Inflammatory Markers and Gait Speed Decline in Older Adults

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Background. Increased inflammatory activity and gait speed decline are common with aging, but the association between the two is not well established. The objective of this study was to determine the influence of inflammatory markers, interleukin-6 (IL-6), and tumor necrosis factor alpha, on gait speed performance and decline in older adults.

Methods. We conducted cross-sectional and longitudinal analyses of 333 adults aged 70 and older (61% women) with gait and biomarker assessments identified from participants in the Einstein Aging Study, a community-based aging study. Gait velocity measured at baseline and annual follow-up visits (median follow-up 2.3 years) was the main outcome.

Results. At baseline, higher interleukin-6 levels were associated with slower gait velocity (estimate –4.90 cm/s, p = .008). Adjusted for age, gender, education, and medical illnesses, a one-unit increase in baseline log IL-6 levels was associated with a 0.98 cm/s faster gait speed decline per year (p = .002). The results remained significant after adjustments for additional potential confounders such as physical activity levels, body mass index, and medications. Participants in the highest IL-6 quartile had a 1.75 cm/s/year faster decline in gait velocity compared with those in the lowest quartile (p = .002). Tumor necrosis factor alpha was not associated with gait velocity at cross-section or with gait speed decline.

Conclusions. IL-6 levels are associated with gait performance in community residing seniors and predicts risk of gait speed decline in aging.

Key Words: Mobility—Gait—Inflammation—Interleukin-6.

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The public health challenge of mobility limitations and decline will continue to grow in our rapidly aging population (1). Hence, identifying modifiable risk factors for mobility decline in seniors is of major importance. Gait velocity is a good proxy for mobility, and it is recommended as a simple screen of functional status in seniors (2,3). Moreover, slow gait predicts major adverse outcomes such as falls, dementia, and death in older individuals (1,4–6).

Aging is associated with increased inflammatory activity including proinflammatory and anti-inflammatory cytokines (7–11). Because of the link between cytokines and several disabling conditions (7), it has been hypothesized that an elevated inflammatory response could be an important pathway for age-related decline in physical function and mobility (12). Higher serum levels of cytokines such as interleukin-6 (IL-6) and tumor necrosis factor alpha (TNFα) have been linked to worse functional and mobility status in cross-sectional studies (12–15). Cross-sectional studies do not disentangle cause and effect from simple association (16). Longitudinal cohort studies may better ascertain the link between inflammation and mobility by establishing that the cause preceded the outcome, which can be then tested in clinical trials (16). However, there is a paucity of prospective studies that have examined the role of inflammatory cytokines in age-related gait speed decline. The few previous studies have had conflicting results with significant association of inflammatory biomarkers with risk of mobility and gait speed decline is some (17,18) but not all studies (19). However, these previous studies were limited to high functioning older adults (19), disabled women (17), used self-reports to define mobility outcomes (18), or had restricted follow-up (19). Hence, the generalizability of the findings of these previous inflammatory biomarker studies to gait speed decline in the community residing elderly population is limited.

We conducted a prospective cohort study to determine the association of inflammatory markers (IL-6 and TNFα) with gait speed in community residing older adults aged...
70 years. We also examined annual rates of gait speed decline as a function of inflammatory marker status at baseline. Establishing the role of inflammation in gait and mobility decline may provide new insights into early biological stages of disablement, improve current risk assessment procedures, and facilitate development of novel preventive strategies for loss of mobility in seniors.

METHODS

Study Population

We conducted a prospective cohort study based at the Einstein Aging Study (EAS) (1,20). The primary aim of the EAS is to identify risk factors for cognitive decline. Study design and methods have been previously reported (4). In brief, potential participants (aged 70 years and older) identified from population lists of Bronx County were contacted by letter explaining the purpose and nature of the study and then by telephone. The telephone interview included verbal consent, medical history questionnaire, and cognitive screening tests (21). Exclusion criteria included severe auditory–visual loss, bed bound due to illness, and institutionalization. Following the interview, an age-stratified sample of participants who matched on a computerized randomization procedure was invited for further evaluation at our research center.

Informed consent was obtained at enrollment according to protocols approved by the local institutional review board.

This mobility substudy began on February 2002 when we started systematically ascertaining gait and mobility in our cohort (4) and ended in September 2010 when we closed enrollment for this investigation. Of the 1,120 Einstein Aging study participants evaluated during this 103-month period, 475 participants received blood tests for inflammatory markers and 340 of these participants also received gait assessments at the time of the blood tests. We excluded 7 participants with prevalent dementia leaving 333 nondemented participants with both biomarker and gait data. Participants who were included were younger ($p < .05$) but were similar in terms of sex and educational status compared with the excluded mobility substudy participants without both gait and biomarker data. Participants returned annually for clinical, neuropsychological, and mobility assessments.

