Low Plasma Carotenoids and Skeletal Muscle Strength Decline Over 6 Years

Fulvio Lauretani,1,6 Richard D. Semba,2 Stefania Bandinelli,3 Margaret Dayhoff-Brannigan,2 Vittoria Giacomini,1 Anna Maria Corsi,1,4 Jack M. Guralnik,5 and Luigi Ferrucci6

1Tuscany Regional Health Agency, Florence, Italy.
2Johns Hopkins School of Medicine, Baltimore, Maryland.
3Azienda Sanitaria Firenze, Florence, Italy.
4Department of Medical and Surgical Critical Care, Thrombosis Centre, University of Florence, Italy.
5Laboratory of Epidemiology, Demography and Biometry, National Institute on Aging, Bethesda, Maryland.
6Longitudinal Studies Section, Clinical Research Branch, National Institute on Aging, Baltimore, Maryland.

Background. Higher intake of fruits and vegetables appears to protect against inflammation, poor physical performance, and disability, but its relationship with muscle strength is unclear. We examined the association between total plasma carotenoids, an indicator of fruit and vegetable intake, and changes in muscle strength over a 6-year follow-up in the participants aged 65 years and older in the InCHIANTI study, a population-based study in Tuscany, Italy.

Methods. Plasma carotenoids were measured at enrollment (1998–2000). Hip, knee, and grip strength were measured at enrollment and 6 years later (2004–2006) in 628 of the 948 participants evaluated at baseline. Poor muscle strength was defined as the lowest sex-specific quartile of hip, knee, and grip strength at enrollment. The main outcome was poor muscle strength at the 6-year follow-up visit among those participants originally in the upper three quartiles of strength at enrollment.

Results. Overall, 24.9% (110/441), 25.0% (111/444), and 24.9% (118/474) participants developed poor hip, knee, and grip strength, respectively. After adjusting for potential confounders, participants in the lowest versus the highest quartile of total plasma carotenoids at enrollment were at higher risk of developing poor hip (odds ratio [OR] = 3.01, 95% CI, 1.43–6.31, p = .004), knee (OR = 2.89, 95% CI, 1.38–6.02, p = .005), and grip (OR = 1.88, 95% CI, 0.93–3.56, p = .07) muscle strength at the 6-year follow-up visit.

Conclusion. These findings suggest that older community-dwelling adults with lower plasma carotenoids levels, a marker of poor fruit and vegetable intake, are at a higher risk of decline in skeletal muscle strength over time.

Key Words: Carotenoid—Fruit—Vegetable—Sarcopenia—inCHIANTI Study.

SARCOPENIA, a condition characterized by loss of skeletal muscle mass and strength with aging, is considered a key factor in the disablement process (1). It is widely recognized that age-related sarcopenia is caused by a combination of intrinsic factors involving changes at the energetic molecular and cellular levels and extrinsic or environmental factors such as nutrition and exercise (2,3). Several lines of research suggest that excessive oxidative stress caused by the accumulation of reactive oxygen species (ROS) is a causal factor in sarcopenia. ROS levels increase when the respiratory chain is malfunctioning and/or antioxidant cellular defense mechanisms are insufficient. Oxidative stress can damage macromolecules such as DNA, proteins, and lipids, thereby causing significant damage to cells and tissues (4,5).

Recent studies suggest that a higher intake of fruits and vegetables, rich sources of antioxidants, including carotenoids, vitamin C, flavonoids, and other polyphenols, is correlated with muscle strength, physical performance, functional limitation, and disability (6–8). In the Women’s Health and Aging Study, low serum carotenoids was associated with poor muscle strength among older, moderately to severely disabled women living in the community (6). Low dietary β-carotene intake was associated with impaired lower extremity performance in older community-dwelling adults in Italy (7). Among older adults in the Atherosclerosis Risk in Communities study, fruit and vegetable intake was inversely correlated with functional limitations and disability (8). Serum carotenoids are considered the most valid indicator of fruit and vegetable intake (9) and, thus, can be considered biomarkers for fruit and vegetable consumption.

Most studies looking at carotenoid intake or circulating levels and their relationship with physical function have been cross-sectional. Thus, it is not known whether carotenoid deficiency is a significant predictor of accelerated functional loss or simply reflects a global deterioration of functional status, with little or no effect on the risk of losing physical function.

To address the hypothesis that low serum carotenoids may predict a greater decline in skeletal muscle strength, we examined the relationship between plasma total carotenoids at enrollment and the decline in hip, knee, and grip muscle strength over a 6-year interval among participants in the InCHIANTI study, a population-based study of older adult living in the Chianti region of Tuscany, Italy.
Participants and Methods

The study participants consisted of men and women, 65 years old or older, who participated in the Invecchiare in Chianti, “Aging in the Chianti Area” (InCHIANTI) study, conducted in two small towns in Tuscany, Italy (www.inchantistudy.net). The rationale, design, and data collection have been described elsewhere, and the main outcome of this longitudinal study is mobility disability (10). Briefly, in August 1998, 1270 people 65 years old or older were randomly selected from the population registry of Greve in Chianti (population 11,709) and Bagno a Ripoli (population 4704). Of 1256 eligible persons, 1155 (92.0%) agreed to participate. Of the 1155 participants, 1055 (91.3%) participated in the blood drawing. Participants received an extensive description of the study and participated after written, informed consent. The participants were seen again for a 3-year follow-up visit (2001–2003) and a 6-year follow-up visit (2004–2006), at which times they underwent a repeat phlebotomy and laboratory testing and assessment of physical performance. The study protocol complied with the Declaration of Helsinki and was approved by the Italian National Institute of Research and Care on Aging Ethical Committee.

Demographic information and information on smoking and medication use were collected using standardized questionnaires. Average daily intakes of energy (kcal), vegetables, and fruits were estimated using the European Prospective Investigation into Cancer and Nutrition food frequency questionnaire which has been validated for use in the older population (11). All participants were examined by trained geriatricians, and diseases were ascertained according to standard, pre-established criteria and algorithms based on those used in the Women’s Health and Aging Study for coronary heart disease, diabetes mellitus, chronic obstructive pulmonary disease, osteoarthritis, and cancer (12). Weight was measured using a high-precision mechanical scale. Standing height was measured to the nearest 0.1 cm. Body mass index (BMI) was calculated as weight/height² (kg/m²). Waist to hip ratio (WHR) was calculated as waist circumference (cm) divided by the hip circumference (cm). Mini-Mental Status Examination (MMSE) was administered at enrollment (13). The level of physical activity in the year prior to the interview was classified on an ordinal scale based on responses to a modified standard questionnaire (10) into: (i) hardly any physical activity; (ii) mostly sitting (occasionally walks, easy gardening); (iii) light exercise (no sweat) 2–4 h/wk; (iv) moderate exercise (sweat) 1–2 h/wk; or (vi) intense physical activity (at the limits) >3 h/wk. For analytical purposes, we grouped the participants as: (i–iii) inactive or having light physical activity; (iv and v) having moderate physical activity; or (vi) having intense physical activity. The score of the Short Physical Performance Battery (SPPB) was derived from performance on three objective tests of physical function: 4-meter walking speed, repeated chair rises, and standing balance in progressively more challenging conditions.
positions. Previous studies have demonstrated that older, nondisabled persons with low SPPB score are at high risk of developing disability (14). Calf cross-sectional muscle area (CSMA) (1) and calf muscle density (15) were evaluated from a transverse scan performed at 66% of the tibia length from the distal tip of the tibia by using a recent pQCT generation device (XCT 2000; Stratec, Pforzheim, Germany).

In this study, the process that leads to sarcopenia was operationalized as decline of muscle strength. Low muscle strength appears to be more important than low muscle mass as predictor of disability and mortality (1,16). Therefore, in the analysis presented here we focused on the effect of baseline carotenoid levels on change over time in three different measures of muscle strength.

At enrollment and at the 6-year follow-up visit, isometric muscle strength was assessed on eight muscle groups of the lower extremity by using a handheld dynamometer and a standard protocol (17). All measures of lower extremity muscle strength were highly correlated (Pearson’s correlation coefficients ranging from 0.87 to 0.92). Therefore, only hip flexion and knee extension strength were considered in the analysis to indicate lower extremity muscle strength. Measures of upper extremity muscle strength available in the InCHIANTI study were isometric shoulder adduction and handgrip. Between them, we selected the handgrip for the present analysis because the assessment of handgrip is easy, reliable, and has been used by a larger number of studies (1,18). There is strong evidence in the literature that handgrip is a strong predictor of disability and mortality (18,19). We included both measures of lower and upper extremity muscle strength because previous studies suggested that the rate of age-associated decline in muscle strength is quite different in these two anatomical regions (1). In fact, the correlation between handgrip and isometric strength of the lower extremity muscle groups was only moderately high, ranging from 0.70 to 0.72. Some participants were unable to come to the testing center and were evaluated only for grip strength during their home visit.

Blood samples were collected in the morning after a 12-hour fast. Aliquots of serum and plasma were immediately obtained and stored at −80°C. Aliquots of plasma were shipped on dry ice to Dr. Semba’s laboratory for measurements of plasma carotenoids. Carotenoids were measured using high performance liquid chromatography (HPLC) (20). Total carotenoids were calculated as the sum of α-carotene, β-carotene, β-cryptoxanthin, lutein/zeaxanthin, and lycopene in micromoles per liter. Within-run and between-run coefficients of variation, respectively, were 7.3% and 9.6% for α-carotene, 4.5% and 5.4% for β-carotene, 2.7% and 3.5% for β-cryptoxanthin, 2.6% and 7.1% for lutein, 6.2% and 6.8% for zeaxanthin, and 7.5% and 7.8% for lycopene.

Variables are reported as means (standard deviations [SD]) for normally distributed parameters or as percentages. The present analysis was limited to participants who were seen at enrollment and 6-year follow-up visits. Quartiles of total plasma carotenoids at enrollment were defined at the following cutoffs: <1.37, 1.37–1.74, 1.75–2.16, and >2.16 μmol/L. Poor hip, grip, and knee strength were defined by the lowest sex-specific quartile of hip, knee, and grip

![Figure 1. Percentage of participants who fell in a lower quartile of hip (a), knee (b), and grip (c) muscle strength from baseline to 6-year follow-up, according to baseline strength and carotenoid level quartile.](https://academic.oup.com/biomedgerontology/article-abstract/63/4/376/625627)
strength at enrollment using the following cutoff values: 13.0, 10.45, and 16.0 kg for women, and 20.5, 16.45, and 28.0 kg for men. The longitudinal analyses included participants who were in the upper three quartiles of hip, knee, and grip strength, for each analysis. The outcome measure was a decrease in hip ($n = 441$), knee ($n = 444$), and grip ($n = 474$) strength below the cutoff for the lowest sex-specific quartile of baseline strength by the 6-year follow-up visit.

Means were compared using $t$ tests, and percentages were compared using chi-square tests. Logistic regression models were used to examine relationships between total plasma carotenoids and other risk factors and the development of poor hip, grip, and knee strength at the 6-year follow-up visit. All analyses were performed using SAS (v. 8.2; SAS Institute, Inc., Cary, NC) with a statistical significance level set at $p < .05$.

**Results**

Of the 1155 participants $\geq$65 years seen at enrollment, 1055 (91.3%) participated in the blood drawing. There were 948 (82.1%) participants at enrollment that had both plasma carotenoids and at least one of the three measures of strength (hip, knee, and/or grip strength) available for this analysis. Individuals who did not participate in the blood drawing were generally older and had greater comorbidity than did participants in the blood drawing, as reported elsewhere (21). The characteristics of the study population at enrollment are shown in Table 1.

There were 628 participants who had measurements of muscle strength conducted at the 6-year follow-up visit. Of 328 people who were not seen at the 6-year follow-up visit, 179 had died, 122 refused to participate, and 14 moved out of the study area. We found no significant difference of plasma carotenoids levels between participants evaluated versus those not evaluated at the 6-year year follow-up study (carotenoids mean levels: 1.80 vs 1.84 $\mu$mol/L, $p = .23$, respectively).

After including only participants who at baseline were in the upper three quartiles of hip, knee, and grip strength, 24.9% (110/441) developed poor hip strength, 25.0% (111/444) developed poor knee strength, and 24.9% (118/474) developed poor grip strength. Participants who had died or refused to participate in the 6-year follow-up visit had lower baseline plasma carotenoids compared to those considered in this study (1.75 $\pm$ 0.65 vs 1.87 $\pm$ 0.68, respectively; $p = .034$).

