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RESEARCH ARTICLE

Individualized estimated years from onset of Alzheimer's disease– related decline for adults with Down syndrome

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Abstract

Introduction: Adults with Down syndrome (DS) are at increased risk for Alzheimer's disease (AD) and vary in their age of transition from AD preclinical to prodromal or more advanced clinical stages. An empirically based method is needed to determine individual "estimated years from symptom onset (EYO)," the same construct used in studies of autosomal dominant AD .

Methods: Archived data from a previous study of > 600 adults with DS were examined using survival analysis methods. Age-specific prevalence of prodromal AD or dementia, cumulative risk, and EYOs were determined.

Results: Individualized EYOs for adults with DS ranging in age from 30 to 70+ were determined, dependent upon chronological age and clinical status.

Discussion: EYOs can be a useful tool for studies focused on biomarker changes during AD progression in this and other populations at risk, studies that should contribute to improved methods for diagnosis, prediction of risk, and identification of promising treatment targets.

KEYWORDS
Alzheimer's disease, Down syndrome, estimated years from symptom onset, mild cognitive impairment, prodromal Alzheimer's disease

HIGHLIGHTS

- Years from Alzheimer's disease (AD) onset (EYO) was estimated for adults with Down syndrome (DS).
- EYOs were informed by AD clinical status and age, ranging from 30 to > 70 years.
- Influences of biological sex and apolipoprotein E genotype on EYOs were examined.
- EYOs have advantages for predicting risk of AD-related dementia compared to age.
- EYOs can be extremely informative in studies of preclinical AD progression.

1 | INTRODUCTION

A multi-decade period of preclinical Alzheimer's disease (AD) provides opportunities for identifying biomarkers of its earliest stages of progression.[1–3] In turn, discovery of informative biomarkers can lead to identification of targets for disease-modifying treatments, and a great deal of current research has this as a major focus.

Late onset AD (LOAD), its most prevalent form, is the dominant cause of old age–related dementia, affecting an estimated 6.2 million American adults with an annual cost of paid and unpaid care amounting to > $500 billion[4,5]). While this is the primary AD-related public health concern, wide unexplained variation in vulnerability and the related wide distribution of ages at symptom onset impose severe complications on studies of biomarker progression during preclinical disease. This realization has increased the importance of studies focused on families having rare autosomal dominant mutations that increase risk dramatically and allowing symptom onset for carriers to be more predictable. The Dominantly Inherited Alzheimer Network (DIAN) has been studying these autosomal dominant AD (ADAD) cases since 2008 and has developed methods to track longitudinal biomarker trajectories anchored to a common point in disease progression, an "estimated years from symptom onset (EYO)" that takes into account mutation-specific differences in disease progression.[5]

The method for calculation of EYO for ADAD mutation carriers has evolved over time. Originally, EYO was operationalized as the difference between a mutation carrier's age and the age at which his/her parent mutation carrier first developed symptoms, determined via semi-structured interview and review of available clinical histories.[6] However, more recent methods have broadened the focus to consider other mutation carriers within families, all known carriers of the specific mutation of interest, and actual age of onset for those individuals transitioning in status while being followed longitudinally.[5] Nevertheless, the focus has remained on the expected age of earliest AD-related decline. In principle, that age reflects the initial transition from preclinical to prodromal AD, and under well-controlled circumstances could be operationalized as a transition from a Global Clinical Dementia Rating (CDR) from 0 to 0.5 or an initial diagnosis of mild cognitive impairment (MCI),[7] accepting the imperfect correspondence between these two methods of case classification. In DIAN, this was often determined by systematic reviews of family history to accommodate regional and generational variability in diagnostic practices,[8] but any reliance on recollection of events that can be both subtle and distant in time must be a limitation on accuracy of estimated timing. In fact, considerable variation in EYOs have been evident, even among carriers of the same ADAD mutation.[8]