Gait

Gait speed was measured using a computerized walkway with embedded pressure sensors (GAITRite; CIR systems, Havertown, PA). The GAITRite system is widely used in clinical and research settings and has excellent validity and test–retest reliability (4,5,22). Participants are asked to walk on the walkway at their usual pace in a quiet well-lit room wearing comfortable footwear and without any attached monitors. Participants walked for two trials on a walkway with 15 feet of recording surface till July 2008. Following which, assessments were done for one trial on a walkway with 20 feet of recording surface. The correlation for gait speed measured on the two walkways in 20 of our participants was excellent ($r = .94$). The reliability between two consecutive walking trials on the same walkway was also excellent ($r = .96$). We have ascertained excellent intraclass correlation coefficient (.96) for gait speed in between two trials completed 2–3 hours apart on the same walkway (23). Start and stop points were marked by white lines on the floor and included 3 feet (4 feet for the longer walkway) from the edge of the recording surface to account for initial acceleration and terminal deceleration.

Inflammatory Markers

Serum levels of the inflammatory biomarkers, IL-6 and TNFα, were determined from frozen fasting blood samples at the University of Vermont at Burlington. IL-6 is measured in serum by ultra-sensitive enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, MN). The lower detection limit is less than 0.15 pg/mL. Interassay coefficient of variation is 15%. Circulating IL-6 levels obtained from one time point have been shown to be reproducible and representative of extended time periods (24,25). TNFα is measured in serum by Luminex technology multiplex ELISA using the Human Serum Adipokine Panel B LINCOplex Kit (Linco Research, Inc., St. Charles, MO). The minimum detectable level of TNFα is 0.14 pg/mL. Interassay coefficient of variation is less than 21%.

Covariates

Presence or absence of vascular diseases (diabetes, heart failure, hypertension, angina, myocardial infarction, or strokes) as well as other chronic illnesses (depression, Parkinson’s disease, chronic obstructive lung disease, or severe arthritis) reported by participants at entry into this study was used to calculate a summary illness index (range 0–10) as previously described (21). Participants were asked about prescription and nonprescription medications use at study visits and requested to bring in medication lists, prescriptions, or medicine bottles for verification at study visits. We consulted medical records and contacted family members when available or physicians to verify or obtain further details of illnesses and medications (21). Participants self-reported level of physical activity. Research assistants measured height (cm) and weight (kg) at study visits, and body mass index (BMI) was calculated as previously described (20).

Data Analysis

The distribution of the biomarker levels was skewed to the right and was log-transformed for all analyses. To determine
the longitudinal association of IL-6 and TNFα (per unit increase in log levels) with risk of developing mobility decline (gait speed), linear mixed-effects models (26) controlled for age, sex, education, and medical illness were applied to the 333 eligible participants (model 1). Associations are reported as parameter estimates with 95% CI. The linear mixed effects model can accommodate unbalanced data resulting from missing data points, unequal numbers of follow-up visits, and unequal intervals between visits (27). A random intercept was included in the model to allow entry point to vary across individuals. “Time” represents average rate of change in gait speed over time. An interaction between individual biomarkers and ‘time’ was included to model the effect of baseline IL-6 and TNFα on annual rate of change in gait speed. In additional analyses (model 2), we added the following covariates to account for possible confounding: BMI, low physical activity, and medications that might influence inflammatory marker levels (statins, prednisone, nonsteroidal anti-inflammatory drugs, or estrogens).

We also compared participants whose biomarker levels were in the highest quartile (worst) versus those in the lowest quartile using the linear mixed models described earlier (26). The transformed IL-6 and TNFα levels were divided into quartiles for this secondary analysis. The corresponding nontransformed quartile ranges for IL-6 were less than or equal to 1.99, 1.99 to 3.01, 3.02 to 4.60, and more than 4.60 pg/ml. The quartiles for TNFα were less than or equal to 2.76, 2.77 to 4.44, 4.45 to 6.20, and more than 6.20 pg/ml. Regression diagnostics for all models were examined analytically and graphically and were adequately met.

