
AGE				< 0.001***
Mean (SD), years	37.5 (10.3)	50.9 (5.02)	53.5 (5.77)	
SEX				0.519
Female, *n* (%)	307 (45.1%)	52 (49.5%)	105 (48.6%)	
ID				< 0.001***
Mild, *n* (%)	172 (25.3%)	14 (13.3%)	15 (6.9%)	
Moderate, *n* (%)	317 (46.5%)	61 (58.1%)	124 (57.4%)	
Severe, *n* (%)	126 (18.5%)	24 (22.9%)	65 (30.1%)	
Profound, *n* (%)	66 (9.7%)	6 (5.7%)	12 (5.6%)	
APOE				0.132
ε4 Carriers, *n* (%)	76 (10.3%)	21 (16.2%)	31 (16.2%)	
Progressors				
to prodromal AD, *n* (%)	95 (14%)	–	–	–
to AD dementia, *n* (%)	65 (9.5%)	72 (68.6%)	–	–
Visits				< 0.001***
Mean (SD)	5.10 (3.59)	7.01 (4.89)	5.14 (4.14)	

Note: Continuous data are mean (SD) and categorical data are *n* (%).
Abbreviations: AD, Alzheimer's disease; *APOE*, apolipoprotein E; ID, intellectual disability; SD, standard deviation.
Statistical differences with asterisks denoting significance thresholds:
***($p < 0.001$)
**($p < 0.01$)
*($p < 0.05$)

The sample for the second aim comprised a subset of 353 DS patients with a clinical diagnosis of AD dementia. This group included the participants diagnosed with AD dementia at their first visit ($N = 216$), as well as asymptomatic individuals ($N = 65$) and those with prodromal AD ($N = 72$) who progressed during follow-up visits (see Tables 1 and S3 and Figure S1 for further details).

3.2 | Generational effect on ID level

We first performed a smooth density plot showing the distribution of the four degrees of ID along the birth year (from 1952 to 1996), which evidenced an increase in the proportion of individuals with mild or moderate ID and a decrease in those with profound or severe levels of ID (Figure 1A). To further explore this finding, we divided the