Whatever their limitations in precision, the citations above are just examples of the many studies that have shown the value of EYOs for staging biomarker progression across ADAD mutations. However, the relatively small number of carriers of each specific mutation together with biological variability across mutations, or a genetic risk factor, has presented complications that could be avoided with a larger population sharing a common genotype risk factor contributing to high risk. Adults with Down syndrome (DS) represent one such population. The vast majority of affected individuals share a common genotype driving risk, full trisomy 21, resulting in overexpression of the triplicated gene coding for amyloid precursor protein (APP) located on this chromosome.[9] Although estimates of the age at onset for AD-related cognitive decline have also been shown to vary considerably across individuals, studies have consistently shown that cumulative risk for dementia reaches 50% at or before age 60.[10,11] With a steady birth incidence for DS in the United States (approximately 1 in 700[12]) and dramatically improved survival,[13] this will continue to be the largest population at high AD risk and a significant public health concern in its own right. This has led the National Institutes of Health to fund a major research initiative focused on biomarkers of AD progression in adults with DS, the Alzheimer Biomarker Consortium: Down Syndrome (ABC-DS).[14]

Studies of age-dependent progression of AD in adults with DS have their own complications. First, assessment of decline in cognitive and functional abilities is challenging due to the virtually universal presence of some degree of lifelong intellectual impairment. Thus, findings from assessments of cognition targeting AD in other populations are rarely informative because those procedures are poorly suited for distinguishing between adult-onset impairments and those linked to a developmental disorder. Fortunately, multiple research programs conducted with adults with DS over recent decades have developed assessment methods able to make this distinction by using a combination of direct neuropsychological testing, information gathered from knowledgeable informants, and clinical examinations.[14–16]

A second challenge is a variation in the DS phenotype related to AD vulnerability. With a 50% cumulative dementia risk by approximately age 55 to 60, some individuals obviously experience earlier as well as later symptom onset. In fact, longitudinal studies have identified

RESEARCH IN CONTEXT

1. **Systematic review**: Literature on methods determining "estimated years from symptom onset (EYO)" of Alzheimer's disease (AD) in autosomal dominant AD (ADAD), late onset AD (LOAD), and Down syndrome (DS-AD) were reviewed using traditional sources (e.g., PubMed and related citations).
2. **Interpretation**: Life table analyses provided estimates of individualized EYOs for adults with DS ranging in age from 30 to > 70, informed by their age and clinical stage of AD (preclinical, prodromal, dementia). Findings should be extremely useful for studies of AD progression, especially for understanding biomarker changes during preclinical AD.
3. **Future directions**: Further research is needed to establish the value of these proposed EYOs in studies of AD progression and for predicting individual risk clinical progression in DS-AD, per se, as well as in ADAD and LOAD.

onset as early as the late 30s and as late as the early 80s (although these extremes are rare). While some proportion of this variance can be explained by reference to factors such as apolipoprotein E (*APOE*) genotype, other genetic modifiers of risk,[17] and environmental factors,[18] the underlying contributors to the greater part of this variation have yet to be identified. Given the multifactorial nature of AD, this is not at all surprising, even in this unique cohort of adults with DS whose primary driver of AD is known.

Clearly, studies of AD biomarkers within this population must address this variation and Fortea et al.[19] took an ambitious step in this direction by relating progression in selected AD-related biomarkers to chronological age. Additional analyses compared profiles of biomarker progression between adults with DS and those with ADAD, using the overall median age at onset of prodromal AD as a constant EYO for the entire DS sample. However, any calculated median age at onset must be highly dependent on the particulars of sampling methods and the use of any constant as an anchor for calculating EYO ignores individual differences in vulnerability. More important, this procedure would assign a post-onset EYO to all individuals older than that age even if they have maintained their preclinical status and a pre-onset EYO to younger individuals even if they have developed prodromal or more advanced AD.

Individualized EYOs would be better suited for addressing this variation in risk. The task at hand then becomes the development of evidence-based methods to estimate the expected age of the transition from preclinical to prodromal AD on an individual basis. Operationally, this would be the age at which mild cognitive impairment–Down syndrome (MCI-DS) was initially observed, reflecting a shift from preclinical AD characterized by cognitive stability to prodromal AD. To address this task procedurally, four subpopulations must be recognized within cross-sectional study designs and with studies enrolling participants at varying ages and using limited longitudinal follow-up.

The first subpopulation, and the one best suited for estimating EYOs, includes individuals who are cognitively stable at the time of their baseline assessments and then are tracked longitudinally until they develop MCI-DS. This allows direct estimation of the actual age at onset, having occurred at some point in time between the last indication of stability and the first determination of MCI-DS and operationalized as the midpoint of that interval, to minimize the magnitude of overall estimation error. The individualized EYOs for data and biological samples banked before or collected after this actual age at onset can then be calculated via simple subtraction. Precision should be high, depending only on the interval between assessments. Unfortunately, this is likely to be the smallest subpopulation of participants in AD biomarker studies given the constraints imposed by the slow progression of AD and pragmatic limitations on durations of follow-up.