**Results**

Table 1 shows the characteristics of the cohort at entry into this mobility substudy as well comparisons by IL-6 and TNFα quartiles (highest vs lowest). The 333 eligible participants included 129 men (39%) and 204 women (61%). Mean age at entry was 80.3 ± 5.5 years. The median follow-up time was 2.3 years (827 person-years follow-up). The mean number of annual follow-up visits was 2.2 (range 0–7). The mean levels of IL-6 and TNFα in the study sample at baseline were 3.8 ± 2.9 pg/ml and 5.3 ± 6.1 pg/ml, respectively (cut scores for quartiles presented in the Methods section). The annual rate of decline on gait speed in the sample was 2.25 cm/s/year.

Participants in the highest IL-6 quartile walked slower than the lowest quartile at baseline (Table 1). Participants in the highest IL-6 quartile had a significantly higher prevalence of heart failure and hypertension and a lower prevalence of medications that affect inflammatory markers than those in the lowest quartile. Table 2 shows that participants in the highest TNFα quartile were older with a higher prevalence of strokes but did not show significant group differences in other variables.

**Interleukin-6**

Adjusted for age, gender, education, and medical illness, log IL-6 levels were associated with gait speed at baseline (estimate −4.90 cm/s, 95% CI −8.49 to −1.31, p = .008).

Adjusted for age, gender, education, and medical illness (model 1), each one-unit increase in log IL-6 levels was associated with a 0.98 cm/s/year increased rate of decline in gait speed (114% increased rate of gait speed decline). Table 2 shows that the association remained significant after
adjustments for additional covariates in model 2; each one-unit increase in log IL-6 levels was associated with a 0.77 cm/s/year increased rate of decline in gait speed (81% increased rate of gait speed decline). In analysis restricting follow-up to 2 years, the association of baseline log IL-6 with gait speed decline was not significant (−0.39 cm/s, 95% CI −2.21 to 1.42, \( p = .671 \)).

Figure 1 shows “spaghetti plots” of gait speed over study follow-up in participants whose IL-6 values were in the highest (worst) and lowest quartiles. There is a downward trend over time, with steeper slopes seen in participants in the highest IL-6 quartile. Superimposed on these plots are red lines showing fitted average gait speed as a function of time.

Participants in the highest IL-6 quartile had slower gait speed compared with the remaining participants (estimate −6.20 cm/s, \( p = .023 \)) and to those in the lowest IL-6 quartile (difference −11.91 cm/s, \( p < .001 \)). In model 1, participants in the highest IL-6 quartile had faster decline in gait speed compared with those in the lowest quartile (1.75 cm/s/year faster, \( p = .002 \)) as shown on the right side of Table 2. The strength of the association was reduced after additional adjustments in model 2 (see Table 2). Compared with participants in the lowest quartile, those in the third highest IL-6 quartile (−1.43 cm/s/year, 95% CI −2.72 to −0.14, \( p = .030 \)) but not in the second highest quartile (−0.76 cm/s/year, 95% CI −1.96 to 0.44, \( p = .215 \)) had faster gait speed decline in the fully adjusted model 2. The test of linear trend for the IL-6 quartiles was significant (\( p = .041 \)).

Tumor Necrosis Factor Alpha

Table 3 shows that the log-transformed serum TNFα levels were not associated with gait speed at baseline (estimate

<table>
<thead>
<tr>
<th></th>
<th>Log IL-6 Levels</th>
<th>Highest vs Lowest Quartile of IL-6</th>
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<tbody>
<tr>
<td></td>
<td>Estimate (95% CI)</td>
<td>( p ) Value</td>
</tr>
<tr>
<td>Model 1 IL-6</td>
<td>−4.90 (−8.49 to −1.31)</td>
<td>.008</td>
</tr>
<tr>
<td>Time (1 year)</td>
<td>−0.86 (−1.97 to 0.25)</td>
<td>.127</td>
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<tr>
<td>IL-6 × time</td>
<td>−0.98 (−1.60 to −0.36)</td>
<td>.002</td>
</tr>
<tr>
<td>Model 2 IL-6</td>
<td>−3.41 (−7.00 to 0.18)</td>
<td>.062</td>
</tr>
<tr>
<td>Time (1 year)</td>
<td>−0.95 (−2.13 to 0.23)</td>
<td>.113</td>
</tr>
<tr>
<td>IL-6 × time</td>
<td>−0.77 (−1.44 to −0.11)</td>
<td>.023</td>
</tr>
</tbody>
</table>

Notes: IL-6 = interleukin-6. Model 1 is adjusted for baseline age, sex, and education, medical illness index. Model 2 is in addition adjusted for body mass index, self-reported low physical activity, and medications that might influence inflammation. The term “IL-6” is the estimate of the association between IL-6 and gait speed at baseline. The term “Time” represents the rate of change in gait speed (cm/s) per year. The estimates for the interaction term from the linear mixed model represents the longitudinal effect of log IL-6 (both as a continuous variable as well as comparing the highest vs lowest quartile) on the annual rate of decline on gait speed.

