



Natural history and clinical impact of epilepsy in adults with Down syndrome: a multicentre clinical study



Lucía Maure-Blesa*, María Carmona-Iragui*, Isabel Barroeta, Javier Arranz, Susana Fernández, Íñigo Rodríguez-Baz, Bessy Benejam, Laura Videla, José Enrique Arriola-Infante, Laura Del Hoyo Soriano, Lucía Pertierra, Lúcia Vaqué-Alcázar, Aida Sanjuan, Ana Bueno, Mateus Rozalem Aranha, Oriol Lorente, Alejandra O Morcillo-Nieto, Victoria Ros-Castelló, Alba Sierra-Marcos, Beatriz Sánchez-Moreno, Christos Panagiotis Lisgaras, Esther Blessing, Ricardo S Osorio, Ainara Estanga, Maite García-Sebastián, Naia Ros, Anna Christina Stockbauer, Georg Nuebling, Jan Martin Remi, Mary McCarron, Kálya Lima, Pamela Dunne, Sònia Sirisi, Oriol Dols-Icardo, Olivia Belbin, Daniel Alcolea, Alexandre Bejanin, Alberto Lleó, Sandra Giménez, Nuria Montes, Diego Real de Asua, Eimear McGlinchey, Johannes Levin, Anne-Sophie Rebillat, Miren Altuna†, Juan Fortea†

Summary

Background As individuals with Down syndrome age, they face high risks of Alzheimer's disease and epilepsy. With symptomatic Alzheimer's disease, late-onset myoclonic epilepsy in Down syndrome (LOMEDS) often emerges. We aimed to examine how epilepsy develops in Down syndrome, its timing relative to Alzheimer's disease symptom onset, and its effect on prognosis.

Methods We conducted a multicentre, observational, longitudinal study across seven international cohorts with an aggregate observation window from Oct 24, 2012, to July 28, 2025. We included adults with Down syndrome aged at least 18 years and with at least one longitudinal clinical assessment. Alzheimer's disease staging was done by clinical consensus. Active epilepsy required an epilepsy diagnosis plus ongoing antiseizure medication or at least one seizure within the past 5 years. We analysed active epilepsy prevalence, incidence and cumulative incidence, its timing with respect to symptomatic Alzheimer's disease, and its effect on survival and cognitive trajectories as well as electroencephalogram (EEG) abnormalities.

Findings We included 4804 adults with Down syndrome (mean age 43 years [SD 13]): 3238 (67·4%) were cognitively stable, 267 (5·6%) had non-degenerative cognitive decline, 321 (6·7%) had prodromal Alzheimer's disease, and 978 (20·3%) had Alzheimer's disease dementia. Intellectual disability was mild in 1020 (24·6%) participants, moderate in 2352 (56·7%), and severe to profound in 779 (18·8%). Active epilepsy prevalence was 145·2 per 1000 adults with Down syndrome overall but significantly increased with age, particularly with symptomatic Alzheimer's disease, when epilepsy manifested mostly as myoclonic or tonic-clonic seizures. Cumulative incidence of epilepsy increased linearly after symptomatic Alzheimer's disease, from 9·5% (95% CI 7·8–11·3) at diagnosis to 56·9% (51·7–61·7) after 9 years. Risk of epilepsy increased with time since Alzheimer's disease diagnosis (adjusted odds ratio 1·33 per year [95% CI 1·22–1·45]; $p<0·0001$), severe-to-profound intellectual disability (2·14 per year [1·25–3·70]; $p=0·0057$), and APOE $\epsilon 4$ carriership (1·61 per year [1·04–2·49]; $p=0·034$), independent of age. LOMEDS was associated with increased mortality (hazard ratio 2·10 [95% CI 1·57–2·82]; $p<0·0001$), and faster cognitive decline. Interictal EEG abnormalities showed little diagnostic utility.

Interpretation Epilepsy increases sharply after symptomatic Alzheimer's disease onset in people with Down syndrome. The association of epilepsy with reduced survival and accelerated cognitive decline underscores the need for targeted preventive and therapeutic strategies against Alzheimer's disease-related epileptogenesis and hyperexcitability.

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Introduction

Epilepsy and dementia rank among the leading neurological disorders worldwide.¹ These two conditions are increasingly being studied for their intersection, as evidence suggests epilepsy in older people is frequently associated with neurodegeneration and dementia, particularly Alzheimer's disease.^{2–4} Literature on individuals with sporadic and autosomal-dominant forms of Alzheimer's disease^{5,6} shows higher rates of epilepsy than in the general population, which has been

associated with faster cognitive decline and higher mortality risk.⁷

Down syndrome is the commonest genetic cause of intellectual disability. Individuals with Down syndrome also represent the largest genetically determined Alzheimer's disease population, due to *APP* gene triplication on chromosome 21, with near-universal neuropathology by age 40 years and a lifetime risk of dementia greater than 90%.⁸ Early series reported overall epilepsy prevalences of 5·5%^{9,10} in people with Down

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*Joint first authors

†Joint last authors

Sant Pau Memory Unit, IR
SANT PAU, Hospital de la Santa
Creu i Sant Pau, Universitat

Autònoma de Barcelona,
Barcelona, Spain
(L Maure-Blesa MD,

M Carmona-Iragui MD PhD,

I Barroeta MD PhD,

J Arranz MD PhD,

Í Rodríguez-Baz MD PhD,

B Benejam PhD, L Videla PhD,

J E Arriola-Infante MD PhD,

L Del Hoyo Soriano PhD,

L Pertierra MD,

L Vaqué-Alcázar PhD,

A Sanjuan MSc, A Bueno PhD,

M R Aranha MD PhD,

O Lorente MSc,

A O Morcillo-Nieto MSc,

S Sirisi PhD, O Dols-Icardo PhD,

O Belbin PhD, D Alcolea MD PhD,

A Bejanin PhD, A Lleó MD PhD,

J Fortea MD PhD); Department

of Medicine, Universitat

Autònoma de Barcelona,

Barcelona, Spain

(L Maure-Blesa, J Arranz, A Lleó);

Centro de Investigación

Biomédica en Red en

Enfermedades

Neurodegenerativas

(CIBERNED), Madrid, Spain

(M Carmona-Iragui, I Barroeta,

Í Rodríguez-Baz, L Videla,

L Del Hoyo Soriano,

A O Morcillo-Nieto, S Sirisi,

O Dols-Icardo, O Belbin,

D Alcolea, A Bejanin, A Lleó,

J Fortea); Barcelona Down

Medical Center, Fundació

Catalana Síndrome de Down,

Barcelona, Spain

(M Carmona-Iragui,

S Fernández MD, B Benejam,

L Videla, J Fortea); Global Brain

Health Institute, Trinity College

Dublin, Dublin, Ireland

Research in context

Evidence before this study

We searched MEDLINE (PubMed; from inception to Oct 1, 2025); abstracts from the International League Against Epilepsy, the Alzheimer's Association, and Trisomy 21 Research Society; hand searched reference lists; and performed forward citation tracking. No language limits were applied; non-English articles were translated as needed. Search terms combined controlled vocabulary and free text for three concepts: population ("Down syndrome", "Down's syndrome", "trisomy 21"; epilepsy ("epilepsy", "seizure*", "myoclon*", "late-onset myoclonic epilepsy of Down syndrome", "LOMEDS"), and epidemiology or clinical impact ("prevalence", "incidence", "risk", "age of onset", "hazard*", "survival", "mortality", "cognit*", "functional decline"), with Alzheimer's modifiers ("Alzheimer*", "dementia", "amyloid", "Down syndrome-associated Alzheimer*", "DSAD"). We included observational studies reporting epilepsy prevalence, incidence, or age-specific risk in adults with Down syndrome; studies on the temporal relation between symptomatic Alzheimer's disease and epilepsy; and studies reporting clinical consequences. We excluded single case reports or series (<10 participants) and paediatric-only reports.

Previous work suggested a high overall epilepsy burden with a late-adult peak, but was constrained by small samples, few older adults, and non-standard Alzheimer's disease ascertainment. Consequently, the nature and timing of epilepsy relative to Alzheimer's disease, its clinical and prognostic effect, and its potential as a disease activity marker or therapeutic target remain unclear.

Added value of this study

We report the largest multicentre characterisation of adult epilepsy in Down syndrome (n=4804), with standardised symptomatic Alzheimer's disease assessment (n=1299 with symptomatic Alzheimer's disease), spanning the full adult life

course using time-to-event analyses. We deliver granular, age-specific, and Alzheimer's disease-specific estimates of epilepsy burden and the timing of seizure emergence.

We show that while baseline epilepsy burden in early adulthood is higher than in the general population, it rises sharply with symptomatic Alzheimer's disease when late-onset myoclonic epilepsy in Down syndrome (LOMEDS) emerges. LOMEDS is driven by time since Alzheimer's disease symptom onset rather than chronological age and predicts worse cognition and earlier mortality (hazard ratio 2.10 [95% CI 1.57–2.82]). Scalp electroencephalography has low diagnostic accuracy (area under the curve 0.57).

Implications of all the available evidence

This study establishes LOMEDS as a dominant, clinically distinctive, and prognostically meaningful comorbidity of Alzheimer's disease in Down syndrome. The tight temporal coupling to symptomatic onset, characteristic semiology, and strong associations with survival and cognitive decline identify LOMEDS as both a marker of disease activity and a potentially modifiable mediator of progression. Clinically, adult Down syndrome services should implement systematic seizure surveillance across adulthood and adopt age-specific and Alzheimer's disease stage-informed management pathways. Scientifically, the findings extend evidence from sporadic and autosomal-dominant Alzheimer's disease and position Down syndrome-associated Alzheimer's disease as a uniquely informative model of Alzheimer's disease-related epileptogenesis. Our findings offer concrete parameters for trial design (enrichment around the Alzheimer's disease clinical transition and seizure-related endpoints) and should encourage prospective, biomarker-integrated cohort studies to detect network hyperexcitability before overt seizures and test targeted anti-hyperexcitability interventions, transforming a high-risk marker into a targetable pathway for disease modification.

syndrome, higher than in the general population, but lower than in other forms of intellectual disability;¹¹ nonetheless, these studies included few individuals older than 50 years. When looking at older groups, smaller cohort studies show a sharp age-related increase in epilepsy prevalence, from 15% at a mean age of 42 years to 46% after 50 years, and up to 84–100% among those with symptomatic Alzheimer's disease.^{12–14} This late, Alzheimer's disease-related epilepsy typically presents with tonic-clonic and myoclonic seizures, termed late-onset myoclonic epilepsy in Down syndrome (LOMEDS).^{15–17} Yet, growing evidence suggests that neuronal hyperexcitability might emerge in early stages of Alzheimer's disease,^{18,19} making the systematic study of the natural history of LOMEDS, including its precise temporal relationship with the emergence of symptomatic Alzheimer's disease, its effect on cognitive trajectory, and its implications for survival, both timely

and largely unaddressed. Previous characterisations of LOMEDS have relied predominantly on cross-sectional data from small studies, leaving these questions open. We believe that filling this gap is essential to understand the bidirectional relationship between epilepsy and Alzheimer's disease, to clarify implications of epilepsy for individuals with Down syndrome, and to inform the design of future therapeutic interventions.

Our objectives were to (1) estimate age-specific prevalence and incidence of epilepsy; (2) characterise empirically the timing and seizure semiology of new-onset epilepsy in relation to symptomatic Alzheimer's disease onset and its accordance to previous descriptions of LOMEDS; (3) identify predictors of LOMEDS in symptomatic Alzheimer's disease; (4) examine effects on survival and cognitive trajectories; and (5) assess the diagnostic value of electroencephalogram (EEG) abnormalities.

(M Carmona-Iragui, L Pertierra, E McGlinchey PhD); **Radiology Department, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain** (M R Aranha); **Institut de Neurociències, Universitat Autònoma de Barcelona, Barcelona, Spain** (L Pertierra, L Vaqué-Alcázar, A O Morcillo-Nieto); **Multidisciplinary Sleep Unit, IR SANT PAU, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain** (S Giménez MD PhD); **Center for Research and Memory Clinic, CITA-Alzheimer Foundation, Gipuzkoa, Spain** (A Estanga PhD, M García-Sebastián PhD, N Ros MSc, M Altuna MD PhD); **Department of Clinical and Health Psychology and Research Methods, University of the Basque Country 12 UPV/EHU, Gipuzkoa, Spain** (N Ros, M Altuna); **Epilepsy Research Group, Institut de Recerca Sant Pau (IR SANTPAU), Barcelona, Spain** (V Ros-Castelló, A Sierra-Marcos); **Epilepsy Unit, Neurology Department, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain** (V Ros-Castelló, A Sierra-Marcos); **Department of Psychiatry, New York University Grossman School of Medicine, New York, NY, USA** (C P Lisgaras PhD, E Blessing MD PhD, R S Osorio MD); **Center for Dementia Research, The Nathan S. Kline Institute for Psychiatric Research, New York, NY, USA** (C P Lisgaras); **Department of Neurology, LMU University Hospital, LMU Munich, Klinikum der Universität München, Munich, Germany** (A C Stockbauer MD, G Nuebling MD, J M Remi MD, J Levin MD PhD); **German Center for Neurodegenerative Diseases, Munich, Germany** (A C Stockbauer, G Nuebling, J M Remi, J Levin); **Trinity Centre for Ageing and the Lifecourse in Intellectual Disability, School of Nursing and Midwifery, Trinity College Dublin, Dublin, Ireland** (Prof M McCarron PhD, K Lima PhD, E McGlinchey); **AVISTA CLG, Clonsilla, St Joseph's Hospital, Dublin, Ireland** (Prof M McCarron, P Dunne MSc); **Institut Jérôme Lejeune, Paris, France** (A-S Rebillat MD PhD); **Department of Neurology, Torrecárdenas University Hospital, Almería, Spain**

(J E Arriola-Infante); Servicio de Medicina Interna, Hospital Universitario La Princesa, Madrid, Spain (B Sánchez-Moreno MD PhD, D R de Asua MD PhD); Instituto de Investigación Sanitaria del Hospital Universitario La Princesa – IIS, Madrid, Spain (B Sánchez-Moreno, N Montes PhD, D R de Asua); Departamento de Medicina, Universidad Autónoma de Madrid, Madrid, Spain (D R de Asua); Department of Neurology, Dr Balmis General University Hospital, Alicante Institute for Health and Biomedical Research (ISABIAL), Alicante, Spain (J Arranz)

Correspondence to: Dr María Carmona-Iragui, Sant Pau Memory Unit, Hospital de la Santa Creu i Sant Pau, 08025 Barcelona, Spain MCarmona@santpau.cat

See Online for appendix

Methods

Study design

We conducted a prospective, multicentre, observational, longitudinal study of adults (aged ≥ 18 years) with Down syndrome, pooling harmonised variables from seven clinical cohorts with an aggregate observation window from Oct 24, 2012, to July 28, 2025. The cohorts were DABNI (Barcelona, Spain), AD21 Munich (Munich, Germany), IDSTILDA and AVISTA (Ireland), Institut Jérôme Lejeune (Paris, France), DS-BAI (Donostia, Spain), and HLP (Madrid, Spain; appendix pp 1–2).

Participants and procedures

All patients included were seen within specialist Down syndrome clinics and received equivalent structured follow-up. Information was collected from participants and their caregivers on demographics (including self-reported sex), co-occurring medical conditions, and regular medications including antiseizure medication. Race and ethnicity data were not systematically collected across all seven cohorts included in this study. Following clinical examination and neuropsychological review, we assigned intellectual disability level (mild, moderate, or severe–profound).

We did cognitive staging at each visit during follow-up by clinical consensus using a harmonised taxonomy: (1) cognitively stable (ie, no clinical or neuropsychological suspicion of Alzheimer's disease-related cognitive decline), (2) prodromal Alzheimer's disease (ie, evidence of cognitive decline due to Alzheimer's disease, but no significant effect on baseline activities of daily living), (3) Alzheimer's disease dementia (ie, when the cognitive decline impaired daily activities), and (4) uncertain or non-neurodegenerative cognitive decline (ie, when there were medical, pharmacological, or psychiatric conditions interfering with cognition or daily activities, but no suspicion of neurodegenerative origin). The first medical record noting a cognitive status of prodromal Alzheimer's disease or Alzheimer's disease dementia for each patient was taken as the date of Alzheimer's disease diagnosis and is referred to hereon as Alzheimer's disease diagnosis. Of note, because Alzheimer's disease diagnosis dates often lag behind symptom onset and visits typically occur annually, we defined a symptomatic Alzheimer's disease window starting 1 year before the recorded diagnosis and extending to the end of follow-up. This window was applied uniformly across all cohorts. Sensitivity analyses using alternative windows (6 months, 2 years, and 3 years before diagnosis) as well as full operational definitions and detailed justification of the 1-year threshold are provided in the appendix (pp 2, 5–7). Across cohorts, the clinical diagnoses followed a standardised workflow of independent masked neurological and neuropsychological assessments with consensus review, informed by routine laboratory tests and neuroimaging but masked to Alzheimer's disease biomarkers. All contributing cohorts are members of the

Horizon21 consortium, an international network established to harmonise diagnostic procedures and define common criteria for Alzheimer's disease diagnosis in Down syndrome across sites. Where available, adults with Down syndrome also underwent a specific longitudinal neuropsychological assessment, using the Cambridge Cognitive Examination for Older Adults with Down Syndrome (CAMCOG-DS²⁰), to evaluate global cognition.

Epilepsy was defined at visits according to the International League Against Epilepsy (ILAE) criteria (≥ 2 unprovoked seizures >24 h apart, or one unprovoked seizure with $\geq 60\%$ 10-year recurrence risk, or an epilepsy syndrome diagnosis).²¹ Active epilepsy at last visit required diagnosis of epilepsy with ongoing antiseizure medication use or at least one unprovoked seizure within the previous 5 years. Childhood-onset epilepsy did not preclude inclusion in the prevalence analyses; individuals with childhood-onset epilepsy contributed to adult active epilepsy prevalence estimates if they still met criteria for active epilepsy in adulthood;²² however, adults with active epilepsy already present in childhood were excluded from the adult-incidence of new epilepsy analyses. We excluded from active-epilepsy definitions any acute symptomatic seizure secondary to structural lesions, fever, or other precipitants (ie, acute symptomatic). When available, we ascertained first seizure dates and semiology from caregiver and medical records, mapping semiology to the ILAE classification.²¹ We operationalised LOMEDS as epilepsy arising in parallel with the predefined symptomatic Alzheimer's disease window—ie, any active epilepsy with onset from 1 year before the recorded Alzheimer's disease diagnosis date and thereafter. We applied no age or semiology restrictions, intentionally using a broad Alzheimer's disease-related epilepsy umbrella to enable reappraisal of the term. The 1-year threshold was supported by a change-point analysis identifying a marked acceleration in first seizure incidence beginning approximately 1 year before the formal Alzheimer's disease diagnosis (figure 1; appendix p 4) as well as a piecewise linear regression (appendix p 5). Sensitivity analyses using alternative windows (6 months, 2 years, and 3 years before diagnosis) as well as full operational definitions and detailed justification of the 1-year threshold are provided in the appendix (pp 2–7). Standardised research EEGs (10–20 montage, hyperventilation, intermittent photic stimulation, ≥ 20 min to 30 min) were offered to participants with and without epilepsy, including longitudinal assessments and read by masked epileptologists. Qualitative review captured interictal epileptiform discharges (IEDs) and background abnormalities. APOE genotyping was available for 1468 individuals of the DABNI, IJL, and HLP cohorts (representing 30.6% of the whole sample), and 553 (42.6%) of 1299 in the symptomatic subsample (prodromal Alzheimer's disease or Alzheimer's disease dementia) in which all APOE analyses were done.

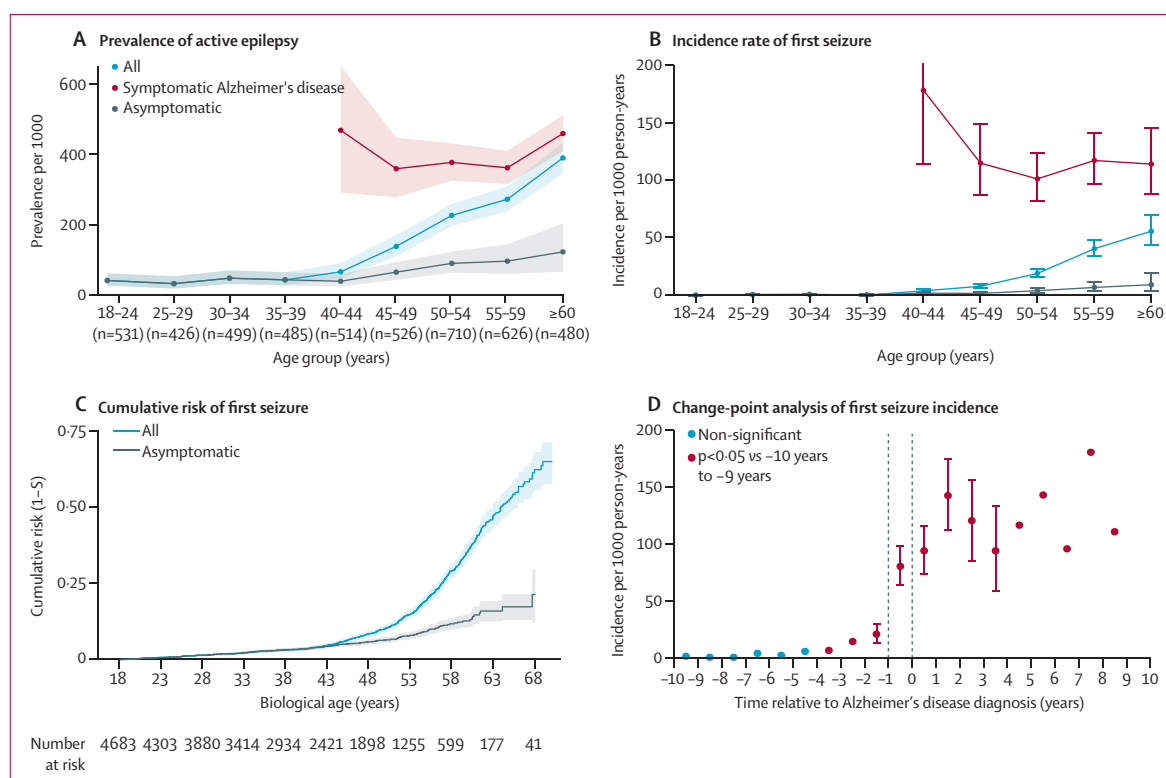


Figure 1: Epilepsy across the adult Down syndrome lifespan

(A) Cross-sectional age-specific prevalence of active epilepsy at last visit, per 1000 individuals with Down syndrome with exact Clopper-Pearson 95% CIs by age group. Symptomatic Alzheimer's disease includes prodromal or dementia-stage Alzheimer's disease at last visit; asymptomatic includes cognitively stable or uncertain non-neurodegenerative. (B) Incidence rate of first seizure per 1000 person-years by age group with exact Poisson 95% CIs. Symptomatic Alzheimer's disease includes participants whose first seizure occurred from 1 year before Alzheimer's disease diagnosis onwards; asymptomatic includes participants whose first seizure occurred more than 1 year before Alzheimer's disease diagnosis or in individuals never diagnosed with Alzheimer's disease. (C) Kaplan-Meier cumulative risk of first seizure from age 18 years. All indicates complete follow-up; asymptomatic includes participants censored from 1 year before Alzheimer's disease diagnosis onwards or end of follow-up if no Alzheimer's disease diagnosis. (D) Change-point analysis of first seizure incidence using annual intervals from -10 years to +10 years relative to Alzheimer's disease diagnosis; reference interval -10 years to -9 years; red points indicate $p < 0.05$ versus reference; blue dotted line marks the operative threshold of 1 year before Alzheimer's disease diagnosis onwards; points are omitted when fewer than 20 person-years at risk and CIs are omitted when fewer than 20 events are recorded. Shaded areas and error bars show 95% CIs.

Obstructive sleep apnoea was assessed only in cohorts that collected such data (IJL, DABNI, DS-BAI, and HLP) and was coded as either present or absent: "present" required polysomnography or polygraphy confirmation and "absent" reflected a negative test or no test when there was no clinical suspicion.

Mortality data were available for all cohorts except AD21 Munich.

All cohorts obtained local ethics approval and informed consent or assent with legally authorised representatives as appropriate. Data were de-identified before pooling; analyses used coded identifiers and secure transfers.

Statistical analysis

To characterise the epidemiology of epilepsy across the adult lifespan in Down syndrome and its relationship to symptomatic Alzheimer's disease, we estimated the age-specific prevalence of active epilepsy and the incidence and cumulative incidence of a first epileptic seizure across age and along the Alzheimer's disease continuum.

Active epilepsy prevalence was estimated by 5-year age bands (18–24 years to ≥ 60 years) per stratum by cognitive status assigned at last visit with exact binomial (Clopper-Pearson) 95% CIs. We estimated the incidence of first epileptic seizures per 1000 person-years, excluding individuals whose first seizure occurred before age 18 years. Person-time was split into single-year age bands aligning each participant's data with integer ages. Analyses were stratified into (1) all adults (aged ≥ 18 years); (2) symptomatic participants, from 1 year before Alzheimer's disease diagnosis onwards; and (3) asymptomatic individuals, from age 18 years up to the cutoff or censoring. Rates were reported with exact Poisson 95% CIs. To characterise the temporal relationship between seizure onset and Alzheimer's disease diagnosis, we did a Poisson-based change-point analysis of first seizure incidence using annual intervals from 10 years before to 10 years after the recorded Alzheimer's disease diagnosis date, with the most distal interval (-10 years to -9 years) as reference.

Cumulative incidence was estimated using Kaplan–Meier (1–S) with 95% CIs for lifetime risk in the overall adult population and in asymptomatic-only individuals. For symptomatic individuals (Alzheimer’s disease–1 window), cumulative incidence of first seizure was estimated using the Aalen–Johansen estimator, treating death as a competing event, to account for the substantial mortality observed in this population. Kaplan–Meier estimates are additionally presented by seizure type within the symptomatic window for descriptive purposes. Additionally, we estimated the cumulative probability of a subsequent generalised tonic-clonic seizure using Kaplan–Meier (1–S) among those individuals whose first recorded post-Alzheimer’s disease seizure was generalised myoclonic. To explore seizure timing relative to age at Alzheimer’s disease diagnosis, we calculated first-seizure incidence (per 1000 person-years) in annual bins from –1 year to +10 years around diagnosis, stratified by age at Alzheimer’s disease onset (<50 years, 50–60 years, >60 years), with exact Poisson 95% CIs.

To identify predictors of active epilepsy in symptomatic Alzheimer’s disease, we did univariable and multivariable logistic regression. The multivariable model was fitted on complete cases and included sex, age at visit, intellectual disability level, time since Alzheimer’s disease diagnosis, obstructive sleep apnoea, and APOE $\epsilon 4$ and $\epsilon 2$ carrier status (defined as $\epsilon 3\epsilon 4/\epsilon 4\epsilon 4$ and $\epsilon 2\epsilon 2/\epsilon 2\epsilon 3$, respectively; $\epsilon 2\epsilon 4$ heterozygotes were analysed separately; appendix p 8). To model time to first seizure onset as a longitudinal outcome, we ran univariable and multivariable Fine–Gray competing risks regression on complete cases, initiating follow-up 1 year before Alzheimer’s disease diagnosis, with death as a competing event and the same covariates.

Odds ratios (ORs) and subdistribution hazard ratios (HRs) are displayed on a log scale. To assess the effect of LOMEDS on survival and cognitive trajectories, we modelled survival since the Alzheimer’s disease diagnosis using a time-dependent Cox model (counting-process form), coding LOMEDS as 0 before onset and 1 thereafter, with onset estimates at 2 years, 4 years, and 6 years following Alzheimer’s disease diagnosis. We did survival analyses in six of the seven participating cohorts with mortality data (all except AD21 Munich). Non-proportional hazards were addressed by allowing the latency effect to vary over time through an interaction with log(time since diagnosis). Cluster-robust SEs were computed by participant identification. Cognitive trajectories (CAMCOG-DS) were modelled with linear mixed-effects broken-stick models centred on LOMEDS onset.

Finally, we assessed EEG-derived features as candidate biomarkers of LOMEDS. Each available EEG was analysed as an independent observation. We recorded the prevalence of EEG-derived features, stratified by cognitive stage and epilepsy status, and analysed their diagnostic performance by constructing receiver operating characteristic curves and areas under the curve (AUCs).

All analyses were done in R (version 4.4.2); key packages included *survival* for Kaplan–Meier and Kaplan–Meier and time-dependent Cox models, *lme4* with *lmerTest* for linear mixed-effects models, and *ggplot2* for graphics (appendix p 21).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

	Overall (n=4804)	Cognitively stable (n=3238)	Non-neurodegenerative cognitive decline (n=267)	Prodromal Alzheimer’s disease (n=321)	Alzheimer’s disease dementia (n=978)	p value	q value	Effect size
Age at visit, years	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	<0·0001	$\eta^2=0·424$
Sex								
Male	2489/4804 (52%)	1740/3238 (54%)	144/267 (54%)	172/321 (54%)	433/978 (44%)	<0·0001	<0·0001	V=0·077
Female	2315/4804 (48%)	1498/3238 (46%)	123/267 (46%)	149/321 (46%)	545/978 (56%)	..	..	..
Intellectual disability								
Mild	1020/4151 (25%)	804/2742 (29%)	22/236 (9%)	57/276 (21%)	137/897 (15%)	<0·0001	<0·0001	V=0·135
Moderate	2352/4151 (57%)	1529/2742 (56%)	141/236 (60%)	160/276 (58%)	522/897 (58%)	..	..	..
Severe or profound	779/4151 (19%)	409/2742 (15%)	73/236 (31%)	59/276 (21%)	238/897 (27%)	..	..	..
Active epilepsy at last visit	699/4804 (15%)	157/3238 (5%)	28/267 (10%)	55/321 (17%)	459/978 (47%)	<0·0001	<0·0001	V=0·473
History of febrile seizures	45/1358 (3%)	24/724 (3%)	2/77 (3%)	5/100 (5%)	14/457 (3%)	0·76	>0·99	V=0·028
History of CNS infection	18/1324 (1%)	10/699 (1%)	0	2/97 (2%)	6/451 (1%)	0·75	>0·99	V=0·033
History of traumatic brain injury	24/1324 (2%)	10/698 (1%)	2/76 (3%)	3/97 (3%)	9/453 (2%)	0·41	>0·99	V=0·037

Data are median (IQR) for age and n/N (%) for categorical variables. Demographic and clinical characteristics by cognitive status of all participants (tables stratified by cohort are available in appendix pp 13–16). Multiplicity was controlled using Bonferroni-adjusted q-values. Effect sizes are reported for all participants: η^2 for age at visit (Kruskal–Wallis) and Cramér’s V for categorical variables (interpretation: <0·10 small, 0·10–0·30 moderate, and >0·30 large). Holm-adjusted pairwise comparisons (Wilcoxon rank-sum for age; Fisher’s exact for binary variables; Fisher’s exact on R $\times$ 2 for multi-category intellectual disability) for variables with q<0·05 are reported in the appendix (p 12). Active epilepsy refers to status at the last visit.

Table: Participant demographics

Results

We recruited 4865 adults with Down syndrome, of whom 4804 (98.7%) had an available cognitive status at last visit and the minimum common dataset, and were therefore included for subsequent analysis. The median age at last visit was 44 years (IQR 32–54), 2315 (48%) were female, and 2489 (52%) were male (table). 3238 (67.4%) participants were cognitively stable, 267 (5.6%) had uncertain or non-neurodegenerative cognitive decline, 321 (6.7%) had prodromal Alzheimer's disease, and 978 (20.3%) had Alzheimer's disease dementia. Intellectual disability was mild in 1020 (24.6%) participants, moderate in 2352 (56.7%), and severe or profound in 779 (18.8%). Mean overall follow-up per patient was 3.38 years (SD 3.11).

Active epilepsy affected 145.2 per 1000 adults with Down syndrome overall and was strongly age dependent, increasing from 39.4 per 1000 at age 18–24 years to 389.6 per 1000 at age 60 years or older, mainly driven by patients with symptomatic Alzheimer's disease (121.2 per 1000 in asymptomatic individuals aged ≥ 60 years vs 459.3 per 1000 in symptomatic individuals aged ≥ 60 years; figure 1A). Incidence rates followed similar age-related gradients (figure 1B), with an overall incidence of 5.07 per 1000 person-years, reaching 56.4 per 1000 person-years at age 60 years and older, again driven by symptomatic individuals (6.9 per 1000 person-years in asymptomatic individuals aged ≥ 60 years vs 109.6 per 1000 person-years in symptomatic individuals aged ≥ 60 years; figure 1B). The cumulative risk of epilepsy in all adults with Down syndrome

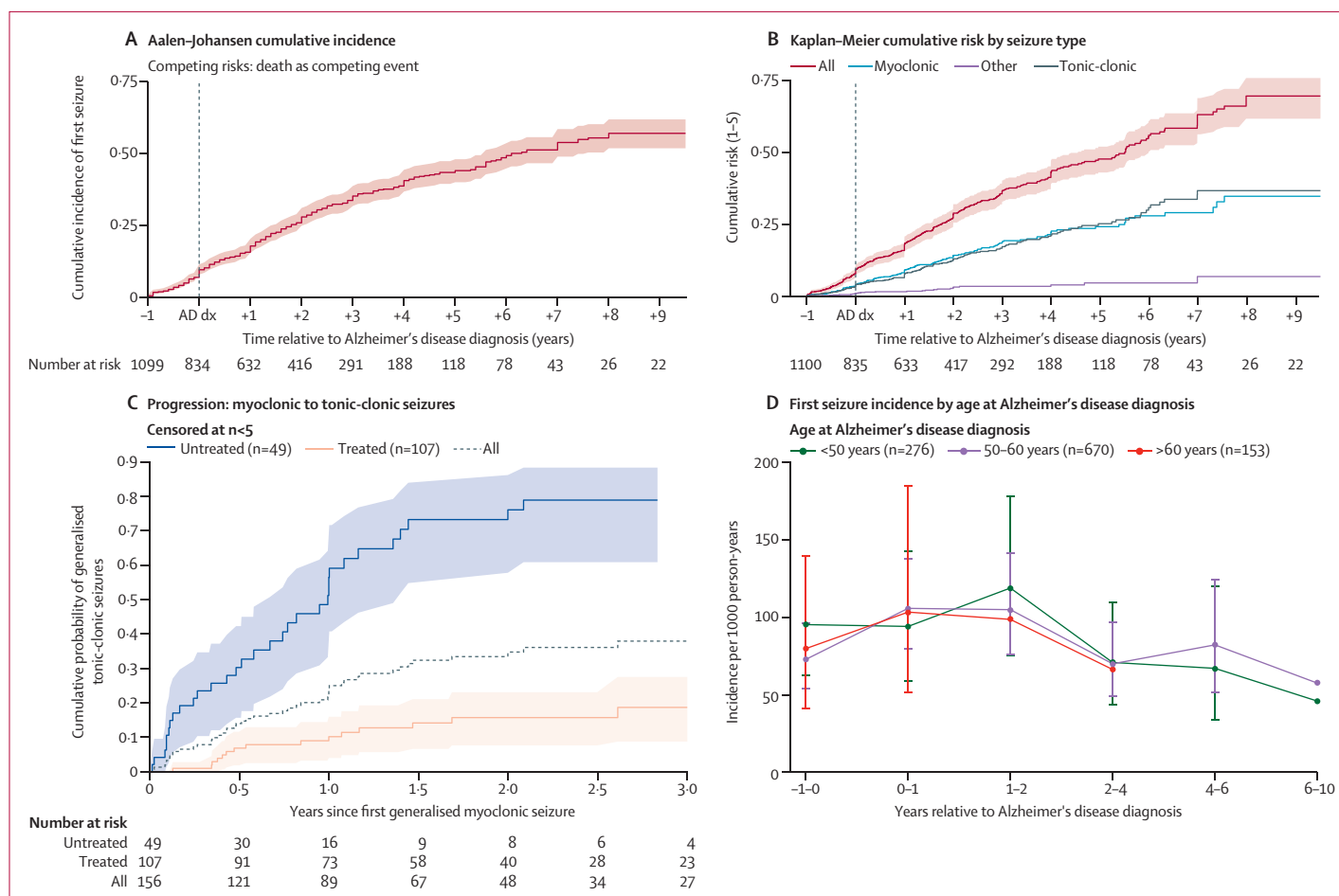


Figure 2: Natural history and semiology of epilepsy arising in parallel to symptomatic Alzheimer's disease (LOMEDS)

All analyses use a symptomatic Alzheimer's disease window defined as 1 year before Alzheimer's disease diagnosis. Time 0 indicates date of Alzheimer's disease diagnosis and curves are shown until fewer than 20 individuals remain at risk (except for panel C). (A) Aalen-Johansen cumulative incidence of first seizure from 1 year before Alzheimer's disease onwards, treating death as a competing event. Numbers at risk refer to individuals entering the symptomatic window without a previous seizure. (B) Kaplan-Meier cumulative risk of first seizure from 1 year before Alzheimer's disease onwards, overall (red) and stratified by seizure type at first event: generalised myoclonic (blue), tonic-clonic (grey), and other (purple). Numbers at risk refer to the overall cohort. (C) Kaplan-Meier cumulative probability of progression from a first generalised myoclonic seizure to a generalised tonic-clonic seizure, in treated (orange) and untreated (blue) individuals, with overall curve (dashed). Censored when fewer than five individuals remain at risk, given the smaller subset analysed in this panel. (D) Incidence rate of first seizure per 1000 person-years by time interval relative to Alzheimer's disease diagnosis, stratified by age at Alzheimer's disease diagnosis (<50 years, 50–60 years, >60 years). Points are shown only when at least three events are recorded and CIs when at least ten events. LOMEDS=late-onset myoclonic epilepsy in Down syndrome. Shaded areas and error bars show 95% CIs. AD dx=Alzheimer's disease diagnosis.

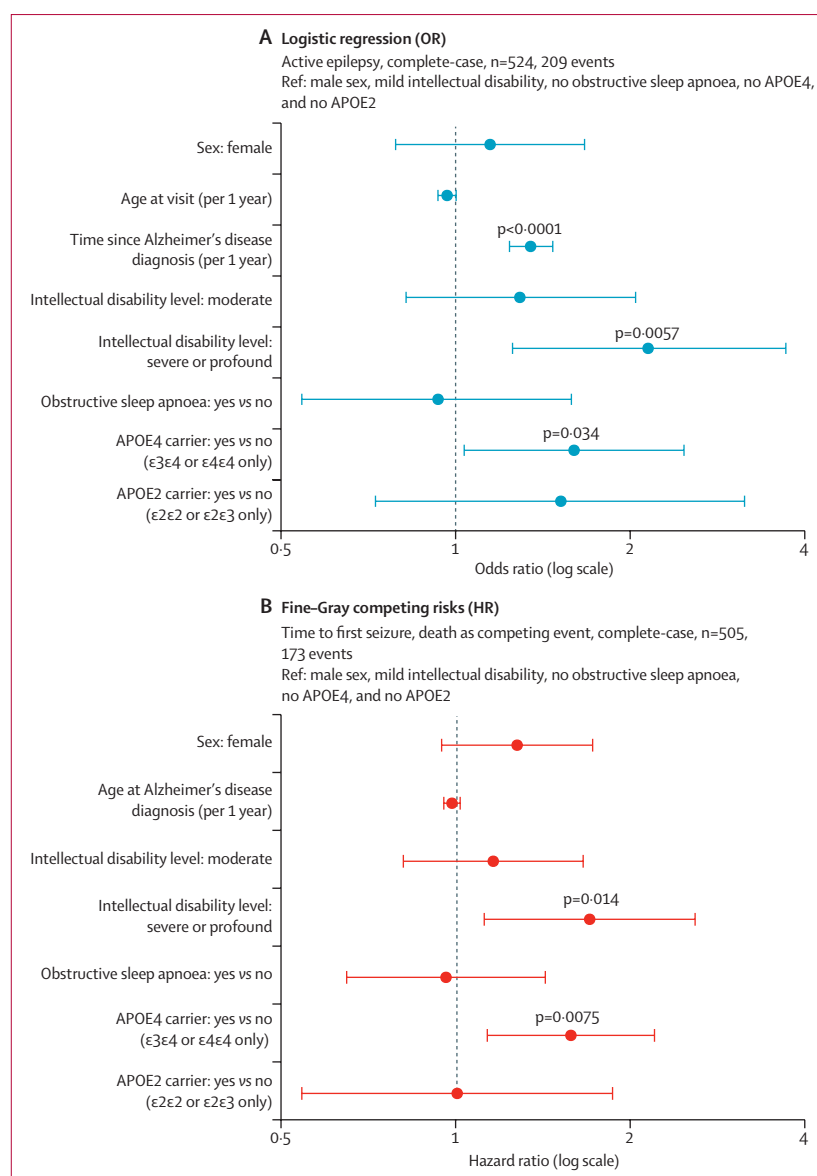


Figure 3: Predictors of active epilepsy in Down syndrome with symptomatic Alzheimer's disease
(A) Multivariable logistic regression showing adjusted ORs for active epilepsy. (B) Multivariable Fine-Gray competing risks model showing adjusted sub-distribution HRs for time to first seizure from 1 year before Alzheimer's disease diagnosis onwards, with death as a competing event. Both models include sex, age at Alzheimer's disease diagnosis (per 1 year), intellectual disability level, time since Alzheimer's disease diagnosis (per 1 year), obstructive sleep apnoea, and APOE4 carrier status (ε3ε4 or ε4ε4 vs remainder). Obstructive sleep apnoea was coded as positive only when confirmed by polysomnography. Dashed line marks an OR or HR of 1, the x-axis is on a log scale, and error bars show 95% CIs. HR=hazard ratio. OR=odds ratio.

increased steadily: 3.3% at age 40 years (2.7–3.8), 9.7% at age 50 years (8.5–10.8), 33.9% at age 60 years (31.1–36.7), and 61.3% at age 70 years (54.3–67.2; figure 1C). When considering only asymptomatic individuals, we also saw an age-dependent increase, but to lower levels (12.0% at age 60 years [9.9–14.0]; figure 1C). Incidence rates of new-onset seizures remained low and stable until a marked acceleration in the final pre-diagnostic year (incidence rate ratio 93.9

vs reference interval [–10 to –9]; p<0.0001; figure 1D; appendix p 4).

The cumulative incidence of LOMEDS, estimated using the Aalen–Johansen method accounting for competing mortality, increased after symptom emergence, from 9.5% (95% CI 7.8–11.3) at Alzheimer's disease diagnosis to 56.9% (51.7–61.7) at 9 years post-diagnosis (figure 2A). Generalised tonic-clonic and myoclonic seizures predominated, with other seizure types being far less frequent (figure 2B). Among individuals whose first post-symptomatic Alzheimer's disease seizure was myoclonic, the cumulative probability of later generalised tonic-clonic seizures differed significantly in participants treated with antiseizure medication after the first recorded myoclonic seizure (9.6% [95% CI 3.4–15.5] at 1 year, 15.5% [7.2–23.1] at 2 years, and 18.7% [8.3–27.8] at 3 years) versus untreated participants (57.9% [39.4–70.7] at 1 year, 77.4% [59.1–87.5] at 2 years, and 80.2% [62.1–89.7] at 3 years; figure 2C). Incidence rates of first seizure showed similar temporal patterns across ages at Alzheimer's disease diagnosis (<50 years, 50–60 years, and >60 years; figure 2D). Additional semiology seizure classification in asymptomatic and symptomatic individuals is provided in the appendix (pp 17–19).

Regarding antiseizure medication at last visit in individuals with LOMEDS (n=515), 410 (79.6%) were on monotherapy, 84 (16.3%) on dual therapy, 18 (3.5%) on polytherapy, and three (0.6%) had no treatment recorded. Within monotherapy, the three most common agents were levetiracetam (225 [54.9%]), valproate (82 [19.9%]), and lamotrigine (48 [11.8%]). Among individuals with myoclonic seizures (205 [39.8%]), 94 (45.9%) reported morning predominance and 41 (20.0%) had falls due to the seizures. Ten (1.9%) individuals with known LOMEDS had an epileptic status that required hospitalisation and in two cases led to death.

In the multivariable complete-case model, time since Alzheimer's disease diagnosis (adjusted OR 1.33 per year [95% CI 1.22–1.45]; p<0.0001), severe or profound intellectual disability (2.14 [1.25–3.70]; p=0.0057), and APOE ε4 carriership (1.61 [1.04–2.49]; p=0.034) were independently associated with LOMEDs (figure 3A). In the multivariable complete-cases model, severe or profound intellectual disability (HR 1.70 [95% CI 1.11–2.58]; p=0.014) and APOE ε4 carriership (1.57 [1.13–2.20]; p=0.0075) were independently associated with LOMEDs (figure 3B; univariable models are shown in the appendix p 8). Exploratory analyses of age at Alzheimer's disease diagnosis by seizure timing are presented in the appendix (p 12).

LOMEDS was strongly associated with increased mortality and faster cognitive decline. In time-dependent Cox models, LOMEDS was associated with increased mortality (HR 2.10 [95% CI 1.57–2.82]; p<0.0001), with earlier onset conferring a substantially worse prognosis: at 8 years of follow-up, the

model-estimated HRs compared with no LOMEDS were 2.10 (1.57–2.82) for onset at Alzheimer's disease diagnosis, 1.63 (1.22–2.18) for onset at 2 years after diagnosis, 1.26 (0.87–1.84) for onset at 4 years, and 0.98 (0.59–1.63) for onset at 6 years post-diagnosis. The association was consistent across all six cohorts ($I^2=8.6\%$; Q-test $p=0.36$; appendix p 7) and was robust to adjustment for intellectual disability level (adjusted HR 2.16 [95% CI 1.60–2.92]; appendix p 8). Cognitive trajectories (CAMCOG-DS) from 360 individuals (1268 visits) showed a decline of 3.6 points per year (95% CI –4.3 to –3.0) in participants with symptomatic Alzheimer's disease without LOMEDS. Following first seizure onset, scores dropped abruptly by 7.1 points per year (–9.6 to –4.6) and the rate of decline increased by a further 4.2 points per year (–6.0 to –2.4), resulting in a total post-LOMEDS decline of 7.8 points per year (95% CI –9.6 to –6.1; figure 4B). The effect of LOMEDS on CAMCOG-DS subdomains is shown in the appendix (p 10). Importantly, baseline CAMCOG-DS scores were similar between individuals who later developed LOMEDS and those who did not (appendix pp 10–11).

In 647 EEGs, IEDs were uncommon without epilepsy (7.6% [27/354; 95% CI 4.9–10.4] in asymptomatic participants, 4.3% [2/47; 0–10.0] in prodromal Alzheimer's disease, and 8.8% [12/137; 4.0–13.5] in Alzheimer's disease dementia) and higher in those with active epilepsy and Alzheimer's disease dementia (17.4% [4/23; 1.9–32.9] in asymptomatic participants, 14.3% [1/7; 0–40.2] in prodromal Alzheimer's disease, and 24.1% [19/79; 14.6–33.5] in Alzheimer's disease dementia) where IEDs, when morphologically and topographically described, were most commonly generalised sharp waves (seven [53.8%] of 13) and spike waves (six [46.2%] of 13). Background (diffuse) slowing increased with clinical severity and was more frequent in individuals with epilepsy among asymptomatic adults (6/23 [26.1%; 95% CI 8.1–44.0] vs 25/356 [7.0%; 4.4–9.7]; $p=0.0068$), but not among those with dementia (33/79 [41.8%; 30.9–52.6] vs 50/137 [36.5%; 28.4–44.6]; $p=0.44$; figure 5). When pooled across symptomatic stages, slowing was markedly more common in symptomatic Alzheimer's disease than in asymptomatic (98/270 [36.3%; 30.6–42.0] vs 31/379 [8.2%; 5.4–10.9]; $p<0.0001$) and, among tracings with subtype data, was predominantly theta (30/37 [81.1%; 68.5–93.7]), with delta features in 21 of 37 participants (56.8% [40.8–72.7]). As classifiers of epilepsy, IEDs showed poor performance (AUC 0.57 [95% CI 0.53–0.61]), and background slowing performed only slightly better (AUC 0.60 [0.55–0.65]), while showing an AUC of 0.64 (0.61–0.67) to discriminate symptomatic Alzheimer's disease.

Discussion

In this large, longitudinal, multicentre study of adults with Down syndrome, we showed that epilepsy is a frequent and clinically significant condition emerging

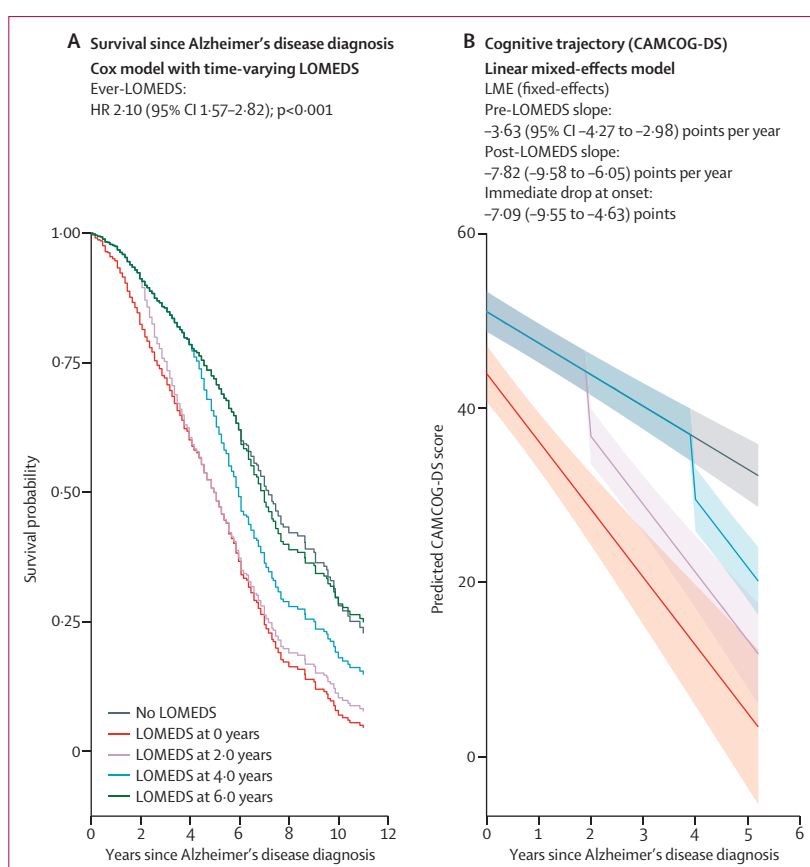


Figure 4: Survival after Alzheimer's disease diagnosis and cognitive trajectory around LOMEDS in adults with Down syndrome

(A) Predicted survival curves from a Cox proportional hazards model with time-varying LOMEDS exposure, showing five scenarios defined by timing of first seizure onset relative to Alzheimer's disease diagnosis (0–6 years); LOMEDS window: 1 year before Alzheimer's disease diagnosis onwards. (B) Predicted CAMCOG-DS trajectories from a linear mixed-effects broken-stick model, showing the pre-LOMEDS slope, immediate drop at seizure onset, and accelerated post-LOMEDS decline for four onset scenarios; ribbons represent 95% CIs around fixed-effect means. CAMCOG-DS=Cambridge Cognitive Examination for Older Adults with Down Syndrome. HR=hazard ratio. LOMEDS=late-onset myoclonic epilepsy in Down syndrome.

around the onset of symptomatic Alzheimer's disease. The incidence of seizures increases steeply following symptomatic Alzheimer's disease diagnosis, with cumulative risk around 60% within a decade. Importantly, LOMEDS (predefined as the peak of epilepsy coinciding with symptomatic Alzheimer's disease) is not only common but also prognostically relevant, being associated with increased mortality and accelerated cognitive decline. These findings position epilepsy as a major component of the clinical trajectory of Down syndrome-associated Alzheimer's disease, extending previous observations from smaller series¹⁴ and emphasising the interplay between neurodegeneration and network hyperexcitability in the Down syndrome population.

Even in the absence of symptomatic Alzheimer's disease, adults with Down syndrome exhibit an increased epilepsy risk, with cumulative rates approaching 15% by age 60 years, far exceeding those observed in the general population (3% at age 74 years and 4.4% at age 85 years).²³

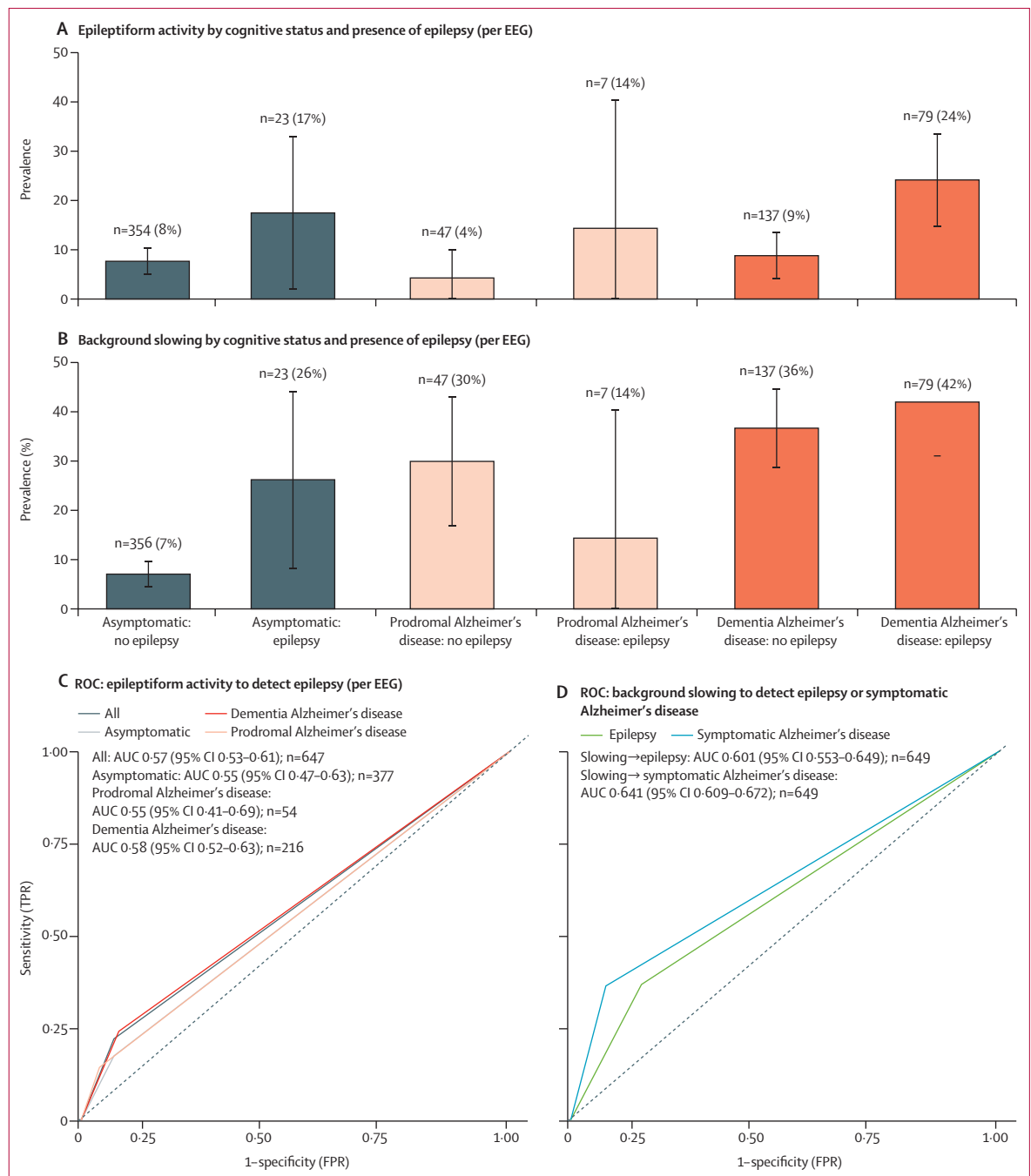


Figure 5: EEG markers by Alzheimer's disease stage and diagnostic performance (per EEG)

(A) IED prevalence. Proportion of EEGs with IEDs across cognitive strata (asymptomatic, prodromal Alzheimer's disease, and Alzheimer's disease dementia) and by epilepsy status at the EEG (yes indicates EEG performed on or after the date of first seizure if present, and no indicates otherwise); bars show point estimates with two-sided 95% Wald CIs, with N as the total EEGs per bar (denominator). (B) Background slowing prevalence (95% Wald CIs, with N as the total EEGs per bar [denominator] annotated). The y-axis is capped at 50% where indicated. (C) IED as a classifier of epilepsy. ROC curves (overall and by cognitive stratum) showing the ability of IED presence to discriminate EEGs of individuals with epilepsy (performed on or after the first seizure) from those of individuals without epilepsy (performed before the first seizure or in patients who never had a seizure). AUCs with 95% CIs are shown; the diagonal represents no discrimination (AUC=0.5). (D) Background slowing performance. ROC curves for background slowing predicting epilepsy (overall) and symptomatic Alzheimer's disease (prodromal Alzheimer's disease or Alzheimer's disease dementia vs asymptomatic). Figure shows AUCs with 95% CIs; diagonal reference shown. AUC=area under the ROC curve. EEG=electroencephalogram. FPR=false positive rate. IED=interictal epileptiform discharge. LOMEDS=late-onset myoclonic epilepsy in Down syndrome. ROC=receiver operating characteristic. TPR=true positive rate (sensitivity).

This finding suggests that lifelong neurodevelopmental alterations in cortical organisation and excitability might predispose individuals with Down syndrome to seizures independently of neurodegeneration. However, the emergence of symptomatic Alzheimer's disease represents a turning point, triggering an accelerated epileptogenic cascade. In this sense, our prospective, systematically collected data allowed us to capture seizure manifestations even in the earliest stages of symptomatic or even pre-symptomatic Alzheimer's disease. Nonetheless, our results support that LOMEDS is tightly linked to the Alzheimer's disease-related cognitive decline rather than occurring in the earlier preclinical phase. The most predominant types of seizures in LOMEDs were generalised myoclonic and tonic-clonic, also confirming previous definitions of the syndrome.^{15,16} Age contributes to LOMEDS risk only indirectly, through its association with the onset of Alzheimer's disease dementia. Once Alzheimer's disease is established, the likelihood of developing LOMEDS depends on disease stage (time since Alzheimer's disease diagnosis) and is independent of age itself.

The increased lifetime epilepsy risk in Down syndrome, especially in those with severe intellectual disability, reflects an underlying hyperexcitability predisposition.¹¹ Around the time of Alzheimer's disease onset, additional triggers are likely to emerge as amyloid and tau pathology converge, leading to marked seizure risk (56% within 9 years). Indeed, Alzheimer's disease pathology, rather than all-causes neurodegeneration, has been linked to increased epilepsy among patients with dementia.³ In Down syndrome, *APP* triplication drives early amyloid deposition, similar to autosomal-dominant forms of Alzheimer's disease, where epilepsy is frequent in *APP* duplication carriers.²⁴ Cerebral amyloid angiopathy, common in Down syndrome-associated Alzheimer's disease,²⁵ further promotes network instability through vascular injury and inflammation.^{26,27} The close timing of seizures and Alzheimer's disease conversion suggests a role for emerging tau pathology (so-called catastrophy).²⁸ Locus coeruleus degeneration, an early tau site, might reduce seizure control,³ fostering a feedback loop where seizures and tau propagation reinforce one another.^{29,30}

Our EEG analyses of IEDs and diffuse background showed limited clinical utility in diagnosing epilepsy in this population, possibly reflecting subclinical, fluctuating epileptogenic processes not captured in short-duration scalp recordings.³¹ Emerging studies suggest that high-frequency oscillations (>250 Hz)¹⁹ can precede Alzheimer's disease dementia and LOMEDS and might identify a larger population with underlying hyperexcitability. Whether systematic screening during the peri-symptomatic window could prospectively identify individuals at highest risk of seizure onset represents a promising avenue for future research.

Results suggest that epilepsy arising in parallel with symptomatic Alzheimer's disease is both a symptom of

this Alzheimer's disease continuum and also a driver of the decline, raising the possibility that seizure activity itself contributes to neuronal injury. Indeed, our findings show that LOMEDS carries major prognostic significance. Individuals who develop LOMEDS have over a two-times higher mortality risk than those without LOMEDS, with survival decreasing progressively the earlier epilepsy appears in relation to Alzheimer's disease onset. Cognitive trajectories also decline more steeply after seizure onset, with rates of deterioration roughly twice those seen in symptomatic Alzheimer's disease without epilepsy. These effects align with those reported in the general dementia population (active epilepsy approximately 1.4%; HR 1.79 [95% CI 1.51–2.12]),⁷ but show a stronger effect size, underscoring the particularly adverse effect of epilepsy in Down syndrome-associated Alzheimer's disease. Treated individuals with myoclonic seizures showed lower rates of progression to generalised tonic-clonic seizures compared with untreated individuals. However, as this is an observational study, these findings should be interpreted with caution and do not establish a causal effect of treatment. Randomised controlled trials will be essential to investigate whether early antiseizure medication truly modifies seizure trajectory in Down syndrome-associated Alzheimer's disease.

These results, unprecedented in scale for Down syndrome-associated Alzheimer's disease, highlight epilepsy as a key, yet under-recognised, potentially modifiable and clinically meaningful complication that should be detected and treated early in the Alzheimer's disease continuum. The consistent temporal coupling of LOMEDS with symptomatic Alzheimer's disease onset defines an important window for surveillance and intervention, when timely recognition and management of hyperexcitability could alter disease progression. Furthermore, preventive strategies with well tolerated antiseizure medication around this window might improve survival and cognitive decline. Ongoing trials, such as the LESS-AD trial (EU CT 2024-516148-24-00), will assess whether levetiracetam can safely prevent seizures in Down syndrome-associated Alzheimer's disease and potentially slow neuronal damage and cognitive decline. Beyond seizure control, agents that modulate network hyperexcitability or restore inhibitory tone might hold disease-modifying potential, as shown in sporadic Alzheimer's disease, where low-dose levetiracetam improved cognition in patients with seizures or subclinical epileptiform activity.³² Future trials in Down syndrome-associated Alzheimer's disease should build on these insights, incorporating sensitive electrophysiological endpoints to bridge mechanistic understanding with clinical translation in this uniquely informative population.

The main strength of this study is its large, harmonised, longitudinal, multicentre design, encompassing over 4800 adults with Down syndrome across seven independent

cohorts, enabling the first robust characterisation of epilepsy trajectories, prognosis, and their relationship with symptomatic Down syndrome-associated Alzheimer's disease. Nonetheless, several limitations warrant consideration. Biomarker data were not available in most individuals, precluding precise staging on the basis of amyloid, tau, or neurodegeneration markers. EEG data were variably timed relative to seizure onset, with most recordings done more than 6 months after the first seizure and probably after initiation of antiseizure medication, potentially underestimating diagnostic sensitivity. Recording duration of 20–30 min represents additional methodological limitations. Moreover, although the study spanned diverse clinical settings, ascertainment bias and differences in follow-up intensity might have influenced incidence estimates. Further limitations include reliance on caregiver-reported seizure timing and semiology, derivation of a symptomatic Alzheimer's disease window from diagnosis dates rather than exact symptom onset, limited generalisability given predominance of White European participants and incomplete ethnicity data, incomplete information on seizure control and frequency, and possible misclassification of non-epileptic myoclonus despite our operational definition. Moreover, the category of uncertain or non-neurodegenerative cognitive decline encompasses heterogeneous conditions (including Down syndrome regression disorder, depression, and other psychiatric or medical diagnoses), whose granular causal breakdown and potential relationship with epilepsy could not be examined. Finally, as with all centre-based cohorts, and despite the large sample size and broad age distribution of participants, findings should be interpreted with caution when generalising to the broader Down syndrome population. Future work should integrate fluid and imaging biomarkers to delineate the temporal coupling between epileptogenesis and Alzheimer's disease pathology, serial EEG or magnetoencephalogram use to capture subclinical activity, and investigate whether early treatment of hyperexcitability can alter cognitive trajectories or survival.

In summary, this study establishes LOMEDS as a common, clinically distinctive, and prognostically meaningful comorbidity of Down syndrome-associated Alzheimer's disease. Epilepsy's close temporal association with symptomatic onset, characteristic semiology, and strong links to survival and cognitive decline identify the disease as both a marker and potentially modifiable mediator of disease progression. The findings extend evidence from sporadic and autosomal dominant Alzheimer's disease, positioning Down syndrome-associated Alzheimer's disease as a uniquely informative model of Alzheimer-related epileptogenesis. Targeting hyperexcitability in Down syndrome-associated Alzheimer's disease could open a new therapeutic pathway, transforming a catastrophic marker into an actionable opportunity for disease modification.

Contributors

LM-B, MC-I, MA, and JF developed the study concept and design. LM-B, MC-I, MA, JF, IB, JA, SF, ÍR-B, BB, LV, JEA-I, LDHS, LP, LV-A, AS, AB, MRA, OL, AOM-N, VR-C, AS-M, CPL, EB, RSO, AE, MG-S, NR, ACS, GN, JMR, MM, KL, PD, SS, OD-I, OB, DA, ABe, AL, SG, EM, JL, and A-SR acquired the data. LM-B, MC-I, and JF analysed and interpreted the data, did the statistical analysis, and drafted the manuscript. All authors revised and edited the manuscript and critically revised it for important intellectual content.

Declaration of interests

DA participated in advisory boards for Fujirebio-Europe, Roche Diagnostics, Grifols, and Lilly, and received speaker honoraria from Fujirebio-Europe, Roche Diagnostics, Nutricia, Krka Farmacéutica, Zambon, Neuraxpharm, Alter Medica, Lilly, and Esteve Pharmaceuticals. DA declares holding a patent for markers of synaptopathy in neurodegenerative disease (licensed to ADx NeuroSciences, WO2019175379 markers of synaptopathy in neurodegenerative diseases). JF reports serving on advisory boards or adjudication committees for, or speaker honoraria from AC Immune, Adamed, Alzheon, Biogen, Eisai, Esteve, Fujirebio, Ionis, Laboratorios Carnot, Life Molecular Imaging, Lilly, Novo Nordisk, Perha, Roche, and Zambón. JF reports holding a patent for markers of synaptopathy in neurodegenerative disease (licensed to ADx, WO2019175379). OB reports holding a patent for markers of synaptopathy in neurodegenerative disease (licensed to ADx NeuroSciences, WO2019175379 markers of synaptopathy in neurodegenerative diseases). MRA is a co-founder and partner of Masima Soluções em Imagens Médicas (Porto Alegre, Brazil) and serves as an independent consultant to Ionis Pharmaceuticals. MC-I has received personal fees for service on the advisory boards, speaker honoraria, or educational activities from IMSERSO, Esteve, Lilly, Neuraxpharm, Adium Pharma, and Roche. SG has received personal fees for service on the advisory boards, speaker honoraria, or educational activities from Esteve, Idorsia, Novo Nordisk, and Bioproject. SS is a coauthor of a patent on antibodies for amyloid precursor protein, methods and uses thereof European priority (EP25382226). VR-C has received honoraria as a speaker or for educational activities from UCB and Jazz Pharmaceuticals. AS-M has received honoraria as a speaker or for educational activities from UCB, Jazz Pharmaceuticals, Eisai, Neuraxpharm, Novartis, KRKA, and Nutricia. MA reports receiving speaker honoraria from Esteve Pharmaceuticals, Lilly, Neuraxpharm, Kern Pharma, KRKA, Novo Nordisk, Zambon, and Nutricia. AL reports receiving personal fees for service on advisory boards or speaker honoraria from Almirall, Beckman-Coulter, Biogen, Eisai, Esteve, Fujirebio-Europe, Grifols, KRKA, Lilly, Novartis, Novo Nordisk, Nutricia, Otsuka Pharmaceutical, Roche, and Zambón. AL is coauthor of a patent for markers of synaptopathy in neurodegenerative disease (licensed to ADx, EPI8382175.0) and on antibodies for amyloid precursor, methods and uses thereof European priority (EP25382226). JA has received personal fees for service on the advisory boards, speaker honoraria, or educational activities from Esteve, Lilly, and Roche diagnostics. JL reports speaker fees from Bayer Vital, Biogen, EISAI, Lilly, TEVA, Bial, Zambon, Esteve, Merck, and Roche; consulting fees from Axon Neuroscience, EISAI, Alnylam, and Biogen; author fees from Thieme medical publishers and W Kohlhammer medical publishers; and is inventor in a patent "Oral Phenylbutyrate for Treatment of Human 4-Repeat Tauopathies" (PCT/EP2024/053388) filed by LMU Munich. In addition, he reports compensation for serving as chief medical officer for MODAG, is beneficiary of the phantom share programme of MODAG, and is inventor in a patent "Pharmaceutical Composition and Methods of Use" (EP 22 159 408.8) filed by MODAG, all activities outside the submitted work. All other authors declare no competing interests.

Data sharing

Because of consent limitations and institutional review board requirements, the dataset cannot be made publicly available, as explicit consent for public data sharing was only recently introduced and is therefore not available for many participants. Nevertheless, the included cohorts have supported numerous international collaborations, and data can be shared upon request through standard data transfer agreements. Requests should be directed to each international site principal investigator: JF (jforte@ santpau.cat;

DABNI), A-SR (annesophie.rebillat@institutlejeune.org; IJL), EM (MCGLINE@tcd.ie; IDS-TILDA and AVISTA), JL (johannes.levin@med.uni-muenchen.de; Munich), and MA (maltuna@cita-alzheimer.org; DS-BAI). Data access is restricted to bona fide researchers for scientific purposes, and requests are typically reviewed within 2–3 months.

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References

- Steinmetz JD, Seeher KM, Schiess N, et al. Global, regional, and national burden of disorders affecting the nervous system, 1990–2021: a systematic analysis for the Global Burden of Disease Study 2021. *Lancet Neurol* 2024; **23**: 344–81.
- Piccenna L, O’Dwyer R, Leppik I, et al. Management of epilepsy in older adults: a critical review by the ILAE Task Force on Epilepsy in the elderly. *Epilepsia* 2023; **64**: 567–85.
- Zawar I, Luniewski A, Gundlapalli R, et al. The association of seizure control with neuropathology in dementia. *Brain* 2025; **148**: 2469–80.
- Kamondi A, Grigg-Damberger M, Löscher W, Tanila H, Horvath AA. Epilepsy and epileptiform activity in late-onset Alzheimer disease: clinical and pathophysiological advances, gaps and conundrums. *Nat Rev Neurol* 2024; **20**: 162–82.
- Ryan NS, Nicholas JM, Weston PSJ, et al. Clinical phenotype and genetic associations in autosomal dominant familial Alzheimer’s disease: a case series. *Lancet Neurol* 2016; **15**: 1326–35.
- Tang M, Ryman DC, McDade E, et al. Neurological manifestations of autosomal dominant Alzheimer’s disease from the DIAN cohort and a meta-analysis. *Lancet Neurol* 2016; **15**: 1317–25.
- Zawar I, Quigg M, Ghosal S, et al. Association of seizure control with mortality, cognition, and function in people with dementia. *Ann Neurol* 2025; **97**: 358–68.
- Fortea J, Zaman SH, Hartley S, Rafi MS, Head E, Carmona-Iragui M. Alzheimer’s disease associated with Down syndrome: a genetic form of dementia. *Lancet Neurol* 2021; **20**: 930–42.
- Moore BC. Some characteristics of institutionalised mongols. *J Ment Defic Res* 1973; **17**: 46–51.
- Veall RM. The prevalence of epilepsy among mongols related to age. *J Ment Defic Res* 1974; **18**: 99–106.
- Robertson J, Hatton C, Emerson E, Baines S. Prevalence of epilepsy among people with intellectual disabilities: a systematic review. *Seizure* 2015; **29**: 46–62.
- Prasher VP. Epilepsy and associated effects on adaptive behaviour in adults with Down syndrome. *Seizure* 1995; **4**: 53–56.

- 13 McVicker RW, Shanks OE, McClelland RJ. Prevalence and associated features of epilepsy in adults with Down's syndrome. *Br J Psychiatry* 1994; **164**: 528–32.
- 14 Lai F, Williams RS. A prospective study of Alzheimer disease in Down syndrome. *Arch Neurol* 1989; **46**: 849–53.
- 15 Altuna M, Giménez S, Fortea J. Epilepsy in Down syndrome: a highly prevalent comorbidity. *J Clin Med* 2021; **10**: 2776.
- 16 Corniello C, Dono F, Evangelista G, et al. Diagnosis and treatment of late-onset myoclonic epilepsy in Down syndrome (LOMEDS): a systematic review with individual patients' data analysis. *Seizure* 2023; **109**: 62–67.
- 17 De Simone R, Puig XS, Gélisse P, Crespel A, Genton P. Senile myoclonic epilepsy: delineation of a common condition associated with Alzheimer's disease in Down syndrome. *Seizure* 2010; **19**: 383–89.
- 18 Targa Dias Anastacio H, Matosin N, Ooi L. Neuronal hyperexcitability in Alzheimer's disease: what are the drivers behind this aberrant phenotype? *Transl Psychiatry* 2022; **12**: 257.
- 19 Lisgaras CP, Giménez S, Carmona-Iragui M, et al. High-frequency oscillations >250 Hz in people with Down syndrome and associated Alzheimer's disease dementia. *Alzheimers Dement* 2025; **21**: e70386.
- 20 Esteba-Castillo S, Dalmau-Bueno A, Ribas-Vidal N, Vilà-Alsina M, Novell-Alsina R, García-Alba J. Adaptacion y validacion del Cambridge Examination for Mental Disorders of Older People with Down's Syndrome and Others with Intellectual Disabilities (CAMDEX-DS) en poblacion española con discapacidad intelectual. *Rev Neurol* 2013; **57**: 337–46.
- 21 Beniczky S, Trinka E, Wirrell E, et al. Updated classification of epileptic seizures: position paper of the International League Against Epilepsy. *Epilepsia* 2025; **66**: 1804–23.
- 22 Fisher RS, Acevedo C, Arzimanoglou A, et al. ILAE official report: a practical clinical definition of epilepsy. *Epilepsia* 2014; **55**: 475–82.
- 23 Hauser WA, Annegers JF, Kurland LT. Incidence of epilepsy and unprovoked seizures in Rochester, Minnesota: 1935-1984. *Epilepsia* 1993; **34**: 453–68.
- 24 Grangeon L, Charbonnier C, Zarea A, et al. Phenotype and imaging features associated with APP duplications. *Alzheimers Res Ther* 2023; **15**: 93.
- 25 Carmona-Iragui M, Balasa M, Benejam B, et al. Cerebral amyloid angiopathy in Down syndrome and sporadic and autosomal-dominant Alzheimer's disease. *Alzheimers Dement* 2017; **13**: 1251–60.
- 26 Morcillo-Nieto AO, Zsadanyi SE, Arriola-Infante JE, et al. Characterization of white matter hyperintensities in Down syndrome. *Alzheimers Dement* 2024; **20**: 6527–41.
- 27 Valay L, Potier MC. Reviewing the possible connection between cerebral amyloid angiopathy and blood-brain barrier integrity in Down syndrome. *Alzheimers Dement* 2025; **21**: e70814.
- 28 Wanger F, Steward A, Biel D, et al. The effect of local versus remote Beta-Amyloid on functional connectivity mediated Tau-spread in Alzheimer's Disease. *Alzheimers Dement* 2023; **19**: e081917.
- 29 Wu JW, Hussaini SA, Bastille IM, et al. Neuronal activity enhances tau propagation and tau pathology in vivo. *Nat Neurosci* 2016; **19**: 1085–92.
- 30 Vogel JW, Corriveau-Lecavalier N, Franzmeier N, et al. Connectome-based modelling of neurodegenerative diseases: towards precision medicine and mechanistic insight. *Nat Rev Neurosci* 2023; **24**: 620–39.
- 31 Lam AD, Deck G, Goldman A, Eskandar EN, Noebels J, Cole AJ. Silent hippocampal seizures and spikes identified by foramen ovale electrodes in Alzheimer's disease. *Nat Med* 2017; **23**: 678–80.
- 32 Vossel K, Ranasinghe KG, Beagle AJ, et al. Effect of levetiracetam on cognition in patients with Alzheimer disease with and without epileptiform activity: a randomized clinical trial. *JAMA Neurol* 2021; **78**: 1345–54.