The second and third subpopulations include individuals identified as having prodromal or more advanced AD at the time of baseline assessments, defined as prevalent MCI-DS or dementia (DS-AD), respectively. These individuals, already being older than their actual age at onset, will by definition have an EYO of some positive number. To estimate that number, expected durations of MCI-DS and DS-AD need to be determined, the first by examining the interval intervening between onset of MCI-DS and the initial transition in clinical status to DS-AD and the second by examining survival after DS-AD onset.

The fourth subpopulation includes individuals prior to symptom onset, presumptively in the preclinical stage of AD. By definition, these individuals will all have EYOs that are negative and strongly associated with chronological age. With maintenance of preclinical status, future ages at onset would then need to be predicted, with individualized EYOs determined by simple subtraction (note that ages at evaluation for this group, whether at a single time or at the last evaluation in a longitudinal series, will have a bias toward underestimation of the true duration of cognitive stability).

The following analyses addressed each of the needs for developing individualized EYOs for the last three subpopulations of adults with DS (those with prodromal AD, those with more advanced AD, and those in the preclinical stage). Survival analysis methods were selected as the main analytic tools used for these analyses, understanding that these methods have inherent limitations in the current context (see Wang and Yang[20]) and that potential biases can be associated with the specifics of and variation in: (1) age at enrollment, (2) age-associated competing events, and (3) duration of follow-up. Therefore, a tiered approach to analysis was used to help reduce their potential impacts.

2 | METHOD

Archived data from a previous large, longitudinal study of aging and AD in adults with DS provided data describing demographic characteristics together with cognitive and functional status. Participants in this study, recruited through contacts with community-based agencies providing direct care, were assessed at approximately 18-month intervals for up to a total of 9 times (baseline plus 8 follow-ups covering a maximum span of approximately 12–15 years). Data were collected between the years 1987 and 2017 and included determinations of clinical dementia status for each individual based on comprehensive assessments, described in multiple previous publications (e.g., Krinsky-McHale et al.[16] and Silverman et al.[21]). These procedures included: (1) in-depth review of clinical records maintained at agencies providing direct services, (2) structured interviews with informants having direct day-to-day knowledge of the individual's behavioral and functional characteristics, and (3) approximately 2 hours of direct one-on-one testing using procedures appropriate for adults with preexisting developmental disability and focused on cognitive domains likely to be affected as AD progressed from its preclinical to prodromal stage. After each assessment cycle, the overall dementia status for each individual was determined in a consensus case conference that considered all available clinical data but without consideration of any biomarker findings (other than routine lab results included in clinical record reviews).

2.1 | Participants

The total sample for the present analyses included 564 adults with DS. These individuals provided data sufficient to determine their clinical

dementia status at baseline (92.0% of the 613 individuals consented). Women were over-represented (65.9%; due to a subproject's specific interest in women's health), ages at baseline ranged from 30.3 to 82.7 years old and IQs (Stanford-Binet or equivalent) ranged from < 25 to 68. For inclusion in the present analyses, individuals had to have a clinical status of (1) cognitively stable (CS, $N = 419$), (2) MCI-DS ($N = 84$), or (3) possible/definite dementia (DS-AD, $N = 61$). (Note that 10 individuals exhibiting evidence of declines together with an unresolved serious illness or traumatic life event were included in the original sample but were excluded from the present analyses because of substantial uncertainty regarding the presumptive cause of their declines. Also, note that risk for age-associated neuropathology unrelated to AD is extremely low in adults with DS while the presence of neuropathological hallmarks of AD is virtually universal. Therefore, all individuals determined to have MCI-DS or DS-AD were presumed to have prodromal or more advanced AD and all CS individuals were presumed to have preclinical AD.)