Figure 1. Relationship of IL-6 to annual decline in gait velocity. The black lines present gait speed measured in individual participants in the high (worst values) and low IL-6 quartiles at baseline and annual follow-up visits. The red lines show the fitted average gait speed as a function of time.
Table 3. TNFα and Gait Speed Decline

<table>
<thead>
<tr>
<th></th>
<th>Log TNFα Levels</th>
<th>Highest vs Lowest Quartile of TNFα</th>
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<tbody>
<tr>
<td></td>
<td>Estimate (95% CI)</td>
<td>p Value</td>
</tr>
<tr>
<td>Model 1</td>
<td>TNFα</td>
<td>1.63 (−1.88 to 5.15)</td>
</tr>
<tr>
<td></td>
<td>Time (1 year)</td>
<td>−0.69 (−1.81 to 0.43)</td>
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<tr>
<td></td>
<td>TNFα × time</td>
<td>−0.03 (−0.59 to 0.53)</td>
</tr>
<tr>
<td>Model 2</td>
<td>TNFα</td>
<td>0.85 (−2.84 to 4.53)</td>
</tr>
<tr>
<td></td>
<td>Time (1 year)</td>
<td>−0.95 (−2.15 to 0.25)</td>
</tr>
<tr>
<td></td>
<td>TNFα × time</td>
<td>−0.39 (−0.47 to 0.29)</td>
</tr>
</tbody>
</table>

Notes: TNFα = tumor necrosis factor alpha. Model 1 is adjusted for baseline age, sex, and education, medical illness index. Model 2 is in addition adjusted for body mass index, self-reported low physical activity, and medications that might influence inflammation. The term “TNFα” is the estimate of the association between TNFα and gait speed at baseline. The term “Time” represents the rate of change in gait speed (cm/s) per year. The interaction term represents the longitudinal effect of log TNFα (both as a continuous variable as well as comparing the highest vs lowest quartile) on the annual rate of decline on gait speed.

In this cohort of community-dwelling older adults, elevated serum levels of IL-6 were associated with worse gait performance at cross-section. Furthermore, serum levels of IL-6 at baseline predicted future risk of gait speed decline; each one-unit increase in log IL-6 (which corresponds to a 1.7 times increase in untransformed IL-6 levels) was associated with a 0.98 cm/s/year increased rate of decline in gait speed. This effect corresponds to a 114% increased rate of gait speed decline per year. The overall annual rate of gait speed decline in this cohort was 2.25 cm/s. The effect of log IL-6 on gait speed decline was attenuated but remained significant even after adjustments for multiple potential confounders. Participant in the highest IL-6 quartile had 1.75 cm/s/year faster decline in gait speed compared with the participants with IL-6 levels in the lowest quartile.

Our findings are supported by some but not all previous studies. High IL-6 levels were associated with slow gait at baseline and faster decline in gait speed over follow-up in women participating in the Women’s Health and Aging Study (17). An interesting synergy with insulin-like growth factor 1 was observed in this cohort; women with high IL-6 and low insulin-like growth factor 1 levels had a higher risk of developing walking limitations and mobility disability compared with women with low IL-6 and high insulin-like growth factor 1 levels (28). Elevated levels of IL-6 and TNFα predicted incident mobility loss, defined as either self-reported inability to walk one-quarter of a mile or climb 10 stairs, in adults aged 70–79 years participating in the Health, Aging and Body Composition (ABC) Study. On the other hand, baseline serum IL-6 levels did not predict decline in gait speed in adults aged 70–79 years in the MacArthur studies of successful aging (19). However, this sample was comprised of seniors with high cognitive and physical function and the prospective analysis included only the subgroup of participants with 7 years of follow-up completed (19). The investigators speculated that the narrow range of variability in this select high-functioning cohort may have obscured the ability to detect associations between inflammation and performance (19). Unlike these previous studies, our sample included both sexes, had wider age representation, was not disabled at baseline, did not restrict follow-up, and used quantitative measures to monitor decline in gait speed improving the reliability and generalizability of our findings. Our secondary analysis suggests that a one-point evaluation of IL-6 levels provides long-term but not short-term prediction of gait speed decline, an issue that was not examined in previous studies. A caveat is that this secondary analysis may lack power to detect smaller magnitude effects of IL-6 on gait speed decline.

