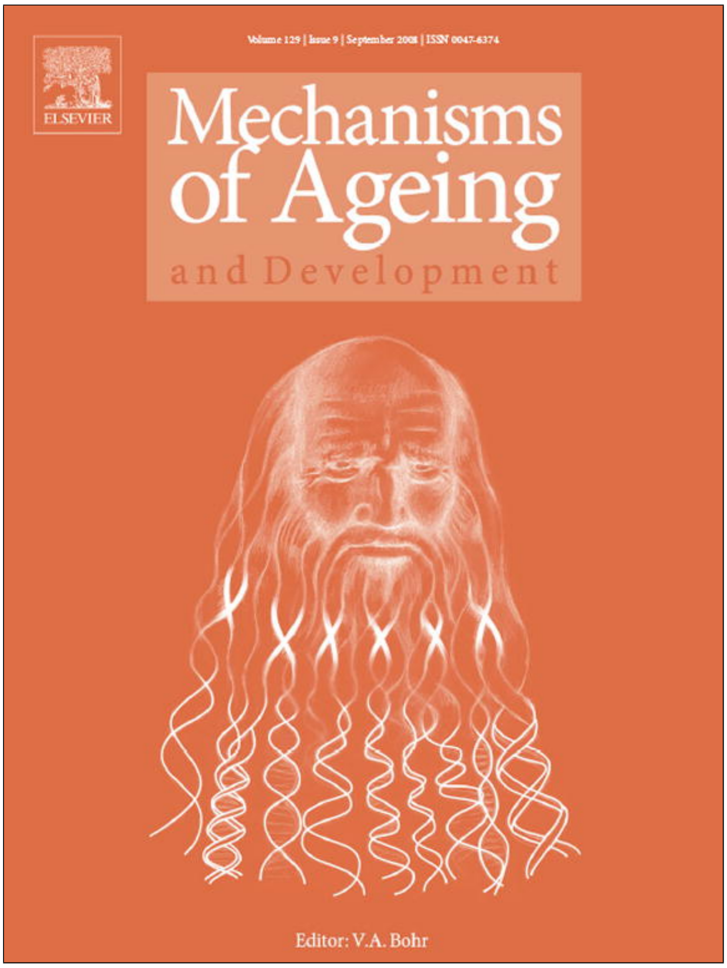
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Higher circulating levels of uric acid are prospectively associated with better muscle function in older persons

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ABSTRACT

Background: Previous studies have shown that oxidative protein damage is independently associated with low grip strength and that dietary intake and circulating levels of antioxidant vitamins are positive predictors of muscle strength among older persons. Since uric acid (UA), has strong antioxidant properties, we tested the hypothesis that UA levels is cross-sectionaly associated with muscle strength and protective against the decline of strength over the aging process.
Subjects and methods: 789 InCHIANTI Study participants underwent baseline serum UA, handgrip and knee extension torque measurements. Of these, 497 participants (226 men and 271 women, mean age 76.0 ± 5.4 years) also had follow-up strength measures. Lifestyle, comorbidities, nutritional profile, inflammatory markers and other laboratory measures were considered as potential confounders.
Results: Follow-up strength measures significantly increased across baseline UA tertiles. After adjusting for potential confounders and analogous baseline strength measures, higher baseline UA levels still remained significantly associated with higher follow-up strength measures.
Conclusions: Our findings suggest that higher levels of UA might represent a protective reaction aimed at counteracting the excessive production of free radicals that cause muscle protein damage and eventually contribute to the decline of muscle mass and strength.

1. Introduction

The circulating levels of uric acid (UA) are higher and more variable in humans and primates than in any other animals, suggesting that the ability to maintain a high concentration of UA results from a powerful natural selection process associated with some important biological advantage.

Since UA has strong antioxidant properties (Hediger et al., 2005; Reyes, 2005), a number of investigators have suggested that the reason for selection is that circulating UA strongly and positively affects human resistance to oxidative stress (Nieto et al., 2000; Skalska et al., 2005; Reyes, 2005; Waring et al., 2006). In fact, once differential concentrations are accounted for, the antioxidant power of UA is substantially higher than other nonenzymatic antioxidants such as ascorbic acid, α-and γ-tocopherol, β-carotene, and probably also of enzymatic antioxidants such as superoxide dismutase and catalase (Hediger et al., 2005). Interestingly, UA is also produced in the vascular endothelium (Reyes, 2005) and there is evidence that in its antioxidant activity, UA interacts with ascorbic acid (Sevanian et al., 1991).

