

Epilepsy And Alzheimer's Disease: A Multicentre Clinical Study In Adults With Down Syndrome

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Background : Aging individuals with Down syndrome (DS) are at elevated risk for Alzheimer's disease (AD) and epilepsy, with late-onset myoclonic epilepsy in DS (LOMEDS) often developing in those with symptomatic AD. To better understand the progression of epilepsy in this population, its temporal relationship with AD symptoms, and its prognostic implications, we examined a large, multicenter cohort of adults with DS.

Methods : We conducted a multicentre, observational, longitudinal study across seven international cohorts between 2012 and 2025. We included adults with DS ≥18 years and ≥1 longitudinal clinical assessment. AD staging was determined by clinical consensus. Active epilepsy required an epilepsy diagnosis plus ongoing antiseizure medication and/or ≥1 seizure within 5 years. We analysed active epilepsy prevalence, incidence and cumulative incidence, its timing with respect to symptomatic AD and its impact on survival and cognitive trajectories as well as EEG abnormalities.

Results: We recruited 4865 adults with DS, of which 4804 had an available cognitive status at last visit and the minimum common dataset,

Demographic table	Overall N = 4,804 ¹	Cognitively stable (aDS) N = 3,238 ²	Non-degenerative cognitive decline (uDS) N = 267 ¹	Prodromal AD (pDS) N = 321 ¹	AD Dementia (dDS) N = 978 ¹	p-value ³
Age at visit, years, median [IQR]	44.42 [32.42; 54.19]	37.31 [28.42; 46.34]	48.89 [39.71; 54.72]	54.67 [51.75; 58.78]	57.37 [53.08; 61.18]	<0.0001
Sex, % female	2,310/4,793 (48)	1,494/3,230 (46)	122/265 (46)	149/321 (46)	545/977 (56)	<0.0001
Intellectual disability, n (%)						<0.0001
Mild	1,020 (25)	804 (29)	22 (9.3)	57 (21)	137 (15)	
Moderate	2,352 (57)	1,529 (56)	141 (60)	160 (58)	522 (58)	
Severe/Profound	778 (19)	409 (15)	73 (31)	59 (21)	238 (27)	
Active epilepsy at last visit, n/N (%)	699/4,804 (15)	157/3,238 (4.8)	28/267 (10)	55/321 (17)	459/978 (47)	<0.0001

¹Median [Q1; Q3]; n/N (%); n (%)
²Global p-values: Kruskal-Wallis for Age_at_visit; Pearson's chi-squared or Fisher's exact for categorical variables, as appropriate.

Active epilepsy affected 145.2 per 1,000 overall and was strongly age-dependent, increasing from 39.4 per 1,000 at 18–24 years to 389.6 per 1,000 at 60 years or older, mainly driven by patients with symptomatic AD. Incidence rates followed similar age-related gradients

The cumulative risk of epilepsy in all adults with DS rose steadily: 3.3% at 40 years - 61.3% at 70. When considering only asymptomatic individuals, we also saw an age-dependent increase, but to lower levels (12.0% at 60 years).

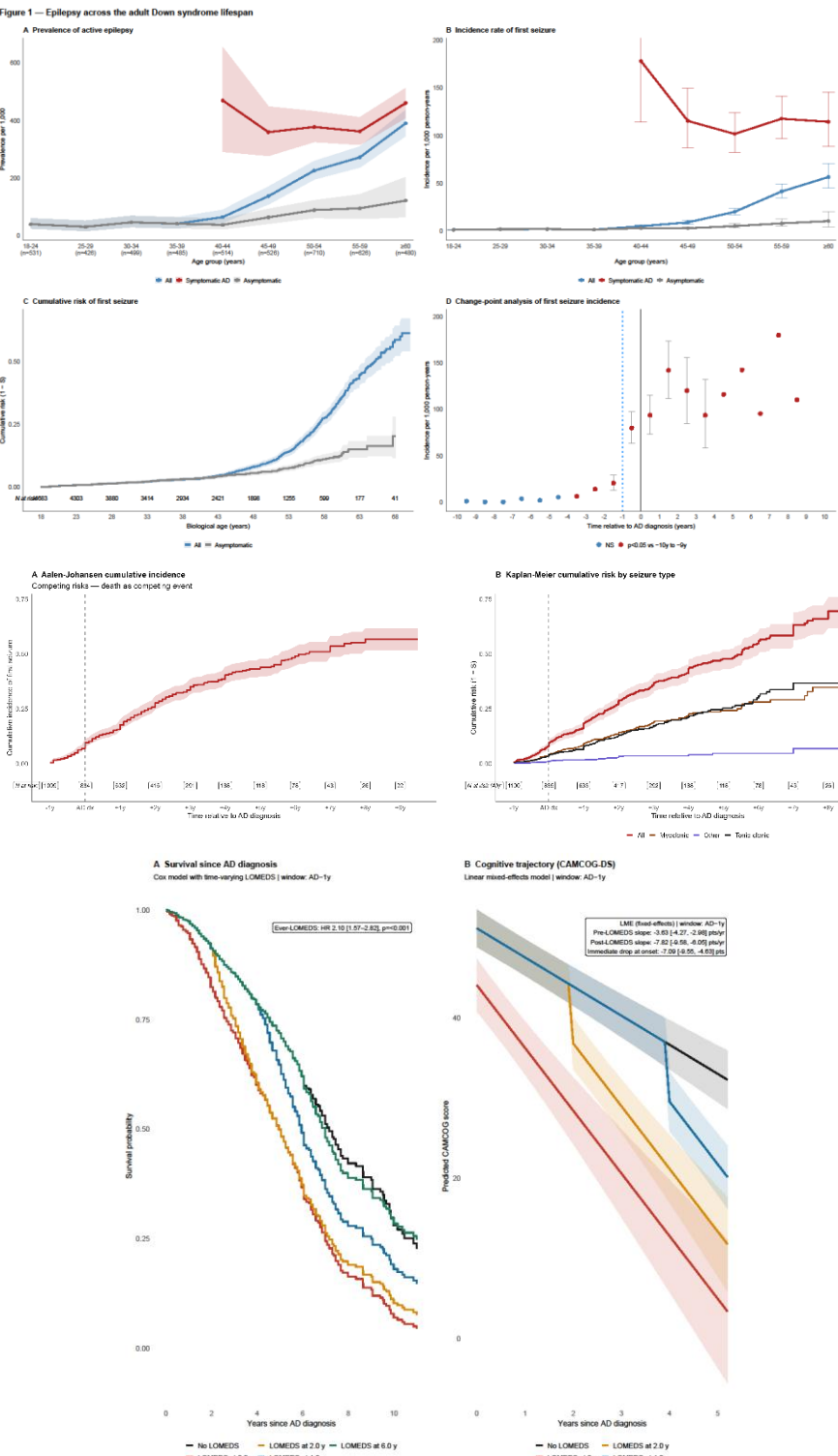
New onset of seizure incidence rates remained low and stable until a marked acceleration in the final pre-diagnostic year

The cumulative incidence of LOMEDS rose after symptom emergence, from 9.5% (95% CI 7.8–11.3%) at AD diagnosis, to 56.9% (51.7–61.7%) at 9 years post-diagnosis. Generalized tonic clonic (GTC) and myoclonic seizures predominated, with other seizure types being far less frequent

Time since AD diagnosis, severe–profound ID and APOE4 carriership raised risk (OR 1.33, 2.14 and 1.61 per year, respectively), independent of age. Interictal EEG abnormalities showed limited diagnostic utility

LOMEDS was strongly associated with reduced survival and faster cognitive decline. In time-dependent Cox models, LOMEDS was associated with higher mortality (HR 2.10, 95% CI 1.57–2.82, p<0.0001), with earlier onset conferring a substantially worse prognosis. Cognitive trajectories (CAMCOG-DS) showed a decline of 3.6 points per year (95% CI -4.3 to -3.0) in symptomatic AD without LOMEDS. Following first seizure onset, scores dropped abruptly by 7.1 points (95% CI -9.6 to -4.6) and the rate of decline increased by a further 4.2 points per year (95% CI -6.0 to -2.4), resulting in a total post-LOMEDS decline of 7.8 pts/yr (95% CI -9.6 to -6.1; Figure 4B).

Discussion: Epilepsy increases sharply after symptomatic AD onset in DS. Its association with reduced survival and accelerated cognitive decline underscores the need for targeted preventive and therapeutic strategies against AD-related epileptogenesis and hyperexcitability.



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