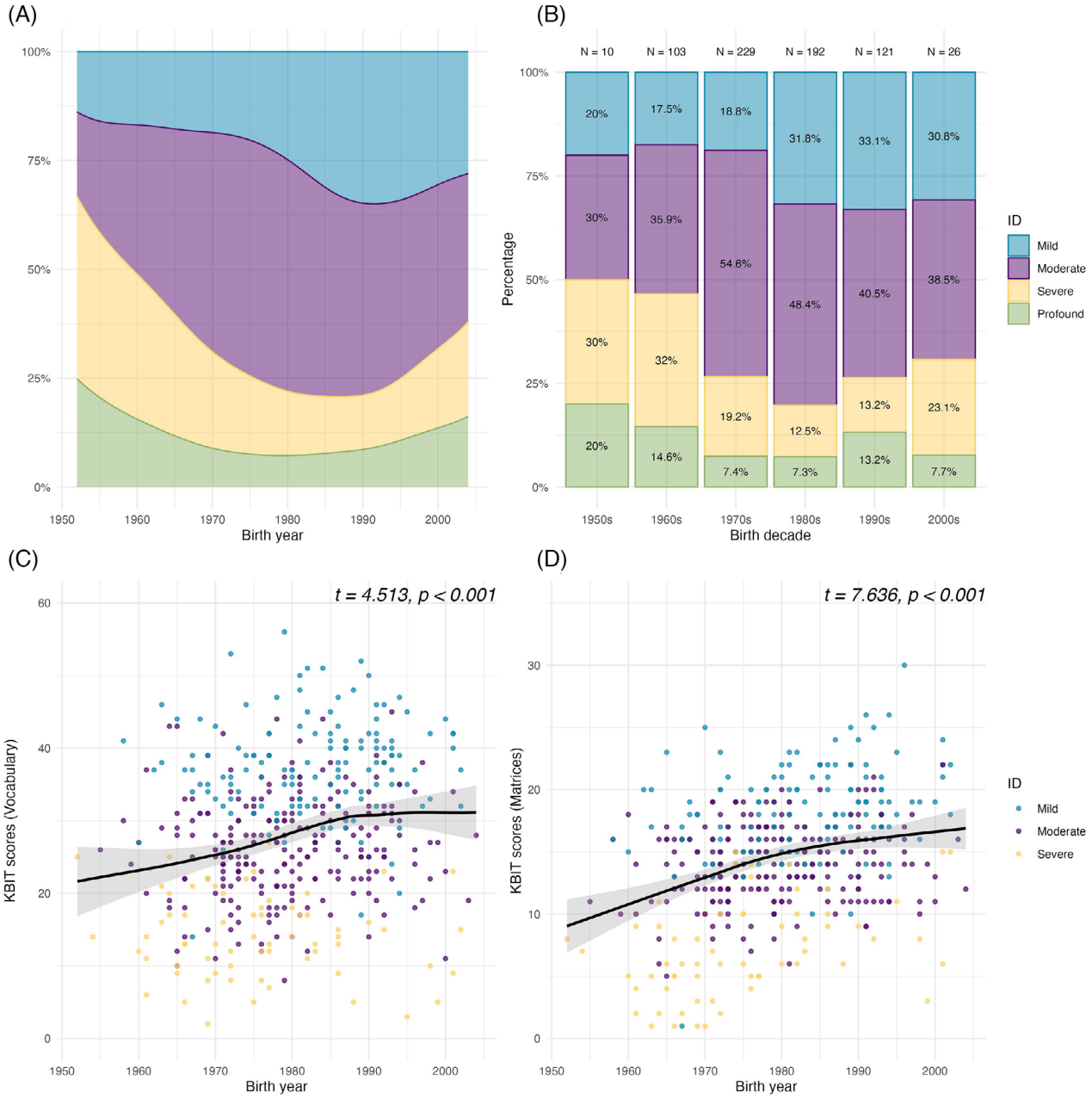

FIGURE 1 Generational effect on ID level and KBIT scores. Upper panel: plots showing the percentage distribution of the four degrees of ID (mild, moderate, severe, and profound) (A) along the birth year (from 1955 to 1995) with a smoothed density plot and (B) by decades of birth (from the 1950s to 1990s) using a stacked bar chart. Lower panel: plots illustrate the association between KBIT (C) vocabulary and (D) matrices scores by birth year across ID levels (mild, moderate, severe). Individual data points are colored by ID groups, whereas a LOESS smoothing curve (black line) highlights the overall trend, with confidence intervals shaded in gray. Subsample of $N = 455$ asymptomatic DS, split by ID level: mild ($N = 147$), moderate ($N = 239$), and severe ($N = 69$). Raw scores are displayed for KBIT vocabulary and matrices. DS, Down syndrome; ID, intellectual disability; KBIT, Kaufman Brief Intelligence Test; LOESS, locally estimated scatterplot smoothing.

sample by decade of birth (1950s–2000s) and analyzed the percentage of subjects in each ID level. The results showed a marked generational (decade of birth) effect on the distribution of IDs ($\chi^2 = 45.041$, $p < 0.001$; Figure 1B).

Moreover, since KBIT scores were used to categorize asymptomatic individuals across different ID levels, the relationship between this variable and the year of birth in the sample was examined. After excluding participants with outlier values or a floor effect (i.e., those in the profound ID group), a total of 455 participants were included in the regression analysis (see Figure S1 and Table S4). The results revealed a significant positive relationship between the year of birth and both the verbal (KBIT vocabulary: $t = 4.513$, $p < 0.001$; Figure 1C) and non-verbal (KBIT matrices: $t = 7.636$, $p < 0.001$; Figure 1D) subscales, indicating that later years of birth were associated with higher KBIT scores.

Of note, the aforementioned generational trend for ID levels reversed in those born after the year 2000, but we did not see this effect in the KBIT measures.