In spite of the strong theoretical rationale and the evidence from pre-clinical studies, both suggesting a strong positive effect of UA on human health, a number of epidemiological and clinical studies (Jankowska et al., 2007; Shankar et al., 2007; Perlstein et al., 2006; Bos et al., 2006; Sundstrom et al., 2005; Fang and Alderman, 2000) have suggested that UA is an important risk factor for cardiovascular diseases and cardiovascular mortality and has a strong negative effect on the clinical evolution of hypertension and chronic heart failure. Interestingly, while other studies failed to confirm the independent, negative prospective relationship between UA and cardiovascular morbidity and mortality (Forman et al., 2007; Coutinho et al., 2007; Hozawa et al., 2006; Wheeler et al., 2005; Hu et al., 2001; Moriarty et al., 2000; Culleton et al., 1999), evidence that UA is a protective factor or a marker of good

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health status is limited to few studies on acute cerebral ischemia (Chamorro et al., 2004) and the protective effect of UA on oxidative stress generated during physical activity (Waring et al., 2003). Several mechanisms may explain the hypothetical negative effect of UA on health, including a direct stimulating effect of soluble non-crystalline UA on inflammation, the impairment of endothelial function and the development of pro-oxidant properties in specific metabolic conditions (Maxwell and Bruinsma, 2001; Alderman, 2002; Hediger et al., 2005).

Understanding whether high UA is detrimental to health or is a protective reaction aimed at counteracting the excessive production of free radicals is a difficult task because of the multiple potential sources of confounding. However, this scientific question is clinically relevant because results may reshape attitudes concerning treatment, especially in older persons, who represent an increasing portion of the population in western countries.

Aging is, in fact, associated with a progressive loss of muscle mass and strength (Morley et al., 2001; Nair, 2005) and previous studies have shown that poor muscle strength is a predictor of incident disability and long-term mortality in healthy middle-aged men (Rantanen et al., 1999, 2000) and of cause-specific and total mortality among older disabled women (Rantanen et al., 2003).

A previous cross-sectional study, using data from the InCHIANTI Study, has found that dietary intake and circulating levels of antioxidant vitamins are positive predictors of muscle strength in older persons, independent of multiple potential confounders (Cesari et al., 2004). Further, a recent study (Howard et al., 2007), using data from the Women's Health and Aging Study (WHAS) I, has shown that oxidative protein damage is independently associated with low grip strength among older women, suggesting that oxidative stress might contribute to the loss of muscle strength and mass in older adults. Finally, Waring et al. (2003) have shown that UA exerts a protective effect on the oxidative stress generated during physical activity. Accordingly, we hypothesized that the ''antioxidant'' UA would be a strong, positive correlate of muscle strength, and we tested this hypothesis in longitudinal perspective using data collected in a population-based sample of older persons.

2. Subjects and methods

2.1. Study sample

The analysis presented in this study is based upon data from the ''InCHIANTI'' (Invecchiare in Chianti, Aging in the Chianti area) Study, a perspective cohort investigation on factors affecting loss of mobility in late life (Ferrucci et al., 2000). The Ethical Committee of the Italian National Institute of Research and Care of Aging approved the study protocol and all participants signed an informed consent to be included in the study. Using a multistage sampling method, 1453 home-dwelling subjects were enrolled in two small towns (Greve in Chianti and Bagno a Ripoli) located in the Chianti countryside. A detailed description of sampling criteria used in the ''InCHIANTI'' Study is reported elsewhere (Ferrucci et al., 2000).

Baseline data collection started in September 1998 and was completed in March 2000. Of the 1453 interviewed participants, 1156 were 65 years or older. Among these, a UA measure was available in 1058 participants, and performance, lower and upper extremity strength measures (see below) were available in 1016, 870 and 848 participants, respectively. Altogether, 789 participants (338 men, mean age 74.2 ± S.D. 6.4 years, and 451 women, mean age 75.4 ± S.D. 6.8 years) had complete baseline data for the analysis presented in this paper.