General characteristics of the population at enrollment and of those evaluated at 6-year follow-up are shown in Table 1. Participants evaluated after 6-year follow-up had a mean age of 73.0 and an average BMI of 27.6 Kg/m$^2$; 54.8% were women. Between enrollment and the 6-year follow-up visit, the overall mean declines ($SD$) in hip strength, knee strength, and grip strength were $-2.28$ (5.24) kg ($p < .0001$), $-0.82$ (5.60) kg ($p < .0001$), and $-1.44$ kg ($p < .0001$), respectively.

Figure 1 shows percentages of participants whose strength declined by at least one quartile over the follow-up, according to baseline muscle strength and carotenoid quartiles. Results are strikingly consistent for the three measures of strength. Regardless of the initial quartile of strength, lower carotenoid levels were associated with progressively higher rates of strength decline from baseline to 6-year follow-up. The average size of decline in hip, knee, and grip strength
by quartile of total plasma carotenoids at enrollment, adjusting for age, sex, and strength at enrollment, are shown in Figure 2. Participants in the lowest quartile of total plasma carotenoids showed the largest declines in hip, knee, and grip strength, whereas those in the highest quartile showed the smallest decline in the respective strength measurements (tests for linear trend, \( p = .0007 \) for hip strength, \( p = .0006 \) for knee strength, and \( p = .04 \) for grip strength).

The univariate relationships between plasma carotenoids and other risk factors at enrollment with the development of poor hip, knee, and grip strength at the 6-year follow-up (defined as a decline in strength below the thresholds that define the lowest baseline quartile) are shown in Table 2. Age, education, BMI, vegetable intake, and calf muscle density were significantly associated with the development of poor hip, knee, and grip strength at the 6-year follow-up. Fruit intake was significantly associated with a higher risk of developing poor hip, knee, and grip strength at the 6-year follow-up. Coronary artery disease, congestive heart failure, peripheral artery disease, and diabetes mellitus were not significantly related to the risk of developing poor strength in any of the three measures.

Multivariate logistic regression models testing the effect of serum carotenoids on the risk of developing poor hip, knee, and grip strength are shown in Table 3. After adjusting for age and sex (model 1), participants in the lowest quartile of total plasma carotenoids at enrollment were at higher risk of developing poor hip strength (odds ratio [OR] = 2.19, 95% confidence interval [CI], 1.34–3.42, \( p = .02 \)), poor knee strength (OR = 1.84, 95% CI, 1.00–3.38, \( p = .051 \)), and poor grip strength (OR = 2.01, 95% CI, 1.06–3.80, \( p = .03 \)) compared to participants in the highest quartile. After adjusting for age, sex, education, BMI, WHR, calf muscle density, CSMA, current smoking, total energy intake, and physical activity (model 2), participants in the lowest quartile of total plasma carotenoids were at higher risk of developing poor hip strength (OR = 3.01, 95% CI, 1.44–6.31, \( p = .003 \)), knee strength (OR = 2.94, 95% CI, 1.41–6.12, \( p = .004 \)), and grip strength (OR = 1.87, 95% CI, 0.97–3.63, \( p = .07 \)) compared to participants in the highest quartile. We also examined additional multivariate models that also included depression and chronic obstructive pulmonary disease in addition to all the other covariates included in model 2. In these additional models, participants in the lowest quartile of total plasma carotenoids were at higher risk of developing poor hip strength (OR = 3.01, 95% CI, 1.43–6.31, \( p = .004 \)), knee strength (OR = 2.89, 95% CI, 1.38–6.02, \( p = .005 \)), and grip strength (OR = 1.88, 95% CI, 0.97–3.64, \( p = .03 \)).

### Table 2. Univariate Relationship Between Baseline Carotenoids and Other Risk Factors and the Development of Poor Muscle Strength at the 6-Year Follow-Up

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Poor Hip Strength*</th>
<th>Poor Knee Strength*</th>
<th>Poor Grip Strength*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
<td>( p )</td>
</tr>
<tr>
<td>Age, y</td>
<td>1.13</td>
<td>1.08–1.18</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Sex, % female</td>
<td>0.91</td>
<td>0.60–1.40</td>
<td>.67</td>
</tr>
<tr>
<td>Education, y</td>
<td>0.92</td>
<td>0.83–0.98</td>
<td>.02</td>
</tr>
<tr>
<td>Current smokers, %</td>
<td>1.10</td>
<td>0.61–1.91</td>
<td>.76</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>0.93</td>
<td>0.87–0.98</td>
<td>.01</td>
</tr>
<tr>
<td>WHR</td>
<td>0.13</td>
<td>0.01–2.84</td>
<td>.20</td>
</tr>
</tbody>
</table>

Total plasma carotenoids (μmol/L)³

<table>
<thead>
<tr>
<th>Quartile</th>
<th>OR</th>
<th>95% CI</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quartile 1</td>
<td>2.54</td>
<td>1.35–4.75</td>
<td>.004</td>
</tr>
<tr>
<td>Quartile 2</td>
<td>1.35</td>
<td>0.69–2.63</td>
<td>.38</td>
</tr>
<tr>
<td>Quartile 3</td>
<td>1.36</td>
<td>0.70–2.64</td>
<td>.36</td>
</tr>
<tr>
<td>Quartile 4</td>
<td>1.00</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Total energy intake, kcal * 100/d | 0.98 | 0.95–1.02 | .38 |

Vegetable intake, g * 100/d | 0.85 | 0.43–0.77 | .0002 |

Physical activity | 0.66 | 0.40–1.09 | .11 |

Muscle density, mg/cm³ | 0.97 | 0.95–0.99 | .0002 |

Calf CSMA, (mm² * 100) | 0.97 | 0.91–1.04 | .004 |

Coronary heart disease | 1.96 | 0.76–5.05 | .16 |

Congestive heart failure | 1.03 | 0.77–1.38 | .83 |

Peripheral artery disease | 1.13 | 0.78–1.63 | .53 |

Stroke | 1.28 | 0.80–2.07 | .31 |

Diabetes mellitus | 1.01 | 0.57–1.78 | .98 |

Chronic obstructive pulmonary disease | 0.86 | 0.51–1.47 | .59 |

Depression | 1.40 | 0.81–2.41 | .23 |

Osteoarthritis³ | 1.39 | 0.99–1.95 | .06 |

Note: *Defined as a decline in strength below the thresholds that define the lowest baseline quartile.

³Highest quartile of total plasma carotenoids is the reference quartile.

³Hip osteoarthritis for poor hip strength model; knee osteoarthritis for poor knee strength model.

OR = odds ratio; CI = confidence interval; WHR = waist to hip ratio; CSMA = cross-sectional muscle area.
0.93–3.56, \( p = 0.07 \) compared to participants in the highest quartile.

Finally, we examined in a multivariate model the relationships between vegetable intake and other risk factors at enrollment with the development of poor hip, knee, and grip strength at the 6-year follow-up. Participants with higher vegetable intake were at lower risk of developing poor hip strength \( [b: -4.9 (1.6) \text{ for each 100 g/day}; OR = 0.995, 95\% CI, 0.992–0.998, \ p = .003] \), knee strength \( [b: -3.4 (1.5) \text{ for each 100 g/day}; OR = 0.997, 95\% CI, 0.997–1.000, \ p = .03] \), and grip strength \( [b: -3.2 (1.6) \text{ for each 100 g/day}; OR = 0.997, 95\% CI, 0.994–1.000, \ p = .05] \). After adjusting for multiple confounders, we found no relationship between fruit intake and poor hip, knee, and grip strength at the 6-year follow-up.

**DISCUSSION**

This study shows that older community-dwelling men and women with low plasma carotenoid concentrations experience a greater decline in hip, knee, and grip muscle strength over a period of 6 years compared to persons with high plasma carotenoids. These findings support and expand the results of previous cross-sectional studies that showed that low carotenoid intake and serum level of carotenoids, natural antioxidants, are independent correlates of poor skeletal muscle strength and impaired physical performance \( (10,11) \). In particular, our longitudinal analysis shows that older community-dwelling men and women with a total plasma carotenoid level <1.37 \( \mu \text{mol/L} \) are at a higher risk of a decline in skeletal muscle strength over time. In addition, we also showed that the participants with higher vegetable intake are at lower risk of loss muscle strength over 6-year follow-up.

To our knowledge, no prospective studies have previously documented the longitudinal relationship of carotenoids with accelerated decline of muscle strength. Our results support the hypothesis that plasma carotenoids are associated with sarcopenia in older adults and bear further support to the hypothesis that intake of natural antioxidants may protect against the development of sarcopenia.

Given the considerable high number of older persons who have inadequate food intake \( (22) \) and a reduced intake of antioxidants \( (22) \), an inadequate antioxidant capability is probably highly prevalent and especially likely to contribute to sarcopenia when coupled with a mismatch between protein requirement and reduced intake. In fact, the decline in food intake that occurs even in healthy older persons, and is probably related to the typical ‘anorexia of aging,’ could result in not only a reduction in protein intake \( (22) \), but also a reduction in consumption of fruits and especially vegetables. Fruits and vegetables are the most important natural antioxidants, are independent correlates of poor muscle strength at the 6-year follow-up.
sources of antioxidants, such as carotenoids and flavonoids, the deficiency of which may have a particularly great effect in muscle where the production of ROS is highest. If the fine physiological balance between oxidative reactions and antioxidants is continuously unbalanced because of a chronically low intake of antioxidants, a detrimental effect of ROS on muscle tissue is likely to occur, regardless of the level of physical activity.

Many studies have reported that skeletal muscle, during aerobic exercise, dramatically increases oxygen uptake, which inevitably results in an increased production of radical ROS. Usually, free radicals produced by the mitochondria of active muscle are removed or scavenged by endogenous antioxidants (23). However, if the amount of free radicals generated exceeds the antioxidant potential capacity, ROS may escape from the mitochondria and oxidize lipids, proteins, sugars, and other cell components. For example, it has been shown that ROS cause lipid peroxidation of polyunsaturated fatty acids in biological membranes and blood, leading to impaired cell functions (24). Based on this assumption, it has been suggested that antioxidant supplementation might be appropriate for athletes before intense physical activity (25).

A limitation of the study is the loss to follow-up of respondents, which may have theoretically biased the results. In addition, other factors not considered in the analyses may explain the study findings. Results may not apply to different age groups and to groups other than the Italian population. Finally, plasma carotenoid measurements at the 6-year follow-up visit were not available. Therefore, whether change over time in carotenoids causes functional status decline in older persons should be tested in future studies.

Strengths of this investigation are the population-based nature of the sample and the availability of longitudinal measures of upper and lower extremity muscle strength. Noteworthy, the strong and consistent relationship between baseline total plasma carotenoids and decline in muscle strength was consistent across the three measures of strength.

The prevention of undernutrition may potentially reduce the risk of disability; however, such a hypothesis would need to be tested through randomized controlled trials. Our results suggest that a higher intake of vegetables may prevent sarcopenia. This hypothesis should be tested in future clinical trials. Given that the carotenoids are biological markers for fruit and vegetable intake (9) and that fruits and vegetables contain a complex mix of antioxidants, fiber, and vitamins, dietary modification toward an increased intake of fruits and vegetables should be evaluated as a potential intervention for disability prevention. Such an approach has been already undertaken with the Dietary Approaches to Stop Hypertension Studies (26) and, recently, a Mediterranean-style diet was shown in a short-term randomized trial to reduce cardiovascular risk factors (27). Although a Mediterranean-style diet that is high in fruits and vegetables has attracted much interest because of an apparent protective effect against cardiovascular disease (28,29), further studies are needed to expand these investigations to sarcopenia (30), decline in physical performance, and progression to disability among older adults.

**Acknowledgments**

This work was supported by National Institute on Aging (NIA) Contracts N01-AG-91643, N01-AG-82136, and N01-AG-5-0002 and NIA Grant R01 AG027012. This research was supported in part by the Intramural Research Program, NIA, National Institutes of Health.

**Author Contributions:** Fulvio Laurentani and Richard Semba: concept and design, analysis and interpretation of data, preparation of manuscript. Stefania Bandinelli: acquisition of participants and data, analysis and interpretation of data. Vittoria Giacomini, Anna Maria Corsi and Margaret Dayhoff-Brannigan: concept and design, interpretation of data, preparation of manuscript. Jack Guralnik and Luigi Ferrucci: concept and design, acquisition of participants and data, analysis and interpretation of data, preparation of manuscript.

**Correspondence**

Address correspondence to Luigi Ferrucci, MD, PhD, National Institute on Aging: Longitudinal Studies Section; Clinical Research Branch, ASTRa Unit, Harbor Hospital 5th Floor, 3001 S. Hanover Street, Baltimore, MD 21225. E-mail: ferruccilu@grc.nia.nih.gov

**References**


Received February 26, 2007
Accepted June 13, 2007
Decision Editor: Darryl Wieland, PhD, MPH