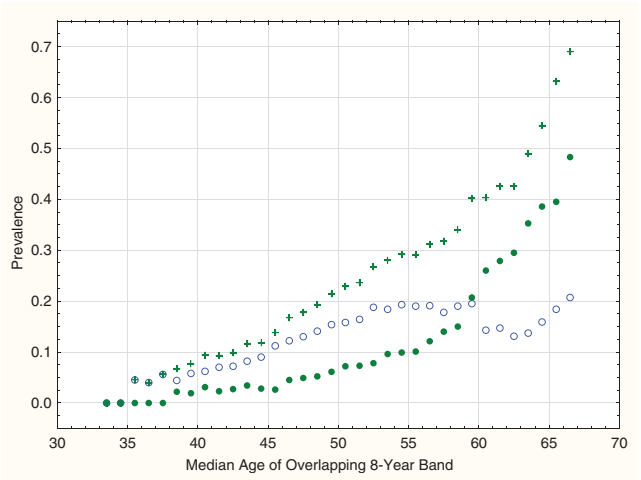

FIGURE 1 Estimated prevalence of MCI-DS (open circles), DS-AD (closed circles), and their combination (pluses) for adults with DS within 8-year age bands encompassing a range of from 30 to 70 years. AD, Alzhiemer's disease; DS-AD, dementia in Down syndrome; MCI-DS, mild cognitive impairment–Down syndrome.

2.2 | Statistical analyses

The descriptive statistics and survival analysis subroutines of Statistica, version 13.2, were used for all analyses. An initial stage of analysis described the relationship between age and prevalence of MCI-DS or DS-AD to provide an overall description of clinical status within this specific sample.

The duration of MCI-DS was estimated by examining differences in cumulative incidence of MCI-DS versus DS-AD using the Kaplan–Meier method. For individuals transitioning from preclinical to prodromal AD (MCI-DS) or developing DS-AD, age at onset was estimated as the midpoint of the interval between the assessment immediately preceding determination of onset and the assessment first detecting the transition. (No cases transitioned directly from preclinical AD to dementia during the interval between assessments, but approximately 10% of cases with an initial consensus determination of MCI-DS were found to be false positives based on improvements in profiles of performance at follow-up judged to be of clinical significance. These cases were retroactively reclassified as CS at that earlier age. No false-positive cases of DS-AD were observed.) For each case that did not experience a transition in clinical status, age at his or her last assessment cycle was used in analyses. To examine survival post-incident dementia, the proportion of individuals surviving over successive 18-month assessment intervals after DS-AD onset provided estimates of expected duration.

The final stage of analysis used the Life Table and Distribution of Survival Times routine of Statistica 13.2 for estimating durations of time until onset of MCI-DS (and corresponding ages at onset) given the maintenance of CS as chronological age increased. A priori, differences between the estimated age at onset and current age were expected to be decreasing as age increased, reflected by progressively less negative EYOs. Further analyses examined available data to determine the impact of biological sex, severity of longstanding intellectual disability (ID), and *APOE* genotype on these estimates, three factors likely to influence AD progression. Categories examined for *APOE* genotype were: (1) ε2/ε2 or ε2/ε3 alleles, (2) ε3/ε3 alleles, and (3) ε4/ε3 or ε4/ε4 alleles (there were only 11 ε2/ε4 cases and these were excluded from analyses). To examine the impact of severity of ID, the overall sample was divided into three subgroups (approximating mild, moderate, and severe ID) based on historical IQ test results available from clinical records. In addition to these three possible risk modifiers, two groups enrolled earliest versus latest were compared to provide an indication of procedural consistency over time.

3 | RESULTS

3.1 | Sample demographics and prevalence of MCI-DS and DS-AD

Initial analyses focused on descriptions of the sample, including examination of the relationship between age and prevalence of MCI-DS or DS-AD. Inspection of baseline data indicated that 8-year intervals provided subsamples of sufficient size to estimate prevalence at ages ranging from 30 to 70 years. Findings are illustrated in Figure 1, with the first data point based on individuals 30 to 37 years of age, the second on individuals 31 to 38 years of age, the third based on individuals 32 to 39 years of age, and so forth. (Note that the number of individuals varied across age bands from a low of 19 [30–37 year of age] to a high of 292 [47–54 years of age] with a median $N = 94$. Only sevem cases > 70 years were included in this sample, precluding stable estimates beyond the late 60s. However, prevalence estimates based on just those seven cases were 0.286, 0.429, and 0.715 for MCI-DS, DS-AD, and their combination, respectively.)

Only a single prevalent case of MCI-DS (at age 39) was observed prior to 40 years of age, with estimated prevalence for MCI-DS and

TABLE 1 Characteristics (means with SDs in parentheses) of cases included in survival analyses determining age-specific risk for MCI-DS and prodromal AD/dementia (DS-AD) in adults with Down syndrome (DS).