During the 3-year follow-up, 46 of the 789 participants (27 men, mean age 80.5 ± S.D. 7.0 years, and 19 women, mean age 83.4 ± S.D. 7.0 years, 5.8% of the sample) died: of these, 23 deaths (50%) were attributable to cardiovascular diseases, 14 (30%) to cancer and 9 (20%) to other causes.

Follow-up data collection started in October 2001 and was completed in March 2003. Of the 743 surviving participants with complete baseline data, performance, lower and upper extremity strength measures (see below) were available in 608, 500 and 599 participants, respectively. Altogether, 497 participants (226 men, mean age 75.6 ± S.D. 5.2 years, and 271 women, mean age 76.2 ± S.D. 5.5 years) also had complete performance and strength measures at 3-year follow-up.

2.2. Uric acid

UA levels (mg/dL) were analyzed using enzymatic-colorimetric methods (Roche Diagnostics, GmbH, Mannheim, Germany). The lower limits of detection were 0.2 mg/dL, range 0.2–25.0 mg/dL, CV intra-assay and inter-assay were equal 0.5% and 1.7%, respectively.

Based upon the distribution of UA levels, participants were grouped according to UA tertiles (<4.4 mg/dL, ≥4.4 and ≤5.5, and >5.5).

2.3. Other laboratory measures

Total cholesterol, HDL cholesterol, triglycerides and creatinine levels were determined by commercial assays (Roche Diagnostics, Mannheim, Germany). Insulin resistance was estimated by the homeostasis model assessment (HOMA-R index) from the fasting glucose and insulin concentration according to the equation HOMA-R index = [insulin (μU/mL) × glucose(mmol/L)]/22.5 (Matthews et al., 1985). Plasma vitamin E (α- and γ-tocopherol) concentrations were measured by reversed-phase HPLC, as previously described by Martin (Cesari et al., 2004). High sensitivity C-reactive protein (hs-CRP) was measured in duplicate using an enzyme linked immunoadsorbent assay (ELISA) and colorimetric competitive immunoassay that used purified protein and polyclonal anti-CRP antibodies. Serum levels of interleukin 1 receptor antagonist (IL-1RA) and interleukin 6 (IL-6), were measured by enzyme linked immunoadsorbent assay using ultrasensitive commercial kits (Human Ultrasensitive, Biosource International Inc., Camarillo, California USA).

2.4. Measures of physical function

Knee extension isometric strength was measured by a hand held dynamometer applied at the calf level and multiplied for the length of the tibia, subtracted by 10 cm, in order to obtain the moment of the knee extension torque, in N dm, and to make results comparable among participants with different heights (Lauretani et al., 2003). Handgrip isometric strength, in kilograms, was used as a measure of upper extremity muscle strength (Lauretani et al., 2003; Semba et al., 2007; Dominguez et al., 2006; Abbatecola et al., 2005). We previously demonstrated that the standardized protocol used in the InCHIANTI Study provides reliable measures of strength (Bandinelli et al., 1999) and that knee extension torque and handgrip are strongly correlated with strength of other muscle groups, respectively, of the lower and upper extremities (Lauretani et al., 2003).

A lower extremity summary performance score (SPS) was derived from performance in three objective tests: walking speed over 4 m, five timed repeated chair rises, and standing balance. Each test was scored from 0 to 4 based upon extensive normative data, and the three scores were summed to achieve a total score, ranging from 0 to 12 (12 best) (Guralnik et al., 1994, 1995; Laukkanen et al., 1995).

