FEATURED ARTICLE

Slowing gait speed precedes cognitive decline by several years

Tobias Skillbäck1,2  |  Kaj Blennow1,3  |  Henrik Zetterberg1,3,4,5  |  Johan Skoog2,6  |  Lina Rydén2,6  |  Hanna Wetterberg2  |  Xinxin Guo2  |  Simona Sacuiu2,6  |  Michelle M. Mielke7  |  Anna Zettergren1,2  |  Ingmar Skoog2,6  |  Silke Kern2,6

1 Institute of Neuroscience and Physiology, Department of Psychiatry and Neurochemistry, The Sahlgrenska Academy at the University of Gothenburg, Mölndal, Sweden
2 Department of Neuropsychiatric epidemiology, Institute of Neuroscience and Physiology, Sahlgrenska Academy, Centre for Ageing and Health (AgeCap) at the University of Gothenburg, Gothenburg, Sweden
3 Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden
4 Department of Neurodegenerative Disease, UCL Institute of Neurology, London, UK
5 Dementia Research Institute at UCL, London, UK
6 Department of Psychiatry Cognition and Old Age Psychiatry, Sahlgrenska University Hospital, Region Västra Götaland, Mölndal, Sweden
7 Department of Health Sciences Research, Department of Neurology, Mayo Clinic, Rochester, Minnesota, USA

Correspondence
Tobias Skillbäck, Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital/Mölndal, S-431 80 Mölndal, Sweden.
Email: tobias.skillback@neuro.gu.se

Ingmar Skoog and Silke Kern contributed equally to the work

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Abstract
Introduction: In this longitudinal study, we aimed to examine if slowing gait speed preceded cognitive decline and correlated with brain amyloidosis.

Methods: The sample (n = 287) was derived from the Gothenburg H70 Birth Cohort Studies, with follow-up between 2000 and 2015. Gait speed was measured by indoor walk, and cognition using the Clinical Dementia Rating (CDR) score. All participants had CDR = 0 at baseline. Some participants had data on cerebrospinal fluid (CSF) amyloid beta (Aβ)1-42 concentrations at the 2009 visit.

Results: Gait speed for participants who worsened in CDR score during follow-up was slower at most examinations. Baseline gait speed could significantly predict CDR change from baseline to follow-up. Subjects with pathological CSF Aβ1-42 concentrations at the 2009 visit had lost more gait speed compared to previous examinations.

Discussion: Our results indicate that gait speed decline precedes cognitive decline, is linked to Alzheimer’s pathology, and might be used for early detection of increased risk for dementia development.

KEYWORDS
Gait, cognitive decline, Alzheimer’s disease, CSF, Aβ42, motor function

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BACKGROUND

Slowing gait speed is a general part of normal aging but has also been linked to cognitive decline in individuals with subjective cognitive impairment (SCI), mild cognitive impairment (MCI), and dementia. Gait, a complex motor function, is affected by many different factors, including pathologic changes in the central nervous system (CNS). Slow gait speed in combination with cognitive complaints has been shown to identify individuals at high risk of progressing to dementia. Different aspects of gait have been studied in relation to anatomic areas of the brain. These studies suggest several specific connections, such as between-step width and the pallidum, or step length and the prefrontal cortex. In addition, specific cognitive domains have been linked to gait domains, such as gait pace correlating with executive function, and gait rhythm correlating with processing speed. Of interest, although motor functions and cognition are closely associated, gait properties have been shown to precede detectable cognitive change by several years and to relate to rate of cognitive decline. Early diagnosis of the disease underlying cognitive impairment is of high importance and might be a key element to being able to administer future treatments in time before irreparable neuronal damage has occurred. The combination of information on gait and cognition may better identify patients who are at high risk of developing dementia than either measure alone.

Methods

2.1 Study sample

The baseline sample was derived from the examinations of the Gothenburg H70 Birth Cohort Studies in Sweden, which occurred in 2000 to 2002. The sample was obtained through systematic sampling by birth date from the Swedish Population Registry and included persons living in private households and individuals in residential care. A total of 775 70-year-olds living in Gothenburg and an additional 105 70-year-olds who previously participated in the Prospective Population Study.
RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the literature using traditional (e.g., PubMed) sources, meeting abstracts, and presentations. Slowing gait speed has been linked previously to subjective cognitive impairment, mild cognitive impairment, and dementia, but longitudinal studies on gait in cognitively healthy subjects are lacking. Studies on cerebrospinal fluid evidence of Alzheimer’s disease in relation to gait in cognitively healthy subjects are also rare.

2. **Interpretation**: Our findings indicate that gait speed decline is an early event in cognitive decline, and possibly linked to AD pathology.

