**Title**: Health Conditions associated with Early versus Late age of amyloid accumulation in People with Down syndrome

**Authors**: Courtney Brothers1, Benjamin Handen2, Julie K. Wisch3, Beau Ances3, James Kennedy3, Sigan Hartley1 and the Alzheimer Biomarker Consortium-Down syndrome.

**Introduction**: Individuals with Down syndrome have more than a 90% lifetime risk for developing symptomatic Alzheimer’s disease (AD) (McCarron et al., 2017) An early hallmark feature of AD, observed decades prior to the onset of symptomology, is the accumulation of amyloid-beta (Aβ) plaques (Wisniewski et al., 1985). The high risk for AD in Down syndrome is primarily due to the triplication of the amyloid precursor protein (APP) located on the 21st chromosome. Having three copies of the APP gene results in a 1.5-fold increase in the production of amyloid (Oyama et al., 1994). Despite sharing trisomy 21, there is marked variability (spanning 20+ years) in the age at which amyloid begins accumulating among individuals with Down syndrome. Research that identifies factors associated with risk (i.e., early amyloid accumulation) or resistance (i.e., late amyloid accumulation) to Aβ accumulation is of critical importance to the Down syndrome community. Individuals with Down syndrome are also at risk for certain types of cardiovascular problems such as congenital heart defects, obesity, hyperlipidemia and pulmonary hypertension and stroke (Bates et al., 2023). AD research on the general adult population has found that cardiovascular disease, particularly having more than one, is associated with an elevated risk for AD (Newman et al., 2005; Purnell et al., 2009). However, research has not yet examined the potential connection between cardiovascular health conditions and the timing of amyloid deposition in individuals with Down syndrome. The goal of the current study was to evaluate the relationship between cardiovascular conditions and risk and resistance to Aβ accumulation in a large cohort of adults with Down syndrome.

**Method**: Participants were 262 adults with Down syndrome (age: M = 43.93 years; SD = 9.29) from the Alzheimer Biomarker Consortium-Down syndrome. Data collection occurred at one of eight sites located in the U.S. or U.K. Participants underwent an MRI and PET scans with amyloid quantified with [11C] PiB or [18F] florbetapir converted into centiloids. Health history was collected from a study partner who was asked about cardiovascular conditions and medications. Systolic and diastolic blood pressure was also obtained. We performed a polynomial regression with age as the independent variable and centiloid as the dependent variable. The risk/resistance (RR) score was calculated as a residual of the actual centiloid values and the predicted centiloid values based on age. We examined the Pearson correlations between the RR score and the sum of cardiovascular health conditions (up to 7) and between the RR score and the total number of health conditions (up to 33). Models were then re-run controlling for centiloid values to ensure that high centiloid was not overly driving associations.

**Results**: Participants who were ApoE allele 2 carriers had a significantly lower RR score (i.e., more resistance) than those without allele 2. Participants with a greater number of cardiovascular conditions had significantly higher RR scores (i.e., greater amyloid deposition) than those with fewer cardiovascular conditions (r = .121, p = .050). A greater overall number of health conditions was also associated with a higher RR score (r = .139, p = .024). This result was robust to the presence of high cortical amyloid burden.

**Discussion:** Identifying risk and resistance factors related to an earlier versus later age of amyloid accumulation in adults with Down syndrome has important implications for understanding mechanisms that could be targeted in clinical trials to delay onset of AD. Findings suggest that efforts to prevent cardiovascular conditions in adults with Down syndrome may be pathways for delaying amyloid accumulation. In addition, ApoE e2 carriers could experience later-age of amyloid accumulation.

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1Waisman Center, University of Wisconsin-Madison

2Department of Psychiatry, University of Pittsburgh

3Department of Neurology, Washington University in St. Louis