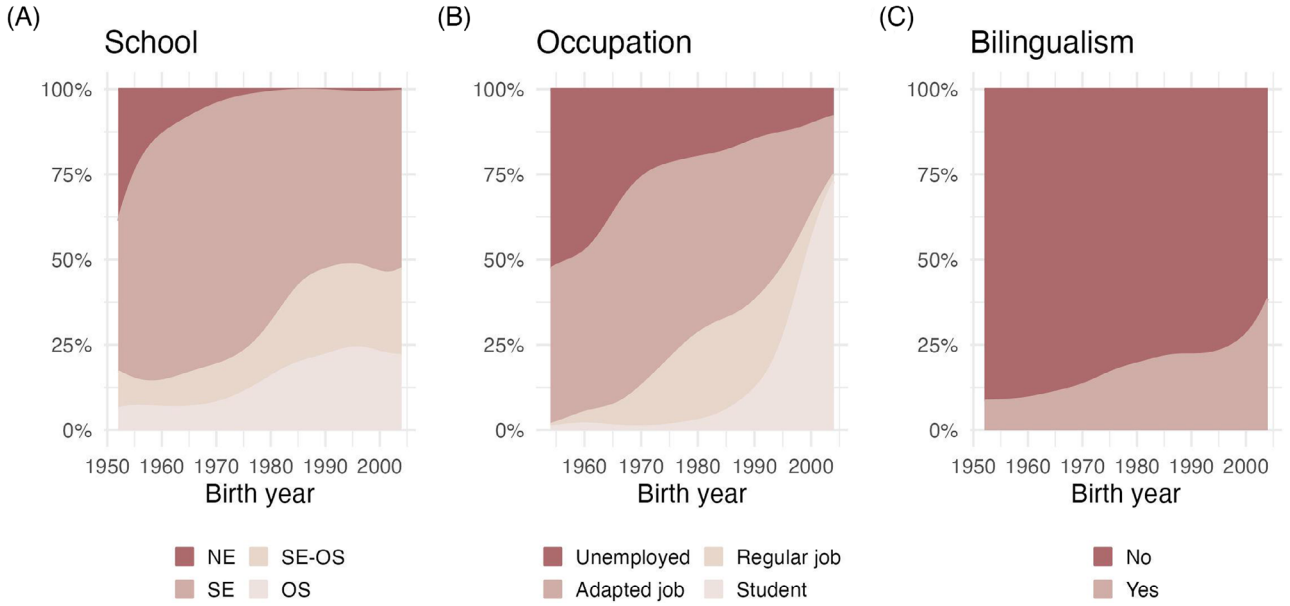

FIGURE 2 Generational effect on schooling, occupation, and bilingualism. The density plots show (A) the type of school, (B) the job status (unemployed, adapted, or regular job, and student), and (C) being or not bilingual as a function of the birth year. Data reported by their caregivers. Plots are based on complete-case data for the specific variables displayed (missing participants ≈10%). NE, non-educated; OS, ordinary school; SE, special education; SE-OS, special education in ordinary school.

3.3 | Generational effect on schooling, occupation, and bilingualism

Furthermore, a generational shift was observed in the variables commonly used as proxies for CR, which may themselves contribute to the generational effect assessed. Regarding the type of school attended, our data revealed that in later birth cohorts, the previously significant percentage of non-schooling (nearly 50% in those born in 1950) dropped to zero after 1980, whereas there was a notable increase in the rate of individuals with DS who attended regular classrooms, either partially or fully (Figure 2A). Furthermore, we confirmed changes in occupational status across different birth years, observing, as expected, a higher proportion of students among younger cohorts, alongside a notable decrease in unemployment rates across generations (Figure 2B). Finally, the number of individuals with DS in our cohort who were bilingual also showed an increase over time (Figure 2C).

3.4 | A higher proportion of individuals acquired intellectual milestones and developed day-to-day function

Similarly, a greater proportion of individuals achieved intellectual milestones, including calculation, language, literacy, writing, reading, and comprehension (Figure 3A–F). In addition, a higher percentage of individuals developed daily living skills autonomously as a function of their birth year (Figure 3G–L). As with the ID levels, the aforementioned generational trend partially reversed in those born after the year 2000.

In addition, we conducted two extra analyses. On the one hand, we divided the sample by sex, operating under the hypothesis that the caregivers could potentially exhibit varying degrees of protectiveness or autonomy limitations based on the DS individual's sex. However, we observed that the trend mirrored that of the overall sample (see Figures S2–S5). On the other hand, we explored how individuals' birth year and ID level together shape the generational effect on the acquisition of intellectual and functional abilities. All groups showed clear positive cohort gains in both intellectual milestones and daily living activities, consistent with what would be expected based on their level of ID (see Figures S6–S8).

3.5 | The age of AD clinical onset in DS is not influenced by ID and has remained stable over decades

The group comparison on the age at AD dementia diagnosis ($N = 353$; see Table S3 for subsample characteristics) did not identify significant differences across ID levels ($p = 0.851$; Figure 4A). The same analysis performed for the prodromal AD age at diagnosis by ID level was displayed in the supporting information (Figure S9). Additionally, in a supplementary analysis we found that *APOE* status did not influence the age at clinical onset of either prodromal AD or AD dementia when its interaction with ID level was examined (see Figure S10).