3. **Future directions**: Gait speed might be used in concert with other modalities for early detection of subjects with increased risk of developing dementia. However, further studies on gait speed in relation to cognitive decline are needed.

2.2 | Gait speed assessment

A physiotherapist performed the examination, which included self-selected (normal) and maximum gait speeds for 30-meter indoor walks with a standing start. At the 2005 and 2009 follow-ups, a 20-meter distance was used for measurement, but with identical protocols. In this study, the 2005 and 2009 measurements have been recalculated by a factor 1.5 to be comparable to the baseline and 2015 measurements.

2.3 | Cognitive assessment

All participants were examined at the Department of Psychiatry Cognition and Old Age Psychiatry, Sahlgrenska University Hospital in Gothenburg. Experienced psychiatric research nurses performed the neuropsychiatric examinations, which comprised ratings of psychiatric symptoms and signs, tests of mental functioning, including assessments of episodic memory (short-term, long-term), aphasia, apraxia, agnosia, executive functioning, and personality changes. Key informant interviews were performed by a psychologist or psychiatric research nurses as described previously. Based on these data, a CDR score was assigned to each participant. CDR score is the most widely used cognitive outcome in clinical AD dementia trials and shows a good correlation to dementia diagnosis. CDR is a rating on a 0-5 point scale, where 0 describes absence of dementia, and each increment on the rating scale indicates more severe symptoms. A rating of 5 signals terminal disease.

2.4 | Apolipoprotein E (APOE) genotyping

The single-nucleotide polymorphisms (SNPs) rs7412 and rs429358 in APOE (gene map locus 19q13.2) were genotyped using KASP PCR SNP genotyping system (LG Genomics, Hoddesdon, Herts, UK). Genotype data for these two SNPs were used to define ε2, ε3, and ε4 alleles. All subjects included for analysis where APOE was used as a confounder in this study were successfully genotyped.

2.5 | Biomarker analysis

Participants were subjected to lumbar punctures in 2009 (n = 30 in the final sample) and CSF was collected in polypropylene tubes, following standard clinical protocols, and immediately transported to the laboratory for centrifugation at 1800 g at 20°C for 10 minutes. The supernatant was gently mixed to avoid possible gradient effects, divided into aliquots in the polypropylene tubes, and stored at −70°C. CSF Aβ1-42 levels were measured using an sandwich enzyme-linked immunosorbent assay (INNOTEST Aβ1-42) specifically constructed for quantitative determination of Aβ1-42 species. Analytic runs had to pass quality control criteria for the calibrators, and internal quality control samples had to be approved, as described in detail elsewhere (PMID: 25155658). Subjects with CSF Aβ1-42 levels ≤530 pg/mL were classified as being Aβ positive in this study.

2.6 | Statistical analysis

Mann-Whitney U tests were used to analyze group differences in gait speed between subject groups based on longitudinal CDR change and Aβ positivity. In this context CDR change was defined as unchanged, minor change (score change = 0.5), or major change (score change ≥ 1) as compared to baseline. Logistic regression was used to analyze the
| TABLE 1 |
|---|---|---|---|---|---|---|---|---|---|
| Follow-up | 2000 | 2005 | 2009 | 2015 |
| | Subjects | Mean (SD) | Median (IQR) | Count | Mean (SD) | Median (IQR) | Count | Mean (SD) | Median (IQR) | Count |
| Age (years) | 287 | 70 (0) | 262 | 70 (70-70) | 160 | 75 (75-75) | 73 | 79 (79-79) | 85 (0) | 85 (85-85) |
| Sex | Female | 164 | 160 | 85 | 42 |
| | Male | 123 | 102 | 75 | 31 |
| Back pain last 3 months | Yes | 114 | 93 |
| No | 168 | 164 |
| Walking aid | None | 280 | 256 |
| Cane | 4 | 6 |
| Walker | 1 | 0 |
| CDR | .0 | 287 | 167 | 79 | 43 |
| | .5 | 0 | 88 | 72 | 21 |
| | 1.0 | 0 | 6 | 5 | 5 |
| | 2.0 | 0 | 1 | 3 | 3 |
| | 3.0 | 0 | 0 | 1 | 0 |
| Max gait (s/30 m) | 16.4 (3.6) | 16 (14 - 18) | 285 | 19.5 (5.1) | 18 (16.5 - 21) | 261 | 21.2 (5.2) | 19.5 (18 - 22.5) | 159 | 22.1 (4.7) | 22 (19-25) | 70 |
| Normal gait (s/30 m) | 23.6 (4.3) | 23 (21 - 25) | 287 | 26.3 (5.4) | 25.5 (22.5 - 27) | 262 | 28.7 (5.4) | 28.5 (25.5 - 31.5) | 160 | 29.2 (6) | 28 (25-33) | 73 |
| CSF Aβ1-42 (ng/L) | 810 (216) | 861 (666 - 961) |