2.5. Other variables

Body mass index (BMI) was calculated from weight, in kilograms, and height, in meters, according to the formula: $W/(H)^2$. Physical activity was considered as an ordinal variable and scored into five progressive grades: 0 = sedentary or light (<3 METS) physical activity <1 h/week; 1 = light physical activity 2–4 h/week; 2 = light physical activity >4 h/week or moderate (3–6 METS) physical activity 1–2 h/week; 3 = moderate physical activity ≥3 h/week; 4 = intense (>6 METS) physical activity several times a week (Ainsworth et al., 2000). Smoking was classed as ''never'', ''current'', or ''former'' if smoke cessation had lasted for at least 6 months. Comorbid conditions, such as diabetes, hypertension, stroke, peripheral artery disease, coronary artery disease and chronic heart failure, were ascertained according to pre-established algorithms that combined information gathered from medical history, medical records, clinical examination, and blood and instrumental tests included in the InCHIANTI Study protocol (Ferrucci et al., 2000). Assessment of current dietary intake was performed using the Italian version of the food frequency questionnaire developed and validated in the context of the European Prospective Investigation into Cancer and Nutrition (EPIC) (Pisani et al., 1997). The EPIC food frequency questionnaire includes colored photographs to identify the portion size usually consumed and provides a detailed assessment of food consumption. Information on dietary intake was transformed by special software into daily intake of energy, macro- and micro-nutrients. Macro-nutrients known to affect UA levels, such as total protein and alcohol, and micro-nutrients known to exert antioxidant effects, such as vitamin C, vitamin E, β-carotene and retinol, were also considered as potential confounders in this study.

2.6. Statistical analysis

Data are reported as mean ± S.D. or as percentages. Statistical analysis was performed using the STATA 7.0 software, from Stata Corporation (Texas, USA) and carried out following a two-step strategy. The association of baseline UA with participants' characteristics, as well as with measures of physical function both at baseline and at 3-year follow-up, was first tested independent of the confounding effect of age and sex, using linear or logistic regression models, as appropriate. The association of baseline UA with measures of physical function was also tested by further adjusting for BMI because large size people tend to have more muscle to counteract gravity and move their larger body. Then, physical function measures that showed a significant association with baseline UA were entered, as dependent variables, into linear regression models in which UA was considered as the independent variable and variables previously shown to be associated with UA as covariates. In the models predicting physical measures at follow-up, analogous baseline physical function measures were included among the independent variables in order to obtain autoregressive models (Rosner et al., 1985). The initial fully adjusted models were reduced to "most parsimonious" models by using backward selection that only retained variables independently associated with physical measures, with a *p*-value <0.05. Continuous variables showing a markedly skewed distribution, such as plasma antioxidants, inflammatory markers and vitamins dietary intake, were log-transformed before being entered into calculations.

3. Results

Table 1 shows associations of baseline UA tertiles with participants' characteristics. Independent of the confounding effect of age and sex, BMI, a diagnosis of hypertension and chronic heart failure, plasma levels of triglycerides, HOMA-R index, serum creatinine, α- and γ-tocopherol, hs-C-reactive protein, IL-1RA and IL-6, vitamin C dietary intake, number of medications and use of diuretics were significantly higher across UA tertiles. On the contrary, HDL cholesterol levels were significantly lower. Physical activity in the past year, cigarette smoking, a diagnosis of diabetes, peripheral and coronary artery disease, stroke, total cholesterol levels, and dietary intake of vitamin E, β-carotene and retinol, were not associated with UA.

Table 2 shows associations of baseline UA tertiles with measures of muscle strength and physical performance, both at baseline and at 3-year follow-up. Independent of the confounding effect of age and sex, both handgrip and knee extension torque at 3-year follow-up significantly increased across UA tertiles and the association remained significant after further adjusting for BMI. The association of UA with handgrip and knee extension torque at baseline was not significant, though both showed a clear-cut increasing trend across UA tertiles. SPS was not associated with UA both at baseline and at 3-year follow-up.

Table 3 shows the general linear autoregressive model testing the relationship between baseline UA tertiles and follow-up handgrip, reduced to a "most parsimonious" model by using backward selection. After adjusting for baseline handgrip and other relevant confounders, higher baseline UA levels were associated with higher follow-up handgrip.

