


RESEARCH ARTICLE

Longitudinal investigation of gait and Alzheimer's disease in adults with Down syndrome

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Abstract

INTRODUCTION: Gait abnormalities are associated with Alzheimer's disease (AD) in the general population, but it is unclear if the same is true for individuals with Down syndrome (DS). This study examined gait across 32 months in relation to

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neuroimaging biomarkers (amyloid beta [$A\beta$], neurofibrillary tangles [NFTs], and hippocampal volume), cognitive decline, and clinical AD status in adults with DS.

METHODS: Participants were 218 adults with DS who underwent $A\beta$ and NFT positron emission tomography (PET) and magnetic resonance imaging (MRI) scans, cognitive testing, and gait assessments at baseline and 32 months. Residual change regression models were conducted.

RESULTS: Higher baseline $A\beta$ PET and NFT PET and lower MRI hippocampal volume were associated with gait declines across 32 months. Cognitive declines were associated with gait declines. Participants with clinical dementia at 32 months had greater gait decline than those who were cognitively stable.

DISCUSSION: Gait impairments are a key feature of DS-associated AD (DSAD). Gait assessments could offer a quick, cost-effective, non-invasive screen for DSAD.

KEYWORDS

amyloid beta, cognitive decline, dementia, gross motor skills, hippocampal volume, neurofibrillary tangles of tau, trisomy 21

Highlights

- Those with clinical status of dementia had lower gait performance than those who were cognitively stable.
- Higher baseline amyloid beta and neurofibrillary tangle volume was associated with more gait impairments.
- Lower baseline hippocampal volume was associated with more gait impairments.
- Greater decline in gait performance was associated with cognitive decline.
- Greater decline in gait performance was associated with more dementia symptoms.

1 | BACKGROUND

Down syndrome (DS) is a developmental disability caused by an extra copy of chromosome 21¹ that occurs in ≈ 1 in 700 live births in the United States.² Adults with DS have a 90% lifetime risk for Alzheimer's disease (AD) dementia,³ which is thought to be driven by the triplication of the amyloid precursor protein (APP) gene located on chromosome 21.⁴ The presence of AD pathology in DS is similar to sporadic AD; however, the accumulation of amyloid beta ($A\beta$) brain plaques occurs several decades earlier,^{5–8} followed by the presence of neurofibrillary tau tangles (NFTs),^{9–12} and then neurodegeneration as evidenced by hippocampal atrophy, altered glucose metabolism, and increased glial fibrillary acidic protein levels.^{13,14} Over the past decade, the timeline of cognitive changes that reflect mild cognitive impairment (MCI) and dementia in DS-associated AD (DSAD) has been described^{15–19} and more recently the relationship with $A\beta$ plaques and NFTs.²⁰ However, little is known about other domains of changes in daily functioning during the progression to DSAD.

In the general adult population, changes in gait have long been associated with AD.^{21–23} Changes in gait were initially found to be associated with later stages of AD, after the onset of dementia.^{24,25} Indeed, there is substantial evidence that adults with AD dementia

experience impairments in balance and gait,^{26–28} such as increased postural sway²⁹ and reduced mobility.³⁰ Recently, gait impairments have also been observed in individuals with MCI.^{31–33} Additionally, gait impairments appear to be associated with the earliest stages of AD development, such as early-stage $A\beta$ deposition.³² The etiology of these gait impairments may be related to disruption of distributed thalamo-cortico-basal ganglia networks related to motor control^{33,34} or to more focal changes of frontal cognitive-motor cortical regions.^{35,36}

It remains uncertain whether changes in gait are a feature of DSAD. Individuals with DS have lifelong difficulties with gait,³⁷ and additional gait impairments may occur as early as the mid-30s.³⁸ In part, changes in gait in middle and late adulthood may be driven by the elevated prevalence of aging-related conditions in DS, such as sarcopenia and osteoporosis,^{39–41} as well as atlantoaxial subluxation throughout the lifespan.³⁹ However, AD pathology may also contribute to gait impairments.⁴² In a dual-task assessment (counting while walking), Van Pelt et al.⁴³ found that adults with DS who had AD dementia showed significant reductions in gait velocity compared to those who were cognitively stable. However, this finding may be due to the cognitive load required for a dual-task assessment. In a different study ($n = 66$), the Tinetti Performance Oriented Mobility Assessment⁴⁴ (POMA, also

known as Tinetti) Gait subscale distinguished adults with DS with MCI and dementia from those who were cognitively stable.⁴⁵ The current study built on these prior studies by evaluating change in gait across 32 months in relation to positron emission tomography (PET) and magnetic resonance imaging (MRI) biomarkers of AD pathology, cognitive decline, and clinical AD status in a sample of 218 adults with DS. The study aims were to: (1) examine gait across 32 months in relation to baseline biomarkers of A β PET, NFT PET, and MRI hippocampal volume; (2) determine whether change in gait across 32 months is associated with change in cognitive functioning during this same interval; and (3) compare changes in gait across 32 months based on clinical AD status (cognitively stable, MCI, or dementia). Based on prior research,^{43,45} we hypothesized that changes in gait would be associated with higher baseline A β and NFT PET, lower MRI hippocampal volume, and greater decreases in cognitive functioning across 32 months. We also predicted that adults with DS who were classified as MCI and dementia at 32 months would exhibit greater declines in gait than those who were cognitively stable.

2 | METHODS

2.1 | Participants

Participants were 218 adults with DS enrolled in the Alzheimer Biomarkers Consortium-Down Syndrome (ABC-DS), a natural history study of DSAD that includes eight data collection sites in the United States and one in the United Kingdom. Study inclusion criteria included ≥ 25 years of age, mental age ≥ 4 years, genetic confirmation of DS (trisomy 21, mosaicism, or translocation), and availability of a study partner who could provide information on the participant with DS's medical history and daily function. Exclusion criteria at study entry included contraindications to neuroimaging (e.g., metallic implants), untreated medical conditions that could impair cognitive function, and no prior diagnosis of AD or concerns about dementia for participants who were not part of legacy studies leading up to ABC-DS. Informed consent and/or assent were obtained from participants prior to study activities. The study was approved by institutional review boards and conducted in accordance with the Declaration of Helsinki.

2.2 | Procedures

At each data collection cycle, the adult with DS and study partner participated in a multiday study visit. The study partner was either a parent, sibling, or caregiver who knew the participant very well. During this visit, the participant completed a neuropsychological battery designed to assess cognitive, gait, and other gross motor functions. We used three cognitive measures from this battery (see Handen et al.⁴⁶ for full battery) shown to be valid and sensitive to AD-related cognitive decline in DS.⁴⁷ The study partner reported on the participant's medical history and cognitive and behavioral functioning. The participant with DS also underwent MRI and A β and NFT PET scans and a blood

RESEARCH IN CONTEXT

1. **Systematic review:** Theoretical and empirical literature on gait changes in Down syndrome-associated Alzheimer's disease (DSAD) and in other forms of AD was reviewed using research search databases. Relevant prior work, including cross-sectional studies on gait in DSAD, is cited.
2. **Interpretation:** Findings indicate that gait changes are part of DSAD, occurring alongside cognitive decline, dementia status, and neuroimaging biomarkers of amyloid, tau, and hippocampal volume. Gait assessments should be part of screening for DSAD.
3. **Future directions:** Future studies using more sensitive technology-based gait mats may be able to detect even earlier subtle changes in gait related to AD pathology and symptomology. The specific domains of gait (e.g., cadence, foot clearance, and step symmetry) impacted by AD pathology and those best able to distinguish among clinical status groups should be identified in future research.

draw. For the current study, we analyzed data collected at the baseline study visit and 32-month study visit of ABC-DS.

2.3 | Measures

2.3.1 | Demographic and health

The study partner reported participant demographic information. Collected information included age (in years), sex (1 = male, 2 = female), and ethnicity/race (categories: Hispanic or Latino, White non-Hispanic, Black, Asian, Native Hawaiian or other Pacific Islander, American Indian or Alaska Native, or multiple races). The study partner also reported on the participant's medical history. In the present study, we examined the presence (vs. absence) of the 11 medical conditions for any associations with gait. These conditions were: Parkinson's disease, tremors, seizures, myoclonus, traumatic brain injury, cataracts, vision impairments, hearing impairments, osteoarthritis, osteoporosis, and gout. We determined apolipoprotein E (APOE) allele $\epsilon 4$ carrier status via genetic testing using blood cell DNA. The level of intellectual disability (ID) prior to any AD-related condition was estimated using the Kaufman Brief Intelligence Test, Second Edition (KBIT-2⁴⁸) or Stanford-Binet Fifth Edition Abbreviated Battery (SB5⁴⁹), conducted as part of ABC-DS prior to concerns about dementia. For the subset of participants with concerns about MCI or dementia upon entry into ABC-DS, medical records were reviewed to find IQ scores from an earlier prior point. Our estimated level of ID was coded as (1) mild, (2) moderate, and (3) severe/profound, which corresponded to the

following mental ages: mild: 9 to 14 years, moderate: 4 to 8 years, and severe/profound: ≤ 3 years. Mental age standard scores were used instead of IQ standard scores due to floor effects on the SB5 Abbreviated IQ Battery and KBIT-2, where the lowest possible IS standard score is 40 or 46, respectively, and thus does not allow differentiation between individuals with moderate and severe/profound ID.