SD, standard deviation; IQR, inter quartile range; CDR, clinical dementia rating; CSF, cerebro spinal fluid; Aβ1-42, Amyloid β1-42.
at baseline (CDR = 0). There were more women than men in the study population at baseline (57%) and at all follow-ups (61% in 2005, 53% in 2009, and 58% in 2015) (Table 1). Participants who dropped out of the study, or for other reasons had no subsequent recording of gait speed, had lower mean gait speeds at baseline (1.6 vs 1.9 m/s maximum speed, $P < .001$ and 1.2 vs 1.3 m/s normal speed, $P < .001$).

3.2 | Gait speed and cognitive decline

The participants were divided into two groups, where the first group comprised subjects who worsened in CDR score at any point during follow-up, and the second group contained subjects who remained at CDR 0 throughout the follow-up period. Maximum (Figure 1A) and normal (Figure 1B) gait speeds for those who worsened in CDR score were significantly lower at most time points (normal 2000: $P = .47$, mean = 23.9 vs 23.0, max 2000 $P = .007$, mean = 16.5 vs 16.1, normal 2005: $P = .033$, mean = 27.1 vs 25.0, max 2005 $P = .003$, mean = 20.0 vs 18.5, normal 2009: $P = .012$, mean = 29.6 vs 26.9, max 2009 $P = .001$, mean = 21.9 vs 19.7, normal 2015: $P = .20$, mean 30.5 vs 26.6, max 2015 $P = .01$, mean = 22.8 vs 20.8). However, gait speeds (maximum and normal) decreased significantly from baseline for all subsequent visits in both the group who worsened in CDR and those who did not ($P < .001$ for all comparisons). Those who remained at CDR = 0 decreased on average 8%, 14%, and 14% in normal gait speed for each subsequent visit as compared to baseline, and 13%, 19%, and 23% in maximum gait speed. Those who worsened in CDR decreased on average 12%, 19%, and 22% in normal gait speed for each subsequent visit as compared to baseline, and 17%, 25%, and 27% in maximum gait speed.

3.3 | Predictive properties of baseline gait speed and gait speed change

Unadjusted gait speeds differed at baseline according to future rate of cognitive decline as measured by CDR, but only significantly for normal gait speed change 2000 to 2005 ($H = 7.2$, $P = .027$) and 2000 to 2009 ($H = 2.4$, $P = .008$) (Figure 2A–C). Unadjusted maximum gait speeds did not differ significantly at baseline in relation to CDR changes at follow-up (Figure 2D–F).

To accommodate for logistic regression the participants were divided into two groups, where the first group comprised subjects who worsened in CDR score at any point during follow-up, and the second group contained subjects who remained at CDR 0 throughout the follow-up period. Logistic regression models, adjusted for sex, age, back pain, and walking aid, showed that maximum gait speed at baseline ($B = 0.087$, $P = .048$) and normal gait speed at baseline ($B = 0.079$, $P = .021$) were associated with CDR change from 2000 to 2005. Normal gait speed, but not maximum gait speed at baseline, was also associated with CDR change from 2000 to 2009 ($B = 0.123$, $P = .006$) as well as 2000 to 2015 ($B = 0.123$, $P = .027$).
FIGURE 2  (A–C) Normal gait speeds at baseline were slower in subjects who subsequently registered a worsened Clinical Dementia Rating (CDR) score at follow-up, but with large overlaps, and only significantly at the 2005 and 2009 follow-up. (D–F) Maximum gait speeds at baseline were slower in subjects who cognitively declined during follow-up, but with large overlaps, and the differences were not statistically significant.
3.4 Gait speed change trajectories and cognitive decline

Participants were sub classified according to what follow-up visit that their CDR score first declined. Local regression trend lines of the gait speed changes in the groups indicate a faster decline in gait speed in patients who worsened in CDR in 2005 versus later in 2009 or 2015 (Figure 3A and B). When tested for differences in gait speed change from baseline to each follow-up in an ANCOVA adjusted for sex, age, back pain, and walking aid, statistically significant differences in normal gait speed change could be detected between non-converters and subjects who first registered an increase in CDR in 2009 at the 2009 follow-up ($P = .040$) and at the 2015 follow-up ($P = .018$). Significant differences in maximum gait speed change could be detected between non-converters and subjects who first registered an increase in CDR in 2009 at the 2009 follow-up ($P = .018$).

No other differences in gait speed change were significant.

3.5 Gait speed and CSF biomarkers

A subset of participants ($n = 30$) had CSF biomarkers measured at the 2009 visit. There were no statistically significant differences in terms of age, gender, CDR scores, or gait speed between participants who were subjected to a CSF biomarker assessment and those who were not. All participants who had their CSF biomarkers measured were sub classified according to exhibiting Aβ$_{1-42}$ concentrations at pathologic levels (Aβ$_{1-42} < 530$ ng/L, $n = 23$) or not ($n = 7$). The Aβ$_{2}$-positive subjects at the 2009 visit had lost significantly more normal gait speed than had the Aβ$_{2}$-negative subjects, both compared to their 2005 visit ($U = 22.5$, $P = .033$) and 2000 visit ($U = 13.0$, $P = .003$). There were no significant differences in changes in maximum gait speed or nominal gait speeds at baseline (2000). There were no significant differences in future change in gait speed measured at the 2015 visit.

Slowing normal gait speed change from 2000 to 2009 ($B = 0.15$, $P = .024$) together with APOE ε4 positivity ($B = 2.75$, $P = .067$) was associated with a higher probability of Aβ$_{2}$ positivity at the 2009 follow-up in the most efficient logistic regression model after backward selection of predictors where sex, age, walking aid, and back pain were excluded from the model by the selection process.

4 DISCUSSION

In this longitudinal study we followed cognition and gait speed of 287 community dwelling 70-year-olds over 15 years and found that slowing gait speed precedes cognitive decline by several years. In this cohort, slower normal gait speed was found to emerge up to 9 years before cognitive symptoms detectable by CDR decline, and slowing gait speed was associated with amyloid positivity at follow-up, suggesting that gait speed might reflect early changes in models of dementia progression.24

Several previous studies have found links between slowing gait speed and cognition, and that gait speed changes precede cognitive decline in the course of preclinical dementia.25–27 The results of this study were in keeping with these findings, as we found that slower gait speed was associated with cognitive decline. Longitudinal studies on gait speed and cognition have indicated that gait speed changes occur as early as 7 to 12 years before dementia development.7,8 This present study had one of the longest follow-ups of studies examining gait in relation to cognition, and could corroborate previous findings of gait changes preceding changes in the CDR score.28 In this cohort, baseline normal and maximum gait speed were associated with cognitive decline 5 years later. In addition, slower normal gait speeds at baseline were also found for those who subsequently increased in CDR at the 2009 and 2015 follow-ups.
Few studies have examined the relationship between CSF amyloid and gait. One study showed an association of gait variability in step length, time and velocity, and CSF amyloid levels. The speed of gait has to our knowledge not been studied in relation to CSF amyloid. In our study, a small subset of patients had CSF $A_β_{1-42}$ levels measured at the 2009 follow-up. We found that normal gait speed slowed faster from baseline until the 2009 follow-up in those who were $A_β$ positive in 2009, suggesting a faster motor function decline in subjects with evidence of cerebral AD pathology. Gait speed decline was also seen when plotting gait speed changes over the follow-up period in relation to time of first detected evidence of cognitive deficiency. Subjects who converted to CDR > 0 at an earlier date declined faster in gait speeds, particularly normal gait speed. This phenomenon of accelerating gait speed decline has also been seen in previous studies.

This study featured the comparison of normal vs maximum gait speeds. The results indicated that normal gait speed was more affected than maximum gait speed in relation to cognitive measures in early cognitive decline. This result is in keeping with the limited literature, where larger effects on normal than on maximum gait speeds have been seen in progression from cognitively healthy to subjective cognitive decline. However, similar effects on both or larger effects on maximum walking speed have been reported at later stages of cognitive decline.

Among the strengths of this study is the long follow-up in the population-based sample, the comprehensive examinations, and the fact that neuropsychiatric examinations were identical at the different examination visits, enabling comparisons of them. However, this study had several limitations. Although response rates were similar between visits, the decreasing number of study participants who had their gait speed tested at each follow-up is a limitation. In addition, the number of participants with CSF $A_β_{1-42}$ was small, and the lack of longitudinal CSF measurements was a limitation. However, performing a lumbar puncture in a population-based cohort of older adults is unique, especially with a long follow-up period.

In conclusion, this study demonstrated that accelerated gait speed decline precedes cognitive decline, and indicated that faster gait speed decline is seen when conversion into detectable cognitive deficiency is imminent. Accelerated decline in gait speed was also associated with pathological CSF $A_β_{42}$ levels, giving further support to the findings. These results strengthen the case for using gait speed in concert with other modalities for early detection of subjects with increased risk of developing dementia.

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