Table 4 shows the general linear autoregressive model testing the relationship between baseline UA tertiles and follow-up knee extension torque, reduced to a "most parsimonious" model by using backward selection. After adjusting for baseline knee

Table 1
Baseline characteristics of InCHIANTI Study participants according to Uric acid tertiles (*n*. 789)[a]

	Uric acid tertiles (mg/dL)			
	<4.4	4.4–5.5	>5.5	p^b
Body mass index (kg/m²) (mean ± S.D.)	26.0 ± 3.7	27.7 ± 4.1	28.3 ± 3.9	<0.001
Physical activity (scale 0–4, 4 best) (mean ± S.D.)	1.2 ± 0.8	1.3 ± 0.9	1.3 ± 0.9	0.587
Cigarette smoking				
Never smoked (%)	68.7	57.7	53.0	
Former smokers (%)	19.3	30.9	35.7	0.621
Current smokers (%)	12.0	11.4	11.2	
Comorbid conditions				
Diabetes (%)	12.0	7.5	12.9	0.995
Hypertension (%)	65.2	72.6	77.9	0.001
Stroke (%)	3.9	5.5	8.0	0.126
Peripheral artery disease (%)	13.7	18.1	20.2	0.253
Coronary artery disease (%)	6.0	6.2	6.2	0.962
Chronic heart failure (%)	2.1	2.6	7.2	0.004
Lab tests				
Total cholesterol (mg/dL) (mean ± S.D.	220 ± 38	220 ± 37	218 ± 41	0.075
HDL cholesterol (mg/dL) (mean ± S.D.)	61 ± 13	57 ± 15	51 ± 15	<0.001
Triglycerides (mg/dL) (mean ± S.D.)	109 ± 51	120 ± 60	153 ± 91	<0.001
Serum creatinine (mg/dL) (mean ± S.D.)	0.8 ± 0.1	0.9 ± 0.2	1.0 ± 0.3	<0.001
HOMA-R index (mean ± S.D.)	2.7 ± 1.8	2.5 ± 1.4	3.2 ± 2.3	<0.001
α-Tocopherol (μmol/L) (mean ± S.D)[c]	29 ± 7	30 ± 8	31 ± 10	<0.001
γ-Tocopherol (μmol/L) (mean ± S.D.)[c]	1.4 ± 0.6	1.4 ± 0.6	1.6 ± 0.8	<0.001
C-reactive protein (mg/dL) (mean ± S.D.)[c]	4.3 ± 7.6	4.3 ± 7.2	6.5 ± 12.3	<0.001
Interleukin 1 receptor antagonist (pg/mL) (mean ± S.D.)[c]	136 ± 78	150 ± 92	180 ± 117	<0.001
Interleukin 6 (pg/mL) (mean ± S.D.)[c]	1.8 ± 2.1	1.9 ± 1.9	2.4 ± 2.6	0.004
Dietary intake (per day)				
Total proteins (g) (mean ± S.D.)	74.2 ± 19.3	77.3 ± 21.3	76.4 ± 25.8	0.451
Alcohol (g) (mean ± S.D.)	10.8 ± 14.5	15.8 ± 23.7	18.4 ± 22.0	0.256
Vitamin C (mg) (mean ± S.D.)[c]	106 ± 544	113 ± 49	117 ± 53	0.005
Vitamin E (mg) (mean ± S.D.)[c]	6.03 ± 1.84	6.40 ± 2.11	6.46 ± 1.98	0.058
β-Carotene (μg) (mean ± S.D.)[c]	2160 ± 1160	2218 ± 1167	2173 ± 1065	0.514
Retinol (μg) (mean ± S.D.)[c]	430 ± 446	545 ± 590	484 ± 600	0.082
Drugs				
No. of medications (mean ± S.D.)	2.0 ± 1.9	2.1 ± 1.9	2.5 ± 2.1	0.001
Allopurinol (%)	0.9	1.3	0.8	0.875
Diuretics (%)	5.6	8.1	16.9	<0.001

[a] According to uric acid tertiles, mean age was 74.4 years ± S.D. 6.7 (*n*. 233, 77% women), 74.8 ± 6.5 (*n*. 307, 54% women) and 75.4 ± 6.8 (*n*. 249, 43% women), respectively.
[b] From age- and sex-adjusted linear or logistic regression models, as appropriate.
[c] Variables log-transformed before being entered into linear regressions due to their markedly skewed distribution.