2.3.2 | Gait

The Tinetti Gait and Balance assessment⁴⁴ was used to measure gait. Only the gait sub-assessment was administered. Gait was assessed during two 15-foot walks: the first walk was completed at the participant's preferred pace and the second walk was at a rapid but safe pace. Participants were scored in eight domains: indication of gait, step length and height, foot clearance, step symmetry, step continuity, path, trunk, and walking time. Each domain is scored from 0 to 1 (4 items) or 0 to 2 points (4 items), with a maximum of 12 points. Lower scores indicate greater gait impairment and higher risk of falls.⁴⁴ The Tinetti has strong reliability and validity in the general elderly population⁵⁰ and populations with gait impairments.^{51,52} The Tinetti has also been used with individuals with ID,⁵³ including DS,⁴⁵ and is correlated with other measures of gait and gross motor skills in expected directions.^{54,55}

2.3.3 | Cognition

The Down Syndrome Mental Status Examination (DSMSE)⁵⁶ is a measure of overall mental status and is used to assess AD-related cognitive decline.⁵⁶ The measure assesses recall of personal information, orientation to time, immediate and delayed memory, language, visuospatial functioning, and motor planning in individuals with DS.^{3,57} The DSMSE can differentiate cognitively stable individuals with DS from those with MCI and dementia⁴⁷ and predicts transition to dementia.³

2.3.4 | Memory

The modified Cued Recall Test (mCRT)⁵⁸ evaluates verbal learning and memory by having participants learn and then recall a series of 12 items shown as pictures. The free recall score is the number of items the participant recalls across three trials. If an item is not freely recalled, a category cue is provided. The cued recall score is the number of items remembered after being given the category prompt across the three trials. Current analyses used the Total mCRT score, which is the sum of the free and cued recall scores. The mCRT has been shown to have high sensitivity and specificity for distinguishing between cognitively stable adults with DS and those with AD.⁵⁹

2.3.5 | Dementia symptoms

The National Task Group–Early Detection Screen for Dementia (NTG)⁶⁰ is an informant-report of changes in function that could indi-

cate dementia. The NTG includes 51 items across six domains: (1) activities of daily living (7 items), (2) language and communication (6 items), (3) sleep–wake change patterns (8 items), (4) ambulation (4 items), (5) memory (9 items), and (6) behavior and affect (17 items). Each item is rated on a 4-point scale of (1) always been the case, (2) always but worse, (3) new symptom in the past year, and (4) does not apply. The purpose of the NTG is to screen for early AD clinical onset and was found to be sensitive to MCI and dementia in individuals with DS.⁶¹

2.3.6 | MRI acquisition and processing

Across sites, MRI scans were acquired on a 3T GE Discovery MR750, Siemens Trio, Siemens Prisma, or GE Signa PET/MR. High-resolution T1-weighted (T1w) images were collected using a 3D fast spoiled gradient echo (FSPGR) or magnetization prepared rapid acquisition gradient echo (MPRAGE) sequence (for details see Handen et al.⁴⁶). The current study included the T1w scans that were parcellated into native space versions of the Desikan–Killiany atlas⁶² using FreeSurfer v5.3.0. Templates were formed from 12 high-quality parcellations and then warped into each participant's native MR space using the Advanced Neuroimaging Tools (ANTs) software package.^{63,64} A final native space atlas was created for each scan by determining the maximum overlap of each parceled region from the 12 warped templates. Results were visually inspected to ensure the final atlas adhered to each participant's MR anatomy. In a handful of cases, the acceptable parcellations were not produced, and thus direct application of FreeSurfer on the scan was used instead. The participant-specific atlas was used to construct the Braak regions.^{10,65} Hippocampal volume (in mm³) was parsed into left and right volumes and then summed for total hippocampal volume.

2.3.7 | PET acquisition and processing

PET scans were acquired on a PET, PET/computed tomography (CT), or PET/MRI platform certified for multicenter studies (see Handen et al.⁴⁶), with A β quantified using [C-11]Pittsburgh compound B (PiB; $n = 101$) or [F-18]florbetapir ($n = 42$) at 50 to 70 minutes post-injection. The tau PET scans were acquired using [F-18]AV-1451 (e.g., [F-18]flortaucipir; $n = 97$) at 80 to 100 minutes post-injection. Images were acquired in 5 minute frames, corrected for motion on a frame-by-frame basis using SPM8, and time averaged. Analyses focused on global A β . PET images were registered with their corresponding anatomical MR images. The MR scan then underwent deformable registration to the 152-subject Montreal Neurological Institute (MNI152) template. Co-registered PET images were warped into the MNI152 template space using the resulting transformation matrix. Standardized uptake value ratios (SUVR) were calculated to capture global amyloid burden using the standard global region, using the whole cerebellum for reference, and converted to Centiloids (see Klunk et al.⁶⁶). The [F-18]AV-1451 tau images were used to calculate NFT burden; PET images were similarly co-registered with corresponding structural T1w MRIs. Concentration of [F-18]AV-1451 was expressed as SUVR in the

parcellation-defined Braak regions, using cerebellar gray matter as reference.

2.3.8 | Clinical AD status

Clinical AD status was determined based on a case consensus conference involving a psychologist, a physician, and at least two other research staff with expertise in DSAD. Reviewers had access to all available cognitive scores, informant-reported measure scores, medical history, recent life events, and premorbid level of ID, but were blinded to neuroimaging results and APOE status (see Handen et al.⁴⁶). Participants were classified as: (1) cognitively stable, in which there was no evidence of cognitive decline beyond normal signs of aging; (2) MCI, indicating subtle and/or limited decline in cognition and/or adaptive behaviors; (3) AD, indicating significant declines in cognition or adaptive behavior over an extended period of time; or (4) unable to determine, in which changes in cognition or adaptive behaviors were not clear in consideration of significant life events or changes in medical history (as reported by the study partner).

2.4 | Statistical analyses

Statistical analyses were completed in IBM SPSS version 28.0.1.0 and R Studio version 2023.09.1. Histograms and descriptive statistics were used to examine the distribution of variables and identify any outliers. Baseline and 32-month Tinetti scores had a negative skew (kurtosis = 5.36). Thus, regression models were run with both raw Tinetti scores and with square root transformation scores. Findings did not differ using the transformed scores, and thus, models using raw Tinetti scores are presented to aid in interpretability. Additionally, three participants were deemed to have Tinetti change scores indicative of being outliers (> 1.5 times the interquartile range). Models were run both with and without these three participants. The overall pattern of findings did not differ when these participants were included versus excluded. Bivariate Pearson correlations, independent sample *t* tests, and one-way analysis of variance were conducted to determine whether demographic (i.e., age, sex, race, ethnicity, tri-somy type, and ID) or health history (i.e., Parkinson's disease, tremors, seizure, myoclonus, traumatic brain injury, cataracts, vision, hearing, osteoarthritis, osteoporosis, and gout) variables were associated with Tinetti scores and thus should be included as covariates in the models.

A series of residual change regression models was conducted to address the study aims. In all models, the 32-month Tinetti Gait score was the dependent variable, and the baseline Tinetti score and relevant sociodemographic variables (i.e., those significantly associated with the Tinetti Gait score) were predictors. To address the first aim of the study, baseline A β PET, NFT PET, and MRI hippocampal volume were included as predictor variables in models. Total intracranial volume (ICV) was also included in the hippocampal volume model to control total brain

size. To address aim 2, residual change in the mCRT, DSMSE, and NTG from baseline to the 32-month follow-up were included as predictors in models. These change scores were created by regressing out the effect of baseline mCRT, DSMSE, or NTG score from the 32-month score. To address aim 3, the 32-month clinical diagnoses (e.g., AD statuses) were included as predictors. Significance was set at $p < 0.05$. See Figure 1 for an example population model.

3 | RESULTS

3.1 | Preliminary analyses

Of the 358 adults with DS enrolled in ABC-DS at the baseline, 218 (61%) participants completed the Tinetti Gait assessment at baseline and the 32-month follow-up. Independent *t* tests and chi-squared tests indicated that the 218 participants included in analyses did not differ from those who did not complete the 32-month follow-up ($n = 140$) in age, sex, race, ethnicity, or ID level ($p < 0.05$; see Table S1 in supporting information). On average, participants were 44.4 years old (standard deviation [SD] = 9.20), 56% were male, and 98% self-identified as White. Most participants had a premorbid ID level in the mild range (56%), while 35% had moderate ID and 9% had severe/profound ID. At baseline, 171 (78%) of participants were cognitively stable, 36 (17%) had MCI, 8 (4%) had dementia, and 3 (1%) had a status of unable to determine. By 32 months, 149 (68%) of participants were cognitively stable, 24 (11%) had MCI, and 41 (19%) had dementia. Three participants deemed to have MCI at baseline reverted to cognitively stable at 32 months, while all other participants with MCI at baseline ($n = 33$) either remained MCI or transitioned to dementia at 32 months. Participants classified as "unable to determine" at 32 months ($N = 5$; 2%) were excluded from the model. See Table 1 for additional demographic information.