	MCI-DS		DS-AD	
	Stable	Transitioning	Stable	Transitioning
N[a]	210	207	238	152
Age (years)	52.8 (8.1)	55.3 (6.2)	53.7 (7.9)	57.3 (5.4)
% male	26.7	38.6	28.2	37.5
IQ	34.7 (9.0)	33.7 (8.8)	34.3 (8.9)	34.6 (8.9)

Abbreviations: AD, Alzheimer's disease; DS, Down syndrome; DS-AD, dementia in Down syndrome; MCI-DS, mild cognitive impairment–Down syndrome; SD, standard deviation.
[a]Samples for examining MCI-DS and DS-AD incidence overlapped.

DS-AD combined gradually increasing to 0.2 by age 50. Thus, a substantial minority of adults with DS had already transitioned from preclinical to prodromal or more advanced AD by that age, suggesting that the standard practice of censoring prevalent cases for examining cumulative incidence could introduce a bias toward underestimating risk at "younger" ages.

3.2 | Estimating duration of MCI-DS

Estimating the duration of MCI-DS requires determination of age-specific risk together with comparable degrees of risk for the transition to DS-AD. Both were defined by survival (or cumulative incidence). Key characteristics of the subsamples included for generating these cumulative incidence estimates are provided in Table 1. As noted above, inclusion criteria included: (1) no fewer than two cycles of assessment, (2) a baseline clinical status determination of CS (for determining incident MCI-DS) or absence of DS-AD, and (3) either an unchanged clinical status or a transition to MCI-DS or DS-AD, respectively. Thus, prevalent cases of MCI-DS or DS-AD were excluded when incidence of MCI-DS was examined but only prevalent DS-AD cases were excluded when incidence of DS-AD was examined. Key findings are summarized in Table 2.

Overall, the findings summarized in Table 2 describe a reasonably stable relationship between risk for MCI-DS and DS-AD over the range of sampled ages, separated by an interval of just over 2 years. Although individual differences are to be expected, the midway point between onset of MCI-DS and onset of DS-AD should minimize estimation error for actual age at onset, yielding an estimated EYO = +1 for prevalent MCI-DS cases.

3.3 | Estimating duration of dementia based on post-onset survival

Up to four cycles of assessment were conducted at approximately 18-month intervals after an initial determination of dementia onset. Simple proportions of cases surviving were calculated to estimate overall mortality risk, showing: (1) 18.9% mortality at 18 months, (2) 48.4% mortality by 36 months, (3) 75.5% mortality by 54 months, and (4) 89.8% mortality by 72 months. With approximately 50% mortality expected by 3 years, an EYO of +3 to +5 should minimize error for prevalent dementia cases, reflecting 2 years of MCI-DS progression plus expected survival once dementia had developed.

TABLE 2 Ages associated with proportions of adults with DS experiencing a transition in clinical status as indicated by onset of MCI-DS or DS-AD.

Cumulative incidence	MCI-DS	DS-AD	Interval (years)
0.1	51.2	52.9	1.7
0.2	53.4	55.5	2.1
0.3	54.6	57.0	2.4
0.4	55.8	58.5	2.7
0.5	58.0	60.5	2.5
0.6	59.9	62.4	2.5
0.7	62.1	64.4	2.3
0.8	64.5	66.6	2.1

Abbreviations: AD, Alzheimer's disease; DS, Down syndrome; DS-AD, dementia in Down syndrome; MCI-DS, mild cognitive impairment–Down syndrome.

3.4 | Examining possible effects of follow-up duration or competing events

To explore the impact of varying duration of follow-up, analyses were repeated on two subsamples differing only in the number of assessment cycles. For the outcome of MCI-DS onset, the first subsample included 84 women and 69 men with exactly three assessment cycles, with a mean age for analysis of 51.8 years (range of 34 to 67). The second subsample included 127 women and 26 men with six to nine assessment cycles with a mean age of 56.7 (range of 45 to 78). For the outcome of DS-AD onset, the two samples included, respectively, 95 women and 72 men with a mean age of 52.9 (range of 35 to 73) and 129 women and 28 men with a mean age of 57.9 (range of 47 to 80). Across the range of cumulative incidences, differences between MCI-DS and DS-AD analyses ranged from 1.5 to 3.6 years, with mean