Table 2
Muscle strength and physical performance measures according to uric acid tertiles

	Uric acid tertiles (mg/dL)				
	<4.4	4.4–5.5	>5.5	p^a	p^b
Baseline data (*n.* 789)[c]					
Muscle strength measures					
Handgrip (kg) (mean ± S.D.)	23.2 ± 10.0	27.3 ± 12.0	28.3 ± 12.1	0.304	0.149
Knee extension torque (N dm) (mean ± S.D.)	332 ± 123	389 ± 169	407 ± 198	0.061	0.232
Lower extremity summary of performance score (mean ± S.D.)	10.3 ± 2.4	10.3 ± 2.5	10.1 ± 2.6	0.127	0.535
Baseline data of participants whose 3-year follow-up data were also available (*n.* 497)[d]					
Muscle strength measures					
Handgrip (kg) (mean ± S.D.)	25.0 ± 10.1	29.4 ± 12.4	32.0 ± 11.2	0.066	0.052
Knee extension torque (N dm) (mean ± S.D.)	330 ± 99	393 ± 135	418 ± 132	0.023	0.113
Lower extremity summary of performance score (mean ± S.D.)	11.0 ± 1.3	10.9 ± 1,7	11.1 ± 1.3	0.706	0.836
3-year follow-up data (*n.* 497)					
Muscle strength measures					
Handgrip (kg) (mean ± S.D.)	25.1 ± 8.0	29.2 ± 11.4	31.1 ± 10.7	0.036	0.034
Knee extension torque (N dm) (mean ± S.D.)	330 ± 99	395 ± 141	418 ± 132	0.001	0.032
Lower extremity summary of performance score (mean ± S.D.)	9.3 ± 3.0	9.1 ± 3.4	9.7 ± 3.1	0.583	0.172

[a] From age- and sex-adjusted linear regressions.
[b] From linear regressions also adjusted for BMI.
[c] According to uric acid tertiles, mean age was 74.4 years ± S.D. 6.7 (*n.* 233, 77% women), 74.8 ± 6.5 (*n.* 307, 54% women) and 75.4 ± 6.8 (*n.* 249, 43% women), respectively.
[d] According to uric acid tertiles, mean age at baseline was 72.5 years ± S.D. 5.4 (*n.* 153, 75% women), 73.2 ± 5.7 (*n.* 196, 51% women) and 73.7 ± 5.1 (*n.* 148, 39% women), respectively.

extension torque and other relevant confounders, higher baseline UA levels were associated with higher follow-up knee extension torque.

4. Discussion

Using data collected in a population-based sample of persons enrolled in the "InCHIANTI" Study we tested the hypothesis that the "antioxidant" UA could be a positive predictor of physical performance and muscle strength in older persons and we found that higher UA levels were prospectively independently associated with better muscle strength.

To our knowledge, this is the first study that has investigated the longitudinal relationship of UA with muscle strength and physical performance. Therefore, our findings cannot be compared with any existing literature.

Sarcopenia, the age-related loss of muscle mass and strength, is considered one of the most important components in the causal pathway leading to frailty, disability and, eventually, to death among older persons (Evans, 1995; Fried and Guralnik, 1997; Rantanen et al., 1999, 2000, 2003). A recent study (Howard et al., 2007) has shown that oxidative protein damage is independently associated with low grip strength among older persons, suggesting that oxidative stress might contribute to the loss of muscle strength and mass. Thus, our findings, showing an independent prospective association of higher UA levels with better muscle function, support the hypothesis that the ability to maintain a higher concentration of UA is associated with some important biological advantage, which may consist in increased resistance to the excessive oxidative stress that occurs in working muscles during everyday physical activity.

Interestingly, UA levels were not prospectively associated with physical performance. This unexpected finding may be explained by the fact that SPS is the final sum of a number of multiple parameters, the result of which is affected not only by muscle strength but also by other critical functions, such as balance and coordination.