Of the 218 participants with both Tinetti Gait scores, 206 completed the DSMSE, 186 completed the mCRT, and 204 completed the NTG. Of the 218 participants, PET A β was available for 143 participants, PET NFT was available for 97 participants, and MRI hippocampal data were available for 81 participants. The remaining participants either did not undergo imaging or imaging was acquired but using procedures that were not harmonized with the ones used in the current analyses. Independent *t* tests and chi-squared tests indicated that the 143 participants with imaging data did not significantly differ from those without imaging data ($n = 75$) in sex, race, ethnicity, or ID level ($p < 0.05$), but did significantly differ in terms of age ($p < 0.05$; see Table 2). The mean age of those with imaging data with significantly less ($\bar{x} = 42.6$) than the mean age of those without imaging data ($\bar{x} = 48.6$).

Table 1 displays the mean and SD for the Tinetti Gait score at baseline and the 32-month follow-up. Analyses were conducted to examine the association between demographic variables and the Tinetti Gait score at baseline. Age was significantly negatively associated with the Tinetti Gait score ($r = -0.405$, $p < 0.01$). Additionally,

$$\widehat{Tinetti}_3 = \alpha + (\beta_1 * DSMSE.residuals) + (\beta_2 * age) + (\beta_3 * ID) + (\beta_4 * Seizure) + (\beta_5 * [OP * OA]) + (\beta_7 * cataracts) + (\beta_8 * Tinetti\ 1) + \varepsilon_i$$

FIGURE 1 Example population model.

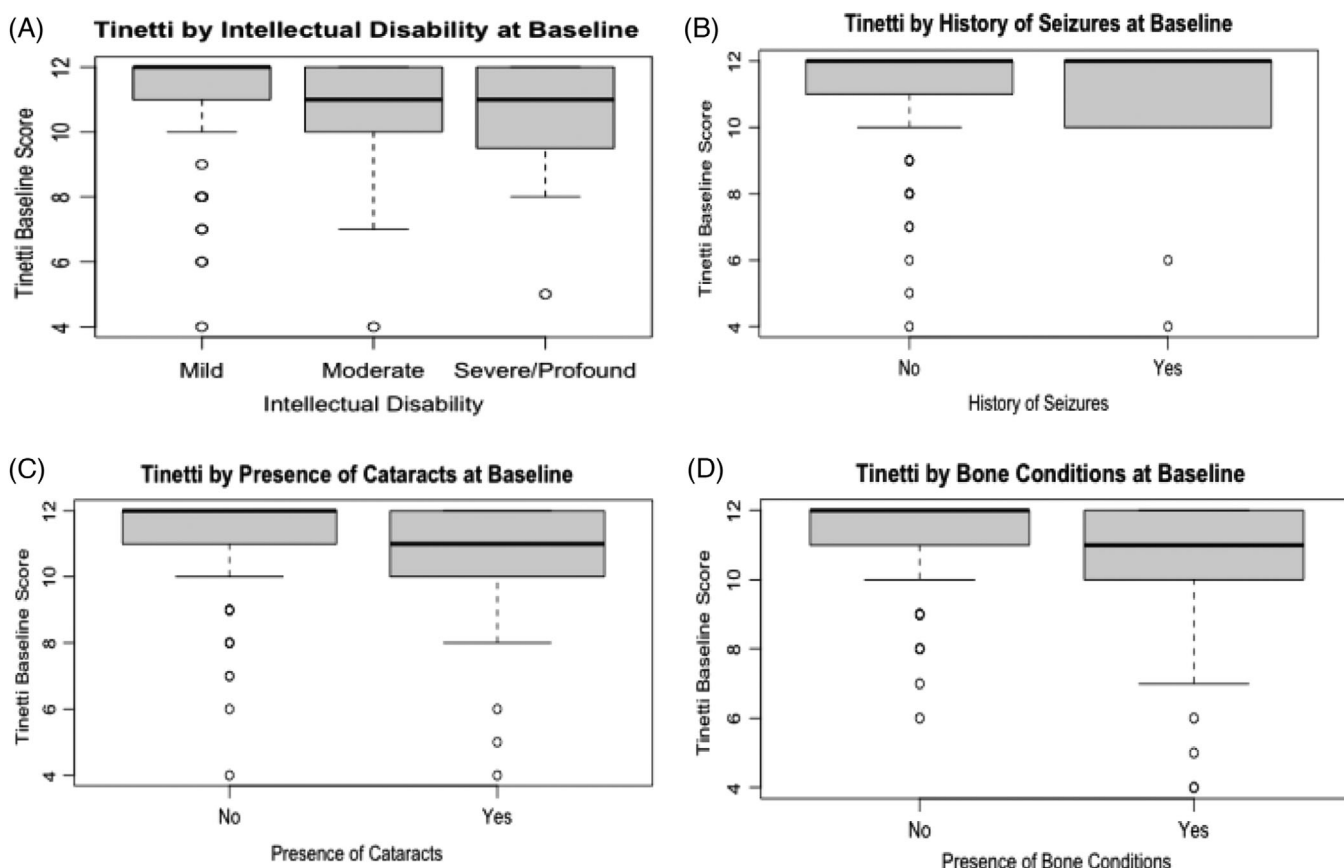


FIGURE 2 Baseline Tinetti Gait score by intellectual disability level (A), presence of seizures (B), presence of cataracts (C), and presence of orthopedic condition (D)

there was a significant difference in the Tinetti Gait score across ID levels ($F[2, 215] = 5.87, p < 0.01$). Tukey post hoc indicated that participants with moderate ID ($p = 0.013$, 95% confidence interval [CI] = [0.17, 1.88]) and severe/profound ($p < 0.01$, 95% CI = [0.38, 2.04]) had significantly lower baseline Tinetti Gait scores than those with mild ID. The presence of seizures ($t[216] = 5.327, p < 0.01$), cataracts ($t[216] = 2.370, p = 0.02$), and osteoarthritis and/or osteoporosis ($t[216] = 6.541, p < 0.01$) were also significantly negatively associated with Tinetti Gait scores. The remaining health conditions (Parkinson's disease, tremors, myoclonus, traumatic brain injury, vision, hearing, and gout) were not significantly related to Tinetti Gait scores ($p > 0.05$). See Table 1 for the proportion of participants with a history of seizures, cataracts, osteoarthritis, and osteoporosis. In subsequent residual change models, age, ID, and presence of seizures, cataracts, and osteoarthritis/osteoporosis were included as covariates. Also see Figure 2 for boxplots comparing the presence and absence of covariates to baseline Tinetti scores.

3.2 | Cognitive decline

Table 1 also provides the mean and SD for cognitive scores at baseline and the 32-month follow-up. In the residual change model, residual change in DSMSE scores significantly predicted the 32-month Tinetti Gait score ($F[8, 198] = 16.24, p < 0.01$). Specifically, Tinetti Gait scores at 32 months were 0.632 points lower for every 1-point reduction in residual DSMSE scores from baseline to the 32-month follow-up, with other predictors held constant ($p < 0.01$). The residual change in mCRT scores also significantly predicted Tinetti Gait scores at the 32-month follow-up ($F[8, 178] = 13.98, p < 0.01$). Tinetti Gait scores were 0.689 points lower for every 1-point reduction in residual mCRT scores from baseline to the 32-month follow-up while holding all other predictors constant ($p < 0.01$). Finally, the residual change in NTG scores significantly predicted Tinetti Gait scores at the 32-month follow-up ($F[8, 196] = 17.96, p < 0.01$). Tinetti Gait scores at 32 months decreased by 0.814 for every 1-point increase in residual NTG reported

TABLE 1 Participant demographic characteristics.