For serum levels of TNFα, we did not find an association with gait speed either at cross-section or longitudinally. TNFα levels were reported to be associated with loss of grip strength but not with decline in lower limb strength in the Health ABC study after accounting for weight changes over follow-up (29). TNFα is a less stable biomarker as suggested by the high interassay coefficient of variation. Moreover, tissue expression of TNFα may not be matched by increased serum levels (30). Although biological interactions between IL-6 and TNFα are well known (31), we found only a weak correlation between IL-6 and TNFα levels (Pearson r = .19) in our participants, as reported previously (32). These factors in part may explain the divergent results in our cohort.

IL-6 is a circulating cytokine that is secreted from a number of different cells including activated macrophages, lymphocytes, and adipose tissue (33,34). It has been proposed that IL-6 is the main circulating candidate in linking systemic inflammation with local pathology although an important role for other cytokines is not excluded (33). IL-6 is unusual among cytokines, in that most of its biological effects is via paracrine and autocrine mechanisms (11,33). It is unclear whether elevated levels of IL-6 are a marker of poor health in aging without independent pathogenic effects or whether it has a direct causal role in age-related
mobility decline (28,35,36). There are multiple potential mechanisms that link IL-6 with gait speed decline. Inflammatory cytokines have a catabolic effect on muscle (14,32,35,37). Higher plasma concentrations of IL-6 and TNFα were associated with lower muscle mass and weaker grip at cross-section in well-functioning older men and women (32). IL-6 has been implicated in the pathogenesis of musculoskeletal disorders including osteoporosis (38) and arthritis (39,40). A recent study showed that old adults with low IL-6 levels had a sevenfold increased chance of being free of osteoarthritis (39). Interestingly, TNFα was not associated with osteoarthritis in that study (39). Inflammatory biomarkers also are reported to have effects on the aging brain (41), which might influence both cognitive and motor functions.

Vascular disease increases risk of gait speed decline in aging (42). Elevated IL-6 levels are associated with increased insulin resistance and endothelial dysfunction, which in turn increase the risk of cardiovascular diseases (43). As expected, a higher prevalence of vascular diseases was seen in our participants with the highest IL-6 levels; however, our results were significant even after adjusting for vascular diseases and medications. The association of IL-6 with walking speed has been reported to be independent of disease status with consistent relationships seen in groups of individuals with chronic obstructive lung disease, cardiac failure, high cardiovascular risk, or self-reported disability (44). Direct measures of vascular pathology were lacking in our cohort and should be explored in future studies. The findings from our and other studies suggest that IL-6 exerts its effect on gait speed decline via multiple mechanisms including but not restricted to vascular pathways. In support, IL-6 levels have been reported to predict functional decline in nondiabetic and diabetic seniors alike in the Health ABC study although the baseline values of IL-6 were higher in diabetics than non-diabetics (45).

There are several limitations to be noted. This study was necessarily restricted to participants in our cohort who received gait and biomarker assessments. Hence, participants enrolled prior to instituting both gait and biomarker assessments in our study had to be excluded. Because our cohort was recruited from the community and we excluded participants with dementia or inability to ambulate at baseline, caution should be applied when attempting to generalize our findings to clinic or nursing home based samples. However, the observed associations may be stronger in less healthy populations. Medical illnesses were based on self-report, so we may have underestimated illness effects. We had no direct measurements of muscle strength that has been suggested to mediate the association of IL-6 with gait speed decline (17). Our quantitative gait assessment yields multiple gait variables (5), but the value of gait variables other than speed to track mobility decline have not been well established. The inflammatory marker levels were specific to our cohort, but ranges and cutscores provided should facilitate future comparisons. Although we controlled for multiple confounders, given the observational nature of this study, we cannot exclude the possibility of unmeasured or residual confounding. For instance, we did not have reliable information on smoking and alcohol consumption, which may influence inflammation levels. The high interassay coefficient of variation for our biomarker assays is a limitation. Although individuals with longer follow-up might influence findings, the results were almost identical when the analyses were repeated excluding outliers with follow-up of 7 years or more (data not shown). The observational nature of this study also does not establish causality, which should be explored in future clinical trials. Given the potential role of inflammation in the pathogenesis of multiple age-related diseases, many interventions are being evaluated for their ability to affect inflammatory marker levels (41,46). We suggest including mobility measures in these intervention trials to help better define the role of IL-6 in mobility disability.

In conclusion, these prospective data indicate that IL-6 strongly predicts risk of gait speed decline in community residing older adults. If our findings are corroborated by other studies, measurement of IL-6 levels could be considered to help improve current mobility and disability risk assessments in older adults as well as develop new disability prevention strategies.

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CONFLICT OF INTEREST
No conflicts of interest to declare.

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