Finally, to broaden our analysis beyond data from our cohort, we explored the relationship between the mean age at onset of AD in DS and the year of study publication across 44 articles ($N = 2,695$ individuals) included in a meta-analysis by Iulita et al.[6] The resulting plot reveals

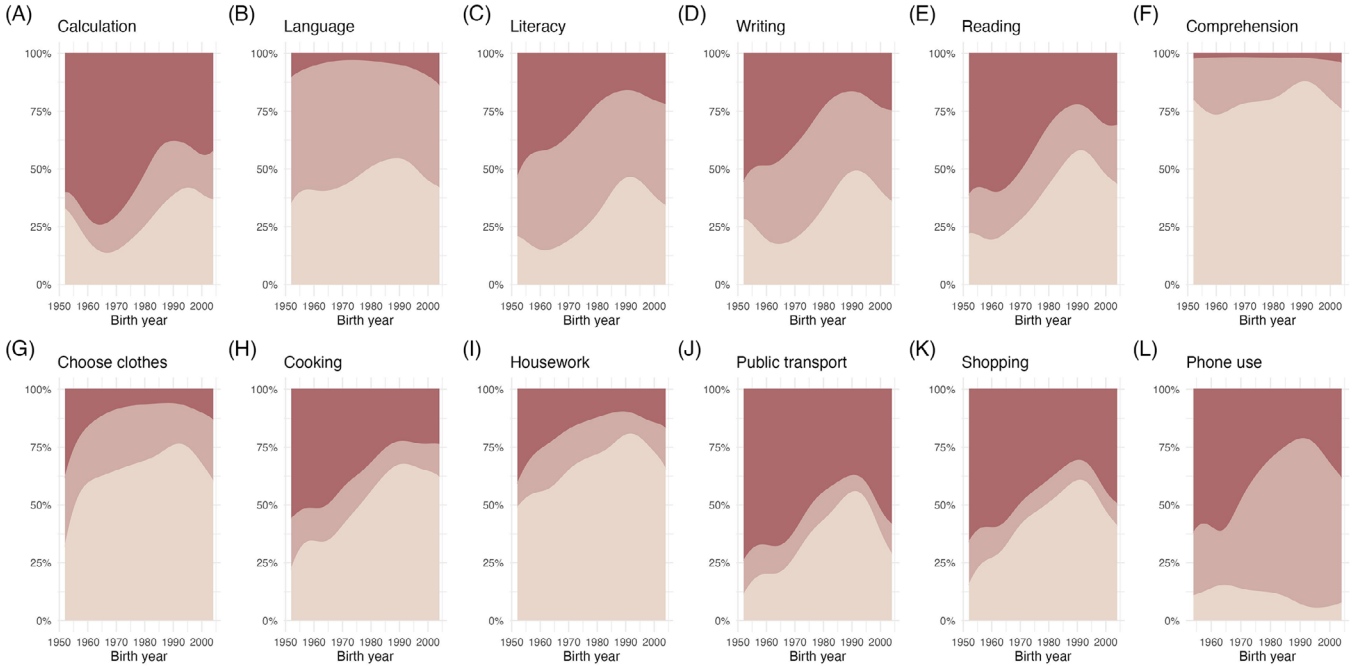

FIGURE 3 Generational effect on intellectual milestone acquisition and day-to-day function autonomy. Smooth density plots display in the upper panel (A)–(F) the distribution of the acquisition, partial acquisition, or not, of intellectual abilities. In the lower panel, (G)–(L) the plots show if the individuals were capable, partially capable, or not capable of carrying out these tasks autonomously. The darker color represents the percentage of individuals who have never acquired this ability, the medium shade indicates those who have partially acquired it, and the lighter color shows the percentage who have achieved this intellectual milestone or have been able to do a day-to-day function autonomously at some point in their lives (at their highest functioning level reported by their caregivers). The categorization for intellectual abilities was based on the Spanish version of CAMDEX-DS. Plots are based on complete-case data for the specific variables displayed (missing participants <5%). Cambridge Examination for Mental Disorders of Older People with Down Syndrome and Others with Intellectual Disabilities.

a flat association, suggesting an absence of a generational effect when considering published data from the past three decades (Figure 4B).

4 | DISCUSSION

The present study provides evidence for a dramatically changing scenario of enhancement in the lives of individuals with DS in the last decades. We observed marked improvements in ID levels and independence in activities of daily living as a function of birth year, but no clear impact on the age at AD dementia diagnosis over the last 35 years.

The degree of ID associated with DS is inherently unique to each individual. However, our findings highlight a significant generational shift in the distribution of ID severity, showing an increased proportion of individuals being diagnosed with mild or moderate ID and a corresponding decrease in those with profound or severe ID. This is further supported by concurrent increases in KBIT scores and a higher proportion of individuals in later birth years achieving key intellectual milestones and developing daily living skills autonomously. Of interest, this trend peaked among individuals born in 1990 for ID and intellectual profile, but importantly, not for KBIT scores. Our interpretation is that the youngest individuals in our study may not have yet reached their full level of functional independence, which could lead us to underestimate their ID. Furthermore, these results could be biased by the modest sample size in the more recent decades. The decoupling of the aforementioned trends and the KBIT scores (that do not reverse) make less plausible the *"Reversal Flynn Effect"*[30] observed in the general population. In addition, we cannot rule out the possibility that generations born since the 1990s are highly digitized, with screen time potentially displacing other cognitively and socially enriching activities.

In addition, the drastic decline in non-schooling rates and the increase in attendance in regular classrooms for those born after 1980, reflect broader societal changes in inclusion and access to education for individuals with DS. It is worth noting that adapted education programs in Spain are particularly successful, and that although these results are broadly comparable across high-income countries, significant differences might still exist between nations, even among developed ones. These changes were paralleled by increases in the number of bilingual people. Bilingualism might help to compensate for the development of AD neuropathology, delaying the emergence of clinical symptoms up to 4–5 years in the general population.[31] Overall, although plasticity mechanisms are limited in individuals with DS, contributing to their characteristic cognitive deficits,[32–34] our findings suggested that they are benefiting from environmental enrichment. This provides grounds for optimism regarding the effectiveness of interventions aimed at enhancing cognitive function and fostering social and leisure activities. Moreover, it reinforces the necessity of increasing access to education and employment opportunities for