Age (years), M ± SD	44.4 ± 9.2
BMI, M ± SD	31.5 ± 7.2
Sex, N (%)	
Male	122 (56.0%)
Female	96 (44.0%)
Race, N (%)	
White	213 (97.7%)
Black or African American	3 (1.4%)
Asian	2 (0.9%)
Ethnicity, N (%)	
Hispanic or Latino	10 (4.6%)
Intellectual disability level, N (%)	
Mild	121 (55.5%)
Moderate	77 (35.3%)
Severe/profound	20 (9.2%)
Clinical AD status at 32 months, N (%)	
Cognitively stable	149 (68.3%)
MCI	24 (11%)
Dementia	41 (18.8%)
Unable to determine	5 (2.3%)
APOE ε4, N (%)	
Presence of at least one allele	50 (23%)
Trisomy type, N (%)	
Full	196 (89.9%)
Mosaic	10 (4.6%)
Translocation	12 (5.5%)
Orthopedic condition, N (%)	
Combined	67 (30.7%)
Osteoarthritis	36 (16.5%)
Osteoporosis	31 (14.2%)
Cataracts, N (%)	72 (33.0%)
Seizure history, N (%)	14 (6.4%)
Tinetti gait, M ± SD	
Baseline	11.04 ± 1.51
32-month	10.52 ± 2.16
DSMSE, M ± SD	
Baseline	58.29 ± 16.77
32-month	56.60 ± 19.01
mCRT, M ± SD	
Baseline	27.19 ± 10.71
32-month	26.81 ± 10.78
NTG, M ± SD	
Baseline	6.11 ± 9.07
32-month follow-up	5.33 ± 8.26

Abbreviations: AD, Alzheimer's disease; APOE, apolipoprotein E; DSMSE, Down Syndrome Mental Status Examination; MCI, mild cognitive impairment; mCRT, modified Cued Recall Test; NTG, National Task Group–Early Detection Screen for Dementia; SD, standard deviation.

TABLE 2 Regression models of change in cognitive functioning predicting gait at 32 months.

Variable	β	SE	t value	p value
DSMSE	0.632	0.139	4.817	2.89 e-06***
Age	−0.0342	0.0158	−2.162	0.0318*
ID moderate	0.130	0.257	0.504	0.615
ID severe/profound	−0.624	0.435	−1.432	0.154
Seizure	−0.316	0.501	−0.631	0.529
Orthopedic condition	−0.565	0.308	−1.834	0.0682
Cataracts	0.0240	0.270	0.089	0.929
Tinetti baseline	0.533	0.0888	5.999	9.29 e-09***
mCRT	0.689	0.128	5.37	2.50 e-07***
Age	−0.0132	0.0164	−0.804	0.423
ID moderate	0.204	0.262	0.776	0.439
ID severe/profound	−0.590	0.443	−1.33	0.185
Seizure	−0.355	0.539	−0.659	0.511
Orthopedic condition	−0.737	0.313	−2.35	0.0199*
Cataracts	0.202	0.271	0.748	0.456
Tinetti baseline	0.507	0.0910	5.572	9.18 e-08***
NTG	−0.814	0.132	−6.15	4.39 e-09***
Age	−0.0325	0.0153	−2.12	0.0353*
ID moderate	0.140	0.248	0.565	0.573
ID severe/profound	−0.468	0.429	−1.09	0.277
Seizure	−0.0972	0.499	−0.195	0.850
Orthopedic condition	−0.573	0.299	−1.91	0.0571
Cataracts	0.639	0.263	0.243	0.808
Tinetti baseline	0.528	0.0880	6.00	9.29 e-09***

Note: Orthopedic condition comprises osteoarthritis and osteoporosis. Abbreviations: DSMSE, Down Syndrome Mental Status Examination; ID, intellectual disability; mCRT, modified Cued Recall Test; NTG, National Task Group–Early Detection Screen for Dementia; SE, standard error.

* $p < 0.05$.

*** $p < 0.001$.

symptoms from baseline to the 32-month follow-up while holding all other predictors constant ($p < 0.01$). See Table 2 for an overview of each assessment's residual change model and Figure 3 for the change in Tinetti compared to the change in each assessment.

3.3 | Neuroimaging AD biomarkers

Baseline A β PET, NFT PET, and ICV controlled hippocampal volume were implemented into respective residual change models. Baseline A β significantly predicted the 32-month Tinetti Gait score ($F[8, 135] = 9.134, p < 0.01$). The 32-month Tinetti Gait scores decreased by 0.0143 points with each 1 Centiloid higher baseline A β PET, holding all other predictors constant ($p < 0.01$). Baseline tau PET was also a

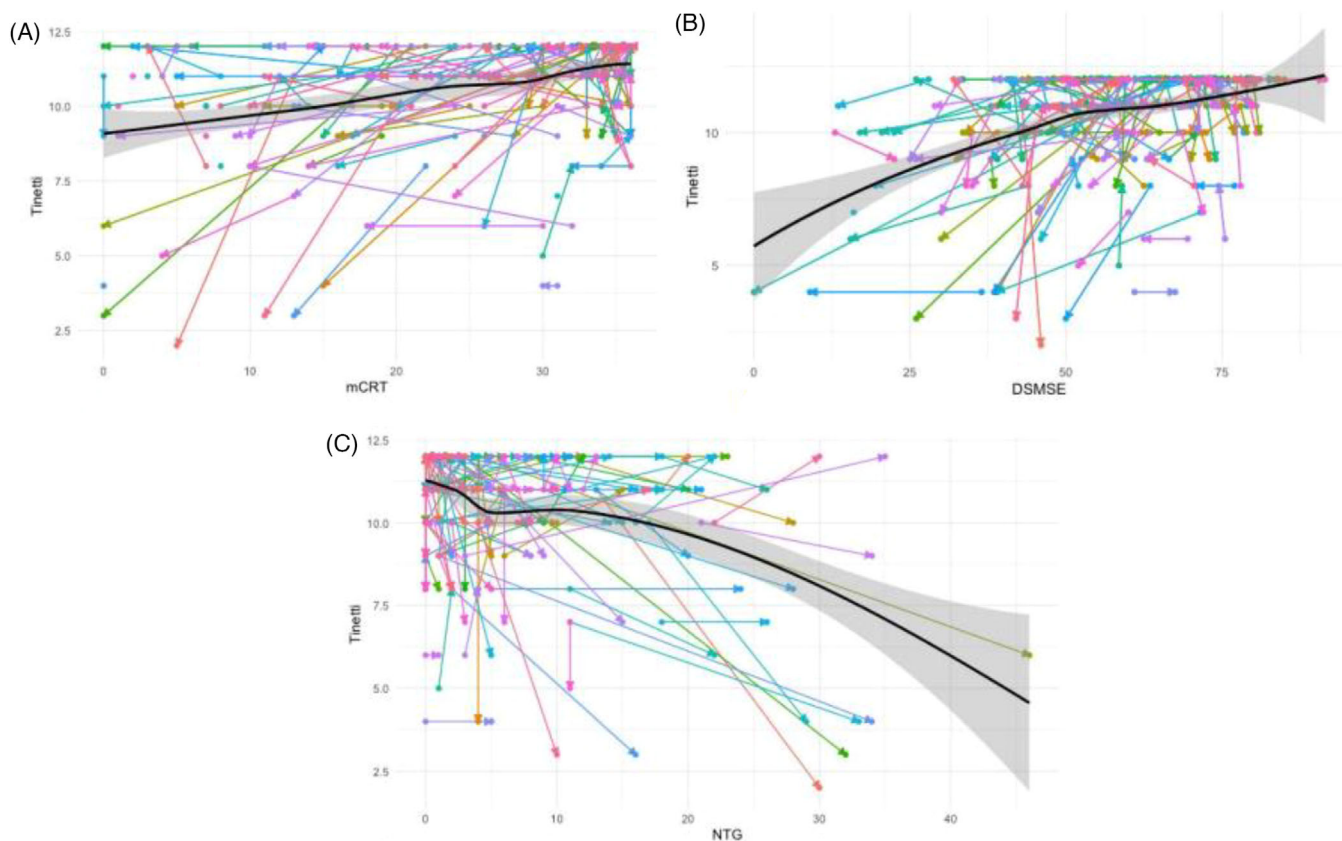


FIGURE 3 Change in cognitive functioning in relation to change in Tinetti score from baseline to 32-month follow-up. A, Modified Cued Recall Test (mCRT). B, Down Syndrome Mental Status Examination (DSMSE); C, National Task Group—Early Dementia Screener (NTG). Each line represents a participant. Circles denote scores at baseline and arrows denote scores at the 32-month follow-up. The solid black line represents the locally estimated scatterplot smoothing data trend, and the gray band represents the 95% confidence interval

significant predictor of Tinetti Gait scores at 32 months. The model predicted a 3.94-point decrease in Tinetti Gait scores for every 1 SUVR increase in baseline tau PET representing regions consistent with Braak stages I and II while holding all other predictors constant ($p < 0.01$). Additionally, Tinetti Gait scores decreased by 5.10 and 5.12 points for every 1 SUVR increase in baseline tau PET in regions representing Braak stages III and IV and V and VI, respectively, while holding all other predictors constant ($p < 0.01$). Finally, the residual change model of total hippocampal volume was found to be a significant predictor of 32-month Tinetti Gait scores ($F[9, 72] = 4.372, p < 0.01$). ICV was included in this model to control total brain size. Tinetti Gait scores decreased by 9.26×10^{-4} points for every 1 mm^3 reduction in hippocampal volume while holding all other predictors constant ($p < 0.01$). See Table 3 for an overview of the residual change models for A β , tau, and hippocampal volume and Figure 4 for the change in Tinetti by each neuroimaging procedure.