With regard to cross-sectional data, previous studies performed on the same population sample have found that dietary intake and serum concentration of antioxidant vitamins are a positive predictor of physical performance and muscle strength in older persons (Cesari et al., 2004). However, our cross-sectional findings did not confirm the association between the "antioxidant" UA and physical measures, though baseline handgrip and knee extension

Table 3
General linear model testing the relationship between baseline uric acid tertiles and follow-up handgrip after adjusting for baseline handgrip and other relevant confounders. The initial fully adjusted model was reduced to a "most parsimonious" model by using backward selection ($p < 0.05$)

Final model: Obs = 497; F = 432; Prob > F < 0.001; adjusted R^2 = 0.782		
Follow-up handgrip (kg)	β ± S.E. (β)	p
Age (years)	−0.35 ± 0.04	<0.001
Female sex	−8.70 ± 0.61	<0.001
Uric acid tertiles (trend)	0.70 ± 0.29	0.016
- Uric acid 1st tertile (<4.4 mg/dL) (reference)	–	–
- Uric acid 2nd tertile (4.4–5.5 mg/dL)	1.08 ± 0.53	0.047
- Uric acid 3rd tertile (>5.5 mg/dL)	1.41 ± 0.58	0.015
Baseline handgrip (kg)	0.41 ± 0.03	<0.001

The initial fully adjusted model included: age, sex, BMI, hypertension, chronic heart failure, HDL cholesterol, triglycerides, creatinin, HOMA-R index, α- and γ-tocopherol, C-reactive protein, interleukin 1 receptor antagonist, interleukin 6, vitamin C intake, number of medications, use of diuretics and baseline handgrip.

Table 4
General linear model testing the relationship between baseline uric acid tertiles and follow-up knee extension torque after adjusting for baseline knee extension torque and other relevant confounders. The initial fully adjusted model was reduced to a "most parsimonious" model by using backward selection ($p < 0.05$).

Final model: Obs = 497; F = 145; Prob > F < 0.001; adjusted R^2 = 0.657		
Follow-up knee extension torque (N dm)	β ± S.E. (β)	p
Age (years)	−2.97 ± 0.71	<0.001
Female sex	−82.40 ± 9.72	<0.001
Uric acid tertile (trend)	9.86 ± 4.62	0.040
- Uric acid 1st tertile (<4.4 mg/dL) (reference)	–	–
- Uric acid 2nd tertile (4.4–5.5 mg/dL)	18.35 ± 9.01	0.048
- Uric acid 3rd tertile (>5.5 mg/dL)	20.48 ± 9.75	0.041
Body mass index (kg/m^2)	2.66 ± 1.00	0.008
n° of medications	−5.99 ± 1.96	0.002
Baseline knee extension torque (N dm)	0.39 ± 0.03	<0.001

The initial fully adjusted model included: age, sex, BMI, hypertension, chronic heart failure, HDL cholesterol, triglycerides, creatinin, HOMA-R index, α- and γ-tocopherol, C-reactive protein, interleukin 1 receptor antagonist, interleukin 6, vitamin C intake, number of medications, use of diuretics and baseline knee extension torque.

torque showed a clear-cut increasing trend across UA tertiles. We may hypothesize that our cross-sectional findings are due to the fact that low muscle strength indicates poor health status which may be associated with excessive oxidative stress and possible reactive increment in UA. However, if the compensatory increment in UA is effective, it may protect against future decline in muscle strength.

Two main potential limitations of the study need to be considered. First, our analysis was based upon UA serum levels that only partially reflect the real amount of UA stored in the peripheral tissues. Secondly, perspective studies that use a single baseline measurement to predict future events are subject to the regression dilution bias (MacMahon et al., 1990; Law et al., 1994). This bias results from the diluting effects of random fluctuations of risk factors over time such that single measures of risk factors systematically underestimate the association between risk factors and events (Grundy et al., 1999) Accordingly, we might have underestimated the real association of some risk factor with the loss of muscle mass and strength in older persons.

In conclusion, our findings show that higher levels of ''antioxidant'' UA are prospectively associated with better muscle function suggesting that UA might represent a protective reaction aimed at counteracting the excessive production of free radicals that cause protein damage and eventually contribute to the decline of muscle mass and strength in older persons (Howard et al., 2007). Measures available in our epidemiological study do not allow to discriminate whether higher UA levels prevent the loss of muscle fibers or preserve the function of the remaining ones. However, there is large evidence that the origin of age-associated sarcopenia is due to a combination of reduction in muscle mass and intrinsic muscle contractility, