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Summary

Background Alzheimer's disease and its complications are the leading cause of death in adults with Down syndrome. Studies have assessed Alzheimer's disease in individuals with Down syndrome, but the natural history of biomarker changes in Down syndrome has not been established. We characterised the order and timing of changes in biomarkers of Alzheimer's disease in a population of adults with Down syndrome.

Methods We did a dual-centre cross-sectional study of adults with Down syndrome recruited through a population-based health plan in Barcelona (Spain) and through services for people with intellectual disabilities in Cambridge (UK). Cognitive impairment in participants with Down syndrome was classified with the Cambridge Cognitive Examination for Older Adults with Down Syndrome (CAMCOG-DS). Only participants with mild or moderate disability were included who had at least one of the following Alzheimer's disease measures: apolipoprotein E allele carrier status; plasma concentrations of amyloid β peptides 1–42 and 1–40 and their ratio ($A\beta_{1-42/1-40}$), total tau protein, and neurofilament light chain (NFL); tau phosphorylated at threonine 181 (p-tau), and NFL in cerebrospinal fluid (CSF); and one or more of PET with ^{18}F-fluorodeoxyglucose, PET with amyloid tracers, and MRI. Cognitively healthy euploid controls aged up to 75 years who had no biomarker abnormalities were recruited from the Sant Pau Initiative

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Findings Between Feb 1, 2013, and June 28, 2019 (Barcelona), and between June 1, 2009, and Dec 31, 2014 (Cambridge), we included 388 participants with Down syndrome (257 [66%] asymptomatic, 48 [12%] with prodromal Alzheimer's disease, and 83 [21%] with Alzheimer's disease dementia) and 242 euploid controls. CSF $A\beta_{1-42/1-40}$ and plasma NFL values changed in individuals with Down syndrome as early as the third decade of life, and amyloid PET uptake changed in the fourth decade. ^{18}F-fluorodeoxyglucose PET and CSF p-tau changes occurred later in the fourth decade of life, followed by hippocampal atrophy and changes in cognition in the fifth decade of life. Prodromal Alzheimer's disease was diagnosed at a median age of 50·2 years (IQR 47·5–54·1), and Alzheimer's disease dementia at 53·7 years (49·5–57·2). Symptomatic Alzheimer's disease prevalence increased with age in individuals with Down syndrome, reaching 90–100% in the seventh decade of life.

Interpretation Alzheimer's disease in individuals with Down syndrome has a long preclinical phase in which biomarkers follow a predictable order of changes over more than two decades. The similarities with sporadic and autosomal dominant Alzheimer's disease and the prevalence of Down syndrome make this population a suitable

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Introduction

Down syndrome (also referred to as trisomy 21) is the most frequent form of genetic developmental and particularly Alzheimer's disease. The lifetime risk of Alzheimer's disease in people with Down syndrome is now more than 90%,[3] and the disease is the leading cause