3.4 | Clinical AD status

In residual change models, clinical AD status significantly predicted the 32-month Tinetti Gait score ($F[10, 197] = 17.22, p < 0.01$). Compared to participants who remained cognitively stable, participants who had

dementia scored an average of 2.12 less points on the Tinetti Gait assessment ($p < 0.01$). However, Tinetti scores for those with MCI were not significantly different from participants who remained cognitively stable ($p = 0.34$). See Table 4 for an overview of the clinical AD status residual change model, and Figure 5 for boxplots of clinical AD status by change in Tinetti.

4 | DISCUSSION

Gait impairments are a prominent feature of AD, often beginning prior to dementia onset in the general adult population.^{21,22} The present study was the first longitudinal study to assess change in gait in relation to neuroimaging biomarkers of AD pathologies, cognitive decline, and AD clinical status in adults with DS. Overall, findings suggest that gait impairments have robust associations with AD pathology and symptomatology in DS and thus are part of the broader array of functional declines evident in DSAD that should be included in DSAD screening efforts.

Adults with DS who had higher A β and NFT burden at baseline evidenced more gait impairments at 32 months than those with lower A β and NFT burden. These results are in line with findings on late-onset sporadic AD (LOAD) and autosomal-dominant AD, in which

TABLE 3 Regression models of baseline AD biomarkers predicting gait at 32 months.

Variable	β	SE	t value	p value
A β	-0.0143	0.00604	-2.37	0.00288**
Age	-0.0377	0.0243	-1.55	0.0193*
ID moderate	-0.0354	0.340	-0.104	0.917
ID severe/profound	-0.686	0.507	-1.35	0.179
Seizure	-0.0365	0.762	-0.048	0.962
Orthopedic condition	-0.477	0.421	-1.13	0.259
Cataracts	0.0631	0.360	0.175	0.861
Tinetti baseline	0.571	0.149	3.83	1.97 e-04***
NFT I–II	-3.94	1.155	-3.41	9.77 e-04***
Age	-0.0271	0.0304	-0.891	0.375
ID moderate	0.0235	0.434	0.0540	0.957
ID severe/profound	-0.200	0.531	-0.376	0.708
Seizure	-0.0336	1.719	-0.0200	0.984
Orthopedic condition	-0.563	0.557	-1.011	0.315
Cataracts	-0.203	0.434	-0.468	0.641
Tinetti baseline	0.360	0.176	2.047	0.0436*
NFT III–IV	-5.10	1.21	-4.23	5.63 e-05***
Age	-0.0244	0.0283	-0.862	0.391
ID moderate	-0.0476	0.416	-0.115	0.909
ID severe/profound	-0.266	0.515	-0.516	0.607
Seizure	-0.00538	1.67	-0.00300	0.997
Orthopedic condition	-0.600	0.537	-1.12	0.268
Cataracts	-0.152	0.420	-0.362	0.718
Tinetti baseline	0.332	0.171	1.95	0.0548
NFT V–VI	-5.124	1.16	-4.40	3.00 e-05***
Age	-0.0428	0.0261	-1.64	0.105
ID moderate	-0.207	0.410	-0.505	0.615
ID severe/profound	-0.232	0.512	-0.454	0.651
Seizure	0.0861	1.65	0.052	0.959
Orthopedic condition	-0.461	0.528	-0.874	0.385
Cataracts	-0.268	0.419	-0.641	0.523
Tinetti baseline	0.340	0.169	2.00	0.0481*
Hippocampal volume	9.26 e-04	2.36 e-04	3.93	0.000195***
Age	-0.0303	0.0327	-0.925	0.358
ID moderate	-0.0388	0.460	-0.844	0.401
ID severe/profound	0.0201	0.613	0.0330	0.974
Seizure	1.33	1.72	0.773	0.442
Orthopedic condition	-0.0899	0.593	-0.152	0.880
Cataracts	-0.110	0.500	-0.220	0.826
Intracranial volume	-4.25 e-06	1.59 e-06	-2.67	0.00942**
Tinetti baseline	0.640	0.318	2.01	0.0484*

Note: Orthopedic condition comprises osteoarthritis and osteoporosis.

Abbreviations: A β , a myloid beta; AD, Alzheimer's disease; ID, intellectual disability; NFT, neurofibrillary tangle; SE, standard error.

* $p < 0.05$.

** $p < 0.01$.

*** $p < 0.001$.

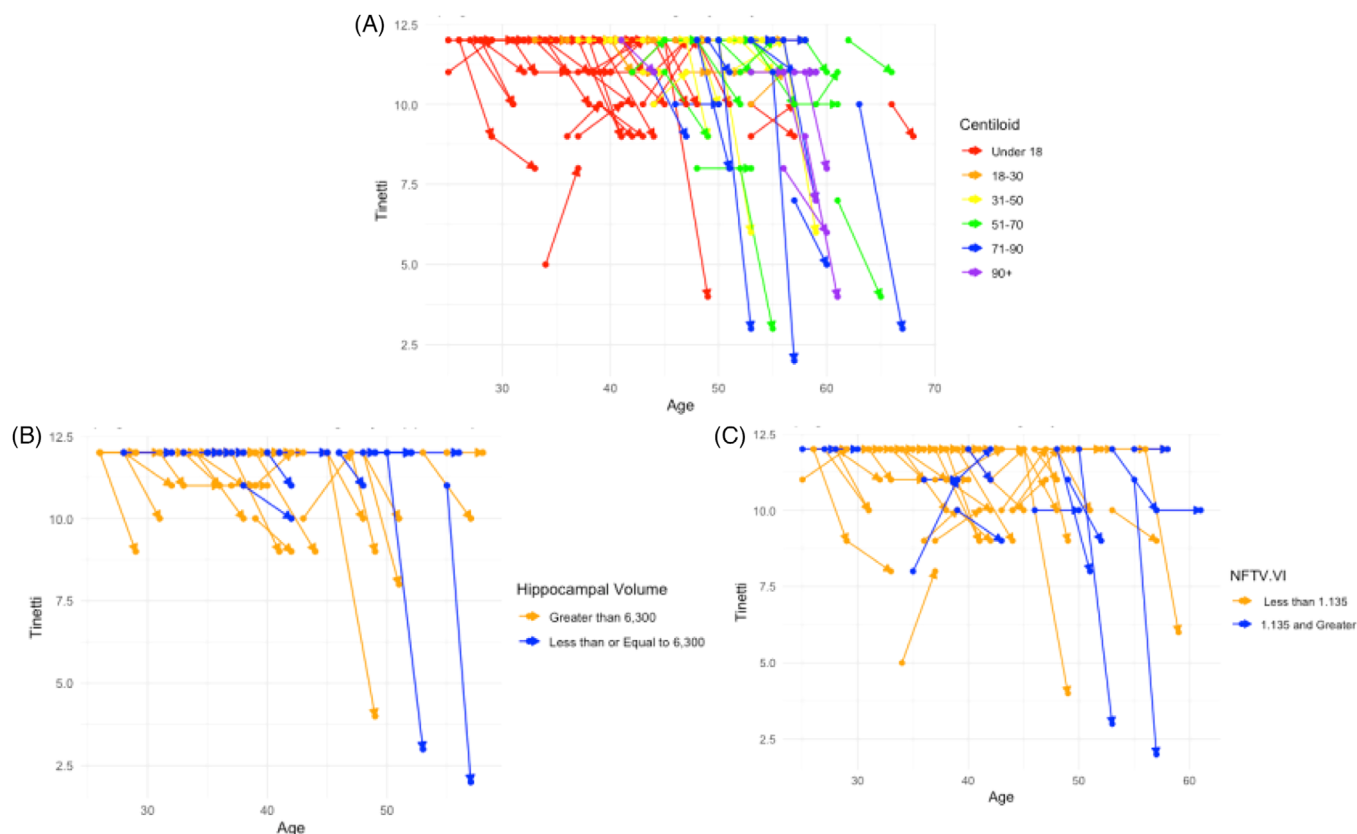


FIGURE 4 Change in Tinetti score from baseline to the 32-month follow-up. Each line represents a participant based on (A) amyloid burden in Centiloids, (B) low versus high hippocampal volume, (C) high versus low neurofibrillary tangles (NFTs) in Braak V and VI regions. Circles denote scores at baseline and arrows denote scores at 32-month follow-up

TABLE 4 Regression model of change in clinical AD status predicting gait at 32 months.

Variable	β	SE	t value	p value
MCI	-0.377	0.398	-0.948	0.344
Dementia	-2.12	0.364	-5.81	2.51 e-08***
Age	-6.04 e-03	0.0173	-0.350	0.727
ID moderate	0.204	0.255	0.799	0.425
ID severe/profound	-0.382	0.424	-0.903	0.368
Seizure	-0.0820	0.305	-0.168	0.869
Orthopedic condition	-0.794	0.305	-2.61	0.00987**
Cataracts	0.0864	0.266	0.325	0.745
Tinetti baseline	0.529	0.0862	6.135	4.73 e-09***

Note: Orthopedic condition comprises osteoarthritis and osteoporosis.