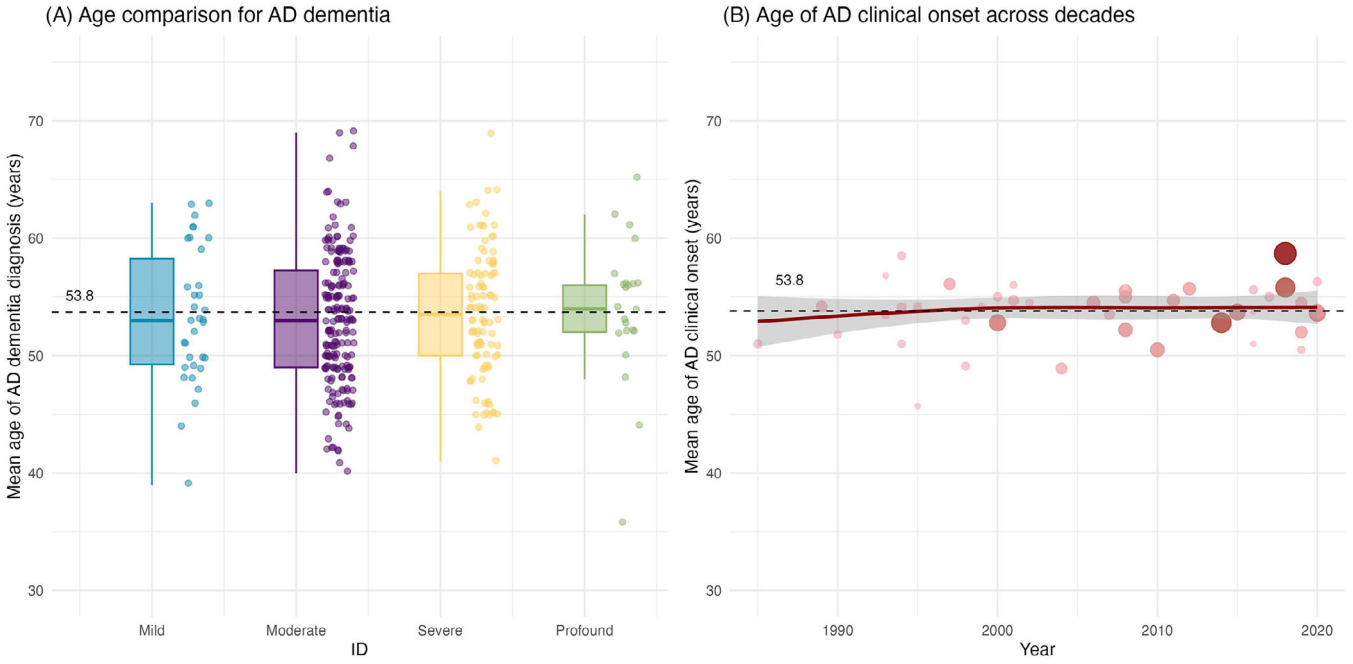

FIGURE 4 Age at AD clinical onset in DS by ID and over decades. (A) Boxplot of mean age on clinical diagnosis for AD dementia ($N = 353$) by ID level: mild ($N = 34$), moderate ($N = 196$), severe ($N = 100$), and profound ($N = 23$). Jittered points display individual data within each group. The dashed line shows the estimated age at onset for AD dementia (53.8 years). (B) Scatterplot depicting the relationship between the mean age at onset of AD in DS and the publication year of the 44 studies. Point size and color reflect the number of individuals in each study. The LOESS curve (in red) shows the trend over time, with a dashed line at 53.8 years representing the pooled mean age with the confidence interval shaded in grey. See Iulita et al.[6] for further details. AD, Alzheimer's disease; ID, intellectual disability.

adults with DS, as they still do not participate to the same degree as the general population.[35]

Notably, our exploratory analysis of sex differences did not reveal significant deviations from the overall generational trends. The findings showed that the percentage of men with profound ID was higher in the older generations, but the proportion of mild/moderate cases was progressively aligning with that observed in women over the decades. Overall, the observed advantages appeared to apply equally to both sexes, suggesting that the fact that, historically, women have had less access to CR contributors, potentially explaining their increased risk of AD,[36] is not reflected in the DS population. Our results examining the joint effects of birth year and ID revealed that generational gains were uniform. However, interpreting subgroup effects by ID level requires caution, since lower-severity individuals inherently attain more education, enter more complex occupations, and exhibit higher baseline functioning. Disentangling true enrichment effects from preexisting cognitive capacity will therefore require alternative reserve markers (e.g., neurobiological measures of resilience) to clarify the causal pathways linking environmental enrichment, ID level, and intellectual-functional outcomes.

The findings from our second aim revealed that the age at dementia diagnosis was consistent across ID levels, which contrasts with theoretical expectations suggesting that greater functionality and intellectual abilities (e.g., individuals with mild ID) might delay the clinical manifestation of AD symptoms.[14] However, aligned with our findings, a recent publication based on a cross-sectional study involving a large multicenter DS sample found no differences in the average age of individuals with prodromal AD or AD dementia by ID.[37] Nonetheless, a previous study assessing the effect of leisure activities (i.e., CR proxy) in DS[38] and employment complexity[39] on dementia symptoms, showed protective effects on AD-related cognitive decline. It is worth noting that the studies comparing AD progression by premorbid ID level in DS have also shown mixed results,[10,25,37,40] but predominantly showed no differences by ID levels. In the general population, a strong association between higher intelligence and a reduced risk of AD symptoms has been repeatedly reported (e.g., ref. [41]). Furthermore, higher educational levels and greater occupational complexity—variables where we have detected a generational effect—have been linked to increased resilience against AD-related pathology in LOAD (e.g., ref. [42]). Parallel findings in autosomal dominant AD exist, demonstrating that each additional year of education delays the onset of cognitive decline,[43] or that greater CR slows the rate of longitudinal deterioration in mutation carriers.[44] In support of these human observations, APP/PS1 transgenic mouse studies have revealed that environmental enrichment not only reduces cerebral amyloid beta accumulation and boosts neurogenesis but also enhances cognitive performance,[45] suggesting that enrichment-driven reserve mechanisms may postpone clinical dementia onset in DSAD. Besides, in our supplementary analysis of *APOE* status, $\varepsilon 4$ carriers showed no overall effect on age at prodromal or AD dementia onset across ID levels. However, sensitivity analyses restricted to mild and moderate ID individuals indicated an earlier onset in carriers.[46] This finding underscored the need for cautious

interpretation and further investigation in larger, well-characterized samples, to examine the gene–environment interaction, and in which it should also be possible to test the demonstrated gene–dose effect of *APOE* in the euploid population.[47]

Aligned with our lack of results on the effects of ID level and clinical AD onset, we observed no changes in the age at dementia diagnosis reported in the last 35 years across studies, including more than 2500 individuals from population-based or convenience cohorts and epidemiological registers or clinical records.

The present work also has some limitations that lay the groundwork for future research based on the findings obtained. First, although this study utilized a well-characterized large cohort, the generational effect studied is closely linked to cultural differences and socioeconomic status. Therefore, future research should replicate these findings in other cohorts accounting for the disparities between high- and low-income countries, which is particularly important given that around 80% of people with disabilities live in low- and middle-income countries.[48] Furthermore, studies involving ethnically diverse populations are needed, and it is important to highlight that culture-dependent factors such as parental authority/permissiveness in determining daily life activities that can be done autonomously also contribute to the difficulty of comparing populations. In this regard, population-based studies are essential to establish consensus across centers for objectively determining ID categorization.[28] Second, because we are investigating a potential generational effect, it is possible that not enough time has passed to observe clear impacts on AD manifestation. This fact might also explain the lack of significant findings in the meta-analysis. The sample included a relatively small number of individuals with severe ID and even fewer with profound ID levels. In addition, these individuals are particularly challenging to evaluate, and establishing a clinical diagnosis of AD in these highly disabled subgroups poses a significant limitation in accurately determining their clinical onset. In this light, incorporating biomarker information would enhance risk stratification for individuals and allow for the testing of resilience mechanisms using robust methodological approaches aligned with the "Reserve and Resilience" framework.[13] In addition, the approach used to evaluate premorbid IQ has limitations, such as floor effects, which could be improved using ID populations as norms, or biases stemming from the weight of the verbal component in final scores. Furthermore, future studies should consider incorporating standardized adaptive behavior scales (i.e., the Vineland Adaptive Behavior Scales or the Adaptive Behavior Assessment System[49]), and additional measures such as the KBIT Riddles subtest, to capture potential generational effects in other cognitive domains (i.e., executive functioning). Shifting the focus to other CR proxies that can be enhanced along the lifespan (e.g., physical activity[50,51]) or to other social dimensions (e.g., quality care, social support[52]), may offer a more comprehensive approach to capturing these potential resilience mechanisms. Finally, it may be advantageous to explore the design of multidomain lifestyle interventions to assess the impact of modifiable factors, as the Finnish Institute for Health and Welfare (FINGER) Project[53] in the general population.

In conclusion, the significant changes identified in the degree of ID, autonomous functionality, and intellectual profile have important implications for the well-being and quality of life of individuals with DS and their caregivers. These findings may influence health, education, policy, and intervention strategies. Further studies are needed to better characterize the effects of sociodemographic and environmental factors (e.g., lifestyles) and to assess the potential influence of modifiable risk and protective factors in adults with DS to delay symptomatic AD. Such research will be crucial in improving the prediction and understanding of variability in responses to interventions.

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CONFLICT OF INTEREST STATEMENT

A.L. has served as a consultant or on advisory boards for Fujirebio-Europe, Roche, Biogen, Grifols, Novartis, Eisai, Lilly, and Nutricia,

outside the submitted work. J.F. reported serving on the advisory boards, adjudication committees, or speaker honoraria from AC Immune, Adamed, Alzheon, Biogen, Eisai, Esteve, Fujirebio, Ionis, Laboratorios Carnot, Life Molecular Imaging, Lilly, Lundbeck, Novo Nordisk, Perha, Roche, Zambón, Spanish Neurological Society, T21 Research Society, Lumind foundation, Jérôme-Lejeune Foundation, Alzheimer's Association, National Institutes of Health (USA), and Instituto de Salud Carlos III. M.C.I. reports receiving personal fees for service on the advisory boards and speaker honoraria or educational activities from Esteve, Lilly, Neuraxpharm, Adium, and Roche diagnostics. J.A. reported receiving personal fees for service on speaker honoraria or educational activities from Lilly, Esteve, Fujirebio-Europe, and Roche diagnostics. A.L. and J.F. report holding a patent for markers of synaptopathy in neurodegenerative disease (licensed to ADx, EPI8382175.0). No other competing interests were reported. Author disclosures are available in the supporting information.

CONSENT STATEMENT

All participants and/or their legally authorized representatives provided written informed consent.

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SUPPORTING INFORMATION

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

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