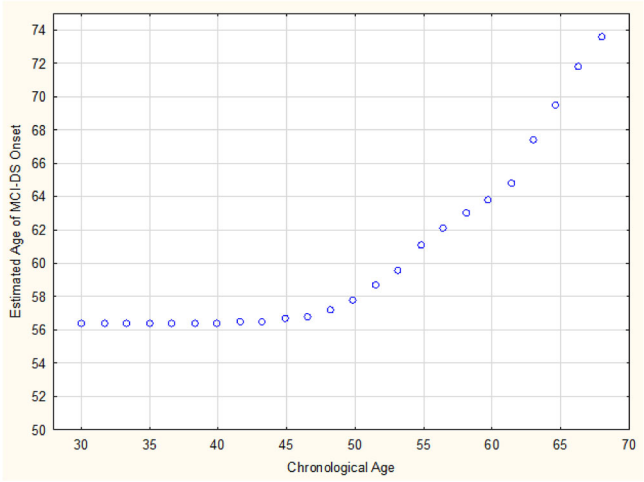

FIGURE 2 The association between chronological age with cognitive stability and estimated age at onset of MCI-DS for adults with DS. DS, Down syndrome; MCI-DS, mild cognitive impairment–Down syndrome.

difference values for the two subsamples of 2.0 and 2.7 years, showing consistency in the finding of primary interest.

Estimates generated by these methods could also be sensitive to the presence of competing events, in the present case limited primarily to death occurring prior to a clinical transition. Therefore, additional analyses were conducted counting CS individuals who died during the study period as cases. Here again, the impact on findings was negligible (mean change = −0.2 years; interquartile range of −0.1 to −0.3).

3.5 | Estimating EYO for preclinical cases

The analyses presented above provide empirical support for estimating actual age at onset for prevalent cases of MCI-DS or DS-AD as 1 or 3 years younger, respectively, than their age at baseline assessments. While these estimates are inherently imperfect and might better be considered a semiquantitative metric, they have two redeeming features. First, they distinguish cases with prodromal and more advanced AD from their peers of the same age who have maintained their preclinical AD status. Second, they provide a basis for including these cases in analyses focused on future age at onset of MCI-DS and EYOs. (Because the estimated EYOs for prevalent cases were recognized as approximations, analyses were repeated based on EYOs of +2 and +5 for MCI-DS and DS-AD, respectively. This resulted in only minor changes in findings [median = 3 months].)

Figure 2 shows the overall profile relating chronological age to projected age at onset of MCI-DS. As indicated, the estimated age at onset remained almost constant until participants reached their mid-40s and increased linearly thereafter. This analysis was repeated for men and women separately, and for categories of *APOE* genotype (ε2/ε2 or ε2/ε3, ε3/ε3, and ε4/ε3 or ε4/ε4, with ε2/ε4 cases excluded). The same overall pattern was observed, the only differences being the initial estimated age at onset (for 30-year-olds), the age at which an inflection in slope occurred and the magnitude of that slope increased. This consistency provided straightforward description of the full range of projected ages at onset of MCI-DS along with their respective EYOs, calculated by simple subtraction of the projected age at onset from the present age of cognitive stability.

Table 3 lists the EYOs for the overall sample of adults with DS and for subgroups defined by biological sex or *APOE* genotype. Note the use of the Life Table method has several important limitations in the present context. First, high-precision estimates rely on huge sample sizes (e.g., US Census data) and therefore the numbers in Table 3 have been rounded to the nearest half-year. Second, the number of intervals defined by chronological age was limited to 30, resulting in the need to estimate values for some intervals via interpolation. Finally, the numbers of cases maintaining cognitive stability beyond age 60 were small and indications of non-monotonicity need not reflect true delays in MCI-DS onset. (Additional comparisons indicated that three subgroups defined by preclinical IQs of ≤30, 31 to 38, and ≥39 had comparable age-specific risk, Cox–Mantel *P*s > 0.48, as did the two subgroups enrolled in our past studies at different points in time, Cox–Mantel $P > 0.39$. Therefore, additional summary statistics for these analyses are not provided.)

4 | DISCUSSION

The present analyses were structured to provide an initial step toward determination of empirically based estimates of individualized EYOs for adults with DS, informed by their chronological ages and clinical status of: (1) preclinical AD, defined as CS aging; (2) prodromal AD, defined as MCI-DS; or (3) more advanced AD, defined as DS-AD. Analyses benefitted from the availability of a rich set of longitudinal data generated over the period spanning from 1987 through 2017, allowing estimates of cumulative incidence of both MCI-DS and DS-AD as well as providing sufficient longitudinal data after onset of DS-AD to provide a reasonable estimate of subsequent survival. Bejanin et al.[22] recently provided a slightly longer estimate of 4.6 (+/− 0.9) years, closer to our estimate after MCI-DS onset. The cause of this small difference might be linked to differences in methods for defining onset operationally. The present study distinguished between MCI-DS/prodromal AD and DS-AD and estimated post-dementia survival after the latter. However, the estimated age at onset reported by Bejanin et al. of 53.8 years suggests that some significant proportion of the 44 studies included in their meta-analysis may have defined onset based on the transition from preclinical to prodromal AD and, if that was the case, it would account for a longer survival estimate. Whatever the source of the differences with the present findings proves to be, the two sets of results are largely in agreement.

Available data also allowed exploration of the influences of biological sex and *APOE* genotype on estimated EYOs. As indicated in Table 3, an age-dependent effect was evident for both of these factors. With respect to biological sex, males had slightly delayed estimated onset of MCI-DS up to 45 to 50 years of age. Subsequently, this initial "advantage" decreased almost linearly, eventually resulting in males having

TABLE 3 Estimated years from onset (EYOs) of MCI-DS for adults with DS able to maintain cognitive stability with increasing age, overall, and considering biological sex or *APOE* genotype.

Age	All DS	Men	Women	ε2	ε3	ε4
N	564	190	374	63	302	92
30	−26.5	−27.0	−25.5	−31.5	−26.5	−23.0
31	−25.5	−26.0	−25.0	−31.0	−26.0	−21.5
32	−24.5	25.5	−24.0	−30.0	−25.0	−21.0
33	−23.0	−24.0	−22.5	−28.5	−23.5	−20.0
34	−22.0	−24.0	−22.0	−28.0	−22.5	−18.5
35	−21.5	−22.5	−21.0	−27.0	−21.5	−18.0
36	−20.5	−22.0	−19.0	−25.5	−21.0	−17.0
37	−20.0	−20.5	−18.5	−25.0	−20.0	−16.0
38	−18.0	−19.0	−17.5	−24.0	−18.5	−15.5
39	−17.5	−18.0	−17.0	−23.5	−17.5	−14.5
40	−16.5	−17.5	−16.0	−22.5	−16.5	−13.0
41	−15.5	−16.5	−14.5	−20.5	−16.0	−12.0
42	−15.0	−15.5	−14.0	−20.0	−15.0	−11.5
43	−13.5	−14.0	−13.0	−19.0	−13.5	−10.0
44	−12.5	−13.0	−12.5	−18.5	−13.0	−9.5
45	−12.0	−12.5	−11.5	−17.5	−12.0	−9.0
46	−11.0	−12.0	−10.0	−16.0	−11.0	−7.5
47	−10.5	−11.0	−9.5	−15.5	−10.5	−7.0
48	−9.0	−9.5	−9.0	−14.5	−9.0	−6.0
49	−8.5	−9.0	−7.5	−13.0	−8.5	−5.0
50	−8.0	−8.5	−7.5	−12.5	−8.0	−4.5
51	−7.0	−7.0	−7.0	−11.5	−7.0	−4.0
52	−7.0	−7.0	−7.0	−11.0	−6.5	−3.0
53	−6.5	−6.5	−7.0	−10.5	−6.0	−3.0
54	−6.5	−6.0	−7.0	−9.0	−6.0	−3.0
55	−6.5	−5.5	−7.0	−8.5	−5.5	−5.0
56	−6.0	−5.0	−6.5	−8.0	−5.5	−5.0
57	−5.5	−5.0	−6.5	−7.5	−5.0	−4.5
58	−5.0	−4.5	−6.0	−7.0	−4.5	−5.0
59	−4.5	−4.0	−5.0	−7.0	−4.0	−4.5
60	−4.0	−3.5	−5.0	−6.5	−3.5	−3.5
61	−3.5	−3.0	−4.5	−5.5	−2.5	−3.0
62	−3.5	−3.0	−5.5	−4.5	−3.0	−2.5
63	−5.0	−1.5	−6.0	−3.0	−4.5	−1.5

Note: Small numbers of cases 63–70 years of age resulted in unstable EYO projections and therefore medians are provided covering this range of aging.

Abbreviations: *APOE*, apolipoprotein E; DS, Down syndrome; MCI-DS, mild cognitive impairment–Down syndrome.

estimated onset slightly earlier than the overall group. The inverse was observed for women. Given the subtlety of these differences and mixed findings from previous studies,[11,23] the decision to adjust EYOs for adults with DS seems best considered optional.

There has been considerable interest in the impact of *APOE* genotype on AD risk for adults with DS, with PubMed (www.pubmed.gov) listing > 200 relevant publications, including descriptions of multiple cohorts across multiple countries.[22,24–27] The present finding is consistent with the preponderance of that previous work, with *APOE* ε2 delaying onset of MCI-DS and *APOE* ε4 associated with earlier onset. Of note, the impact of *APOE* genotype on EYOs was greatest at younger ages, eventually declining in magnitude to approximately 1 year by the late 50s in the case of *APOE* ε4. A similar decline in the relative risk for *APOE* ε4 carriers with advancing age has been described for the neurotypical population at risk for LOAD.[28]

These findings should be extremely useful for studies of progression of AD-related biomarkers, especially during preclinical stages of disease, and should provide a substantive advance over the use of chronological age or any single estimate for the entire sample. However, while this sample of adults with DS is among the largest tracked longitudinally, its characteristics impose some limitations. Only a small number of informative cases were available < 40 ($N = 26$) or > 65 ($N = 37$) and findings of any study of this type are necessarily dependent upon the detailed characteristics of the sample and the degree to which it is representative of the population of interest. In this case, these concerns were mitigated by the sampling procedure, in that it: (1) was community rather than clinically based, (2) encompassed the full range of ages at risk, and (3) was blind to pre-baseline cognitive status. There is no guarantee that other studies focused on DS-AD will have the same distribution of ages, and enrollment of a greater proportion of "younger" adults might shift cumulative risk toward younger ages overall, as might longer durations of their follow-up. Nevertheless, it seems likely that the relative relationships among EYOs determined by age and clinical status will be relatively stable with samples of sufficient size.

A second limitation is an inherent characteristic of the use of survival analysis. Left and right censoring, both considerations in the present case, can introduce bias that is difficult to quantify. On the positive side, duration of follow-up and potentially competing events were both shown to have minimal impacts on findings and other sources of bias should be operating similarly as age increased. Thus, the relative relationships between age and estimated EYOs for preclinical cases described in Table 3 should reasonably approximate actual periods between assessment and future onset of MCI-DS. The test will be the utility of individualized EYOs in future studies of biomarker progression, the potential benefit being substantially stronger associations with biomarker progression compared to the use of chronological age as the reference.

Perhaps the most important limitation of the present analyses is that other than *APOE* genotype, biological sex, and severity of ID, factors potentially modifying age-specific risk within this population were not considered. While using the age associated with 50% risk should minimize overall prediction error, variation around these values was obvious. This variation could be reduced by consideration of the broader genotype (e.g., Lee et al.[17]) and environmental factors that influence overall health and quality of life.[18] There is no doubt that such modifiers can have significant impacts, as shown by recent

analyses of the National Alzheimer's Coordinating Center dataset (>36,000 cases[29]), but we were unable to evaluate the impact of these other modifiers with the available data. This may be of particular relevance to findings, mentioned above, of some longer EYOs after age 62. The decision to interpret non-monotonicity in EYOs at the oldest ages as "noise" was admittedly arbitrary and the possibility remains that the interval between current age and onset of MCI-DS is truly extended in this group of "oldest old" with DS. This clearly needs to be explored further.

Accepting their limitations, the methods developed herein represent a substantial advance over the use of chronological age or any single value of estimated age at onset for studies of AD-related biomarker progression within this largest high-risk population, especially during the preclinical stage of disease. Minimally, the present findings represent a proof of principle for improving the precision of biomarker staging of preclinical AD progression, at least for two important applications. The use of age-anchored EYOs should support improved staging of biomarker changes in the adult population with DS, per se, and should support studies of both qualitative and quantitative differences among DS-AD, ADAD, and LOAD.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest. Author disclosures are available in the supporting information.

CONSENT STATEMENT

Recruitment, informed consent, and study procedures were approved by the institutional review board of the New York State Psychiatric Institute. Participants with capacity provided consent and for individuals who lacked capacity, surrogate consent was obtained from their legally authorized representative.

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