Abbreviations: AD, Alzheimer's disease; ID, intellectual disability; MCI, mild cognitive impairment; SE, standard error.

** $p < 0.01$.

*** $p < 0.001$.

higher A β and NFT burden is associated with slower gait speed,³⁴ decreased cadence,⁶⁷ and lower overall gait quality.^{68,69} In the current study, NFT in Braak stages III and IV and V and VI had the greatest impact on Tinetti Gait scores, suggesting that NFT accumulation in limbic and neocortical areas may take a toll on gait. Hippocampal atrophy was also associated with gait impairments across time in

adults with DS, mirroring findings in the general population of older adults.⁷⁰

The current study also examined associations between gait performance and AD-related cognitive declines in DS. Even after controlling for age, premorbid ID level, and medical conditions that can impact gait (seizures, orthopedic conditions, cataracts), greater decline in gait

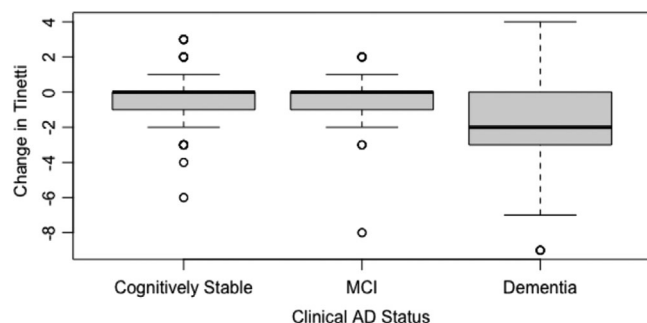


FIGURE 5 Change in Tinetti scores from baseline to the 32-month follow-up by clinical Alzheimer's disease (AD) status at the 32-month follow-up. The y axis represents the change in Tinetti scores from baseline to the 32-month follow-up. Negative numbers represent a decrease Tinetti scores and positive numbers represent an increase in Tinetti scores

performance across the 32 months was associated with cognitive declines (as indicated by the mCRT and DSMSE) and increases in informant-reported dementia symptoms (NTG). In addition, adults with DS who were deemed to have dementia at 32 months (15% developed dementia during the study period while 8% had dementia at baseline) had lower Tinetti Gait scores than those who were cognitively stable. However, Tinetti Gait scores for participants with MCI at 32 months (7% developed MCI during the study period while 3% had MCI at baseline) were not significantly different from those who were cognitively stable. Impairments in gait were most strongly associated with later stages of tau PET NFT burden (i.e., spread across the neocortex). Thus, gait impairments may be observed closer to the onset of dementia than MCI in adults with DS, at least using observable gross measures of gait. However, it is also possible that the limited number of adults with DS and MCI ($N = 24$) obscured detection of more subtle impairments. Instead, more precise gait measures (e.g., technology-based gait mats) may be more sensitive to declines in gait that precede or correspond with onset of MCI in DS. Overall, these findings are consistent with research on LOAD outside of DS in which gait impairments are evident prior to dementia early during the unfolding of AD symptomology, with increasing severity from early to late stages of dementia.^{71–75}

The current study had several strengths. Analyses leveraged a large natural history cohort of adults with DS, and the cognitive and neuroimaging protocols were harmonized across data collection sites. The clinical AD status groups were based on a consensus process that drew on a large battery of direct and informant-reported assessments. Additionally, this study provides robust and multimodal evidence that declines in gait are linked to AD pathology. There were also limitations to the current study. First, the gait assessment was based on observational coding. Raters complete a comprehensive neuropsychological and gait training, but no inter-rater reliability has been established across sites. Second, only some of the ABC-DS data collection sites included the neuroimaging biomarkers of interest, which reduced the sample size for some models. A small number of attempted MRI scans were uninterpretable due to participant movement, but it is possible that this altered sample characteristics to be more representative of

higher functioning adults with DS. It should be noted that the ABC-DS protocol includes data collection on participants every 16 months. However, neuroimaging biomarkers ($A\beta$, NFT, and hippocampal volume) are only obtained at baseline and 32-month visits. Thus, current analyses focused on change across 32 months (baseline to month 32 visit) given our inclusion of neuroimaging biomarkers. In addition, this longer duration (32 vs. 16 months) was deemed to be better suited for detecting changes in cognition and gait. That said, future studies that include longer time intervals and additional data points are needed to better capture individual change trajectories.⁷⁶ Neuroimaging data were only available on a subset of the sample and this subset was younger than those without imaging data. Thus, neuroimaging findings may not fully capture effects in later disease stages. Finally, findings are not representative of non-verbal adults with DS and/or those with a mental age of < 3 years given study inclusion criteria. Future studies should include adults with DS with a broader range of racial/ethnic diversity backgrounds, which is a goal of the ABC-DS study's current recruitment efforts. Future studies should also focus on regional amyloid, tau, and neurodegeneration outcomes to better understand mechanisms underlying the associations between gait change and clinical and neuropathological progression of AD in people with DS. Additionally, future studies using more sensitive technology-based gait mats may be able to detect even earlier subtle changes in gait related to AD pathology and symptomology. Finally, it will also be important for future studies to examine which specific domains of gait (e.g., cadence, foot clearance, and step symmetry) are impacted by AD pathology and are best able to distinguish among DSAD clinical status groups.

In summary, our findings suggest that gait impairments are a key feature of DSAD. The onset of gait impairments is associated with elevated $A\beta$ and NFT burden and hippocampal atrophy and corresponds with early cognitive declines, dementia symptoms, and clinical AD status. In particular, 1 SUVR tau PET change in brain regions corresponding to NFT III and IV and NFT V and VI was associated with an $\approx 40\%$ decrease in Tinetti scores, demonstrating Tinetti's sensitivity to NFT burden. These findings may also have important clinical implications, as gait assessments could serve as a screening tool for AD detection in adults with DS. The Tinetti Gait Test may offer a quick, cost-effective, non-invasive screen for gait impairments that occur as part of the evolution of AD symptomology in adults with DS. Additionally, caregivers may consider monitoring changes in gait, potentially lending early insight to cognitive decline and fall risk. Future studies are needed to further establish the relationship between gait and AD development in adults with DS.

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CONFLICT OF INTEREST STATEMENT

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CONSENT STATEMENT

Informed consent and/or assent were obtained for all participants.

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REFERENCES

1. Lejeune J. Etude des chromosomes somatiques de neuf enfants mongoliens. *C R Hebd Seances Acad Sci.* 1959;248:1713-1727.
2. Centers for Disease Control and Prevention. Living with Down Syndrome. CDC; 2024. https://www.cdc.gov/birth-defects/living-with-down-syndrome/?CDC_AAref_Val=https://www.cdc.gov/ncbddd/birthdefects/downsyndrome/data.html
3. McCarron M, McCallion P, Reilly E, Mulryan N. A prospective 14-year longitudinal follow-up of dementia in persons with Down syndrome. *J Intellect Disabil Res.* 2014;58(1):61-70. doi:10.1111/jir.12074
4. Wiseman FK, Al-Janabi T, Hardy J, et al. A genetic cause of Alzheimer disease: mechanistic insights from Down syndrome. *Nat Rev Neurosci.* 2015;16(9):564-574. doi:10.1038/nrn3983
5. Montoliu-Gaya L, Strydom A, Blennow K, Zetterberg H, Ashton NJ. Blood biomarkers for Alzheimer's disease in Down syndrome. *JCM.* 2021;10(16):3639. doi:10.3390/jcm10163639
6. Boerwinkle AH, Gordon BA, Wisch JK, et al. Comparison of amyloid accumulation between Down syndrome and autosomal-dominant Alzheimer disease. *Alzheimers Dementia.* 2022;18(S1):e063959. doi:10.1002/alz.063959
7. Lao PJ, Handen BL, Betthausen TJ, et al. Longitudinal changes in amyloid positron emission tomography and volumetric magnetic resonance imaging in the nondemented Down syndrome population. *Alz & Dem Diag Ass & Dis Mo.* 2017;9(1):1-9. doi:10.1016/j.dadm.2017.05.001
8. Annus T, Wilson LR, Hong YT, et al. The pattern of amyloid accumulation in the brains of adults with Down syndrome. *Alzheimers Dementia.* 2016;12(5):538-545. doi:10.1016/j.jalz.2015.07.490
9. Wisch JK, McKay NS, Boerwinkle AH, et al. Comparison of tau spread in people with Down syndrome versus autosomal-dominant Alzheimer's disease: a cross-sectional study. *Lancet Neurol.* 2024;23(5):500-510. doi:10.1016/S1474-4422(24)00084-X
10. Schöll M, Maass A, Mattsson N, et al. Biomarkers for tau pathology. *Mol Cell Neurosci.* 2019;97:18-33. doi:10.1016/j.mcn.2018.12.001
11. Rafii MS. Tau PET imaging for staging of Alzheimer's disease in Down syndrome. *Dev Neurobiol.* 2019;79(7):711-715. doi:10.1002/dneu.22658
12. Tudorascu D, Laymon C, Zammit M, et al. Relationship of amyloid beta and neurofibrillary tau deposition in Neurodegeneration in Aging Down Syndrome (NiAD) study at baseline. *A&D Transl Res & Clin Interv.* 2020;6(1):e12096. doi:10.1002/trc2.12096
13. Teipel SJ, Hampel H. Neuroanatomy of Down syndrome in vivo: a model of preclinical Alzheimer's disease. *Behav Genet.* 2006;36(3):405-415. doi:10.1007/s10519-006-9047-x
14. Tramutola A, Lanzillotta C, Di Domenico F, et al. Brain insulin resistance triggers early onset Alzheimer disease in Down syndrome. *Neurobiol Dis.* 2020;137:104772. doi:10.1016/j.nbd.2020.104772
15. Schworer EK, Handen BL, Petersen M, et al. Cognitive and functional performance and plasma biomarkers of early Alzheimer's disease in Down syndrome. *Alz & Dem Diag Ass & Dis Mo.* 2024;16(2):e12582. doi:10.1002/dad2.12582
16. Hartley SL, Handen BL, Devenny D, et al. Cognitive decline and brain amyloid- β accumulation across 3 years in adults with Down syndrome. *Neurobiol Aging.* 2017;58:68-76. doi:10.1016/j.neurobiolaging.2017.05.019
17. Larsen FK, Baksh RA, McGlinchey E, et al. Age of Alzheimer's disease diagnosis in people with Down syndrome and associated factors: results from the Horizon 21 European Down syndrome consortium. *Alzheimers Dementia.* 2024;20:3270-3280. doi:10.1002/alz.13779
18. Petersen ME, Flores-Aguilar L, Head E, et al. Blood biomarkers in Down syndrome: facilitating Alzheimer's disease detection and monitoring. *Alzheimers Dementia.* 2025;21:e14364. doi:10.1002/alz.14364
19. Koehl L, Harp J, Van Pelt KL, Head E, Schmitt FA. Longitudinal assessment of dementia measures in Down syndrome. 2020;12:e12075. doi:10.1002/dad2.12075
20. Schworer EK, Zammit MD, Wang J, et al. Timeline to symptomatic Alzheimer's disease in people with Down syndrome as assessed by amyloid-PET and tau-PET: a longitudinal cohort study. *Lancet Neurol.* 2024;23(12):1214-1224. doi:10.1016/S1474-4422(24)00426-5
21. Pedersen MM, Holt NE, Grande L, et al. Mild cognitive impairment status and mobility performance: an analysis from the Boston RISE study. *J Gerontol A Biol Sci Med Sci.* 2014;69(12):1511-1518. doi:10.1093/gerona/glu063
22. Sheridan PL, Hausdorff JM. The role of higher-level cognitive function in gait: executive dysfunction contributes to fall risk in Alzheimer's disease. *Dement Geriatr Cogn Disord.* 2007;24(2):125-137. doi:10.1159/000105126
23. Beauchet O, Annweiler C, Callisaya ML, et al. Poor gait performance and prediction of dementia: results from a meta-analysis. *J Am Med Dir Assoc.* 2016;17(6):482-490. doi:10.1016/j.jamda.2015.12.092
24. Cedervall Y, Halvorsen K, Åberg AC. A longitudinal study of gait function and characteristics of gait disturbance in individuals with Alzheimer's disease. *Gait Posture.* 2014;39(4):1022-1027. doi:10.1016/j.gaitpost.2013.12.026
25. Marquis S, Moore MM, Howieson DB, et al. Independent predictors of cognitive decline in healthy elderly persons. *Arch Neurol.* 2002;59(4):601. doi:10.1001/archneur.59.4.601
26. Merory JR, Wittwer JE, Rowe CC, Webster KE. Quantitative gait analysis in patients with dementia with Lewy bodies and Alzheimer's disease. *Gait Posture.* 2007;26(3):414-419. doi:10.1016/j.gaitpost.2006.10.006
27. Nakamura T, Meguro K, Yamazaki H, et al. Postural and gait disturbance correlated with decreased frontal cerebral blood flow in Alzheimer disease. *Alzheimer Dis Assoc Disord.* 1997;11(3):132-139.
28. O'Keeffe ST, Kazeem H, Philpott RM, Playfer JR, Gosney M, Lye M. Gait Disturbance in Alzheimer's disease: a clinical study. *Age Ageing.* 1996;25(4):313-316. doi:10.1093/ageing/25.4.313

29. Bollinger RM, Chen SW, Krauss MJ, et al. The association between postural sway and preclinical alzheimer disease among community-dwelling older adults. *J Gerontol A Biol Sci Med Sci*. 2024;79:glae091. doi:10.1093/gerona/glac091
30. Nilsson MH, Tangen GG, Palmqvist S, et al. The effects of tau, amyloid, and white matter lesions on mobility, dual tasking, and balance in older people. *Gerontol A Biol Sci Med Sci*. 2021;76(4):683-691. doi:10.1093/gerona/glaa143
31. Montero-Odasso M, Perry G. Gait disorders in alzheimer's disease and other dementias: there is something in the way you walk. *JAD*. 2019;71(s1):S1-S4. doi:10.3233/JAD-190790
32. Dao E, Hsiung GYR, Sossi V. Cerebral amyloid- β deposition is associated with impaired gait speed and lower extremity function. *JAD*. 2019;71(s1):S41-S49. doi:10.3233/JAD-180848
33. Takakusaki K, Tomita N, Yano M. Substrates for normal gait and pathophysiology of gait disturbances with respect to the basal ganglia dysfunction. *J Neurol*. 2008;255(S4):19-29. doi:10.1007/s00415-008-4004-7
34. Del Campo N, Payoux P, Djilali A, et al. Relationship of regional brain β -amyloid to gait speed. *Neurology*. 2016;86(1):36-43. doi:10.1212/WNL.0000000000002235
35. Tian Q, Chastan N, Bair WN, Resnick SM, Ferrucci L, Studenski SA. The brain map of gait variability in aging, cognitive impairment and dementia—a systematic review. *Neurosci Biobehav Rev*. 2017;74:149-162. doi:10.1016/j.neubiorev.2017.01.020
36. Pieruccini-Faria F, Black SE, Masellis M, et al. Gait variability across neurodegenerative and cognitive disorders: results from the Canadian Consortium of Neurodegeneration in Aging (CCNA) and the Gait and Brain Study. *Alzheimers Dementia*. 2021;17(8):1317-1328. doi:10.1002/alz.12298
37. Zago M, Duarte NAC, Grecco LAC, Condoluci C, Oliveira CS, Galli M. Gait and postural control patterns and rehabilitation in Down syndrome: a systematic review. *J Phys Ther Sci*. 2020;32(4):303-314. doi:10.1589/jpts.32.303
38. Smith BA, Stergiou N, Ulrich BD. Patterns of gait variability across the lifespan in persons with and without Down syndrome. *J Neurol Phys Ther*. 2011;35(4):170-177. doi:10.1097/NPT.0b013e3182386de1
39. Chicoine B, Rivelli A, Fitzpatrick V, Chicoine L, Jia G, Rzhetsky A. Prevalence of common disease conditions in a large cohort of individuals with Down syndrome in the United States. *J Patient Cent Res Rev*. 2021;8(2):86-97. doi:10.17294/2330-0698.1824
40. Coelho-Junior HJ, Villani ER, Calvani R, et al. Sarcopenia-related parameters in adults with Down syndrome: a cross-sectional exploratory study. *Exp Gerontol*. 2019;119:93-99. doi:10.1016/j.exger.2019.01.028
41. Dupre C, Weidman-Evans E. Musculoskeletal development in patients with Down syndrome. *JAAPA*. 2017;30(12):38-40. doi:10.1097/01.JAA.0000526779.77230.79
42. Anderson-Mooney AJ, Schmitt FA, Head E, Lott IT, Heilman KM. Gait dyspraxia as a clinical marker of cognitive decline in Down syndrome: a review of theory and proposed mechanisms. *Brain Cogn*. 2016;104:48-57. doi:10.1016/j.bandc.2016.02.007
43. Van Pelt KL, Koehl L, Caban-Holt A, Anderson-Mooney A, Head E, Schmitt FA. Feasibility of dual-task gait to estimate Alzheimer's related cognitive decline in Down syndrome. *Alzheimers Dement*. 2020;12:e12092. doi:10.1002/dad2.12092
44. Tinetti ME. Performance-oriented assessment of mobility problems in elderly patients. *J American Geriatrics Society*. 1986;34(2):119-126. doi:10.1111/j.1532-5415.1986.tb05480.x
45. Conceição ASGG, Sant'Ana LFG, Mattar GP, et al. Balance and gait: associations with cognitive impairment and dementia in individuals with Down syndrome. *Alzheimer Dis Assoc Disord*. 2023;37(4):349-356. doi:10.1097/WAD.0000000000000580
46. Handen BL, Lott IT, Christian BT, et al. The Alzheimer's Biomarker Consortium-Down Syndrome: rationale and methodology. *Alzheimers Dement*. 2020;12(1):e12065. doi:10.1002/dad2.12065
47. Krinsky-McHale SJ, Zigman WB, Lee JH, et al. Promising outcome measures of early Alzheimer's dementia in adults with Down syndrome. *Alzheimers Dement*. 2020;12:e12044. doi:10.1002/dad2.12044
48. Kaufman AS. *Kaufman Brief Intelligence Test-Second Edition (KBIT-2)*. American Guidance Service; 2004.
49. Peterson KC, Peterson M, Carducci BJ. Stanford-Binet Intelligence Scale: fifth edition. In: Carducci BJ, Nave CS, Nave CS, eds. *The Wiley Encyclopedia of Personality and Individual Differences*. 1st ed. Wiley; 2020:451-455. doi:10.1002/9781118970843.ch145
50. Panella L, Tinelli C, Buizza A, Lombardi R, Gandolfi R. Towards objective evaluation of balance in the elderly: validity and reliability of a measurement instrument applied to the Tinetti test. *Int J Rehabil Res*. 2008;31(1):65-72. doi:10.1097/MRR.0b013e3282f28f38
51. Canbek J, Fulk G, Nof L, Echternach J. Test-retest reliability and construct validity of the Tinetti performance-oriented mobility assessment in people with stroke. *J Neurol Phys Ther*. 2013;37(1):14-19. doi:10.1097/NPT.0b013e318283ffcc
52. Gray WK, Hildreth A, Bilclough JA, Wood BH, Baker K, Walker RW. Physical assessment as a predictor of mortality in people with Parkinson's disease: a study over 7 years. *Mov Disord*. 2009;24(13):1934-1940. doi:10.1002/mds.22610
53. Chiba Y, Shimada A, Yoshida F, et al. Risk of fall for individuals with intellectual disability. *Am J Intellect Dev Disabil*. 2009;114(4):225-236. doi:10.1352/1944-7558-114.4:225-236
54. Kegelmeyer DA, Kloos AD, Thomas KM, Kostyk SK. Reliability and validity of the Tinetti mobility test for individuals with Parkinson disease. *Phys Ther*. 2007;87:1369-1378.
55. Kloos AD, Kegelmeyer DA, Young GS, Kostyk SK. Fall risk assessment using the Tinetti mobility test in individuals with Huntington's disease. *Mov Disord*. 2010;25(16):2838-2844. doi:10.1002/mds.23421
56. Haxby JV. Neuropsychological evaluation of adults with Down's syndrome: patterns of selective impairment in non-demented old adults. *J Intellect Disabil Res*. 1989;33(3):193-210. doi:10.1111/j.1365-2788.1989.tb01467.x
57. Tyrrell JF, Cosgrave MP, McLaughlin M, Lawlor BA. Dementia in an Irish population of Down's syndrome people. *Ir J Psychol Med*. 1996;13(2):51-54. doi:10.1017/S0790966700002408
58. Devenny DA, Zimmerli EJ, Kittler P, Krinsky-McHale SJ. Cued recall in early-stage dementia in adults with Down's syndrome. *J Intellect Disabil Res*. 2002;46:472-483.
59. Krinsky-McHale SJ, Hartley S, Hom C, et al. A modified Cued Recall Test for detecting prodromal AD in adults with Down syndrome. *Alz & Dem Diag Ass & Dis Mo*. 2022;14(1):e12361. doi:10.1002/dad2.12361
60. Esralew L, Janicki MP, Keller SM. National Task Group Early Detection Screen for Dementia (NTG-EDSD). In: Prasher VP, ed. *Neuropsychological Assessments of Dementia in Down Syndrome and Intellectual Disabilities*. Springer International Publishing; 2018:197-213. doi:10.1007/978-3-319-61720-6_11
61. Silverman W, Krinsky-McHale SJ, Lai F, et al. Evaluation of the National Task Group-Early Detection Screen for Dementia: sensitivity to 'mild cognitive impairment' in adults with Down syndrome. *Research Intellect Disabil*. 2021;34(3):905-915. doi:10.1111/jar.12849
62. Desikan RS, Ségonne F, Fischl B, et al. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *NeuroImage*. 2006;31(3):968-980. doi:10.1016/j.neuroimage.2006.01.021
63. Avants BB, Tustison NJ, Song G, Cook PA, Klein A, Gee JC. A reproducible evaluation of ANTs similarity metric performance in brain image registration. *NeuroImage*. 2011;54(3):2033-2044. doi:10.1016/j.neuroimage.2010.09.025

64. Avants BB, Tustison N, Johnson H. Advanced Normalization Tools (ANTs). *Insight J*. 2014;2(365):1-35. doi:[10.54294/uvnhin](https://doi.org/10.54294/uvnhin)
65. Braak H, Braak E. Neuropathological staging of Alzheimer-related changes. *Acta Neuropathol*. 1991;82(4):239-259. doi:[10.1007/BF00308809](https://doi.org/10.1007/BF00308809)
66. Klunk WE, Koeppe RA, Price JC, et al. The Centiloid Project: standardizing quantitative amyloid plaque estimation by PET. *Alzheimers Dementia*. 2015;11(1):1. doi:[10.1016/j.jalz.2014.07.003](https://doi.org/10.1016/j.jalz.2014.07.003)
67. Wennberg AMV, Lesnick TG, Schwarz CG, et al. Longitudinal association between brain amyloid-beta and gait in the Mayo Clinic study of aging. *J Gerontol A Biol Sci Med Sci*. 2018;73(9):1244-1250. doi:[10.1093/gerona/glx240](https://doi.org/10.1093/gerona/glx240)
68. Muurling M, Rhodius-Meester HFM, Pärkkä J, et al. Gait disturbances are associated with increased cognitive impairment and cerebrospinal fluid tau levels in a memory clinic cohort. *JAD*. 2020;76(3):1061-1070. doi:[10.3233/JAD-200225](https://doi.org/10.3233/JAD-200225)
69. Schneider JA, Li J, Li Y, Wilson RS, Kordower JH, Bennett DA. Substantia nigra tangles are related to gait impairment in older persons. *Ann Neurol*. 2006;59(1):166-173. doi:[10.1002/ana.20723](https://doi.org/10.1002/ana.20723)
70. Annweiler C, Beauchet O, Celle S, et al. Contribution of brain imaging to the understanding of gait disorders in Alzheimer's disease: a systematic review. *Am J Alzheimers Dis Other Dement*. 2012;27(6):371-380. doi:[10.1177/1533317512454710](https://doi.org/10.1177/1533317512454710)
71. De Melo Borges S, Radanovic M, Forlenza OV. Functional mobility in a divided attention task in older adults with cognitive impairment. *J Mot Behav*. 2015;47(5):378-385. doi:[10.1080/00222895.2014.998331](https://doi.org/10.1080/00222895.2014.998331)
72. Gillain S, Dramé M, Lekeu F, et al. Gait speed or gait variability, which one to use as a marker of risk to develop Alzheimer disease? A pilot study. *Aging Clin Exp Res*. 2016;28(2):249-255. doi:[10.1007/s40520-015-0392-6](https://doi.org/10.1007/s40520-015-0392-6)
73. Aggarwal NT, Wilson RS, Beck TL, Bienias JL, Bennett DA. Motor dysfunction in mild cognitive impairment and the risk of incident Alzheimer disease. *Arch Neurol*. 2006;63(12):1763. doi:[10.1001/archneur.63.12.1763](https://doi.org/10.1001/archneur.63.12.1763)
74. Allali G, Annweiler C, Blumen HM, et al. Gait phenotype from mild cognitive impairment to moderate dementia: results from the GOOD initiative. *Euro J of Neurology*. 2016;23(3):527-541. doi:[10.1111/ene.12882](https://doi.org/10.1111/ene.12882)
75. Callisaya ML, Launay CP, Srikanth VK, Verghese J, Allali G, Beauchet O. Cognitive status, fast walking speed and walking speed reserve—the Gait and Alzheimer Interactions Tracking (GAIT) study. *GeroScience*. 2017;39(2):231-239. doi:[10.1007/s11357-017-9973-y](https://doi.org/10.1007/s11357-017-9973-y)
76. Parsons S, McCormick EM. Limitations of two time point data for understanding individual differences in longitudinal modeling—what can difference reveal about change?. *Dev Cogn Neurosci*. 2024;66:101353. doi:[10.1016/j.dcn.2024.101353](https://doi.org/10.1016/j.dcn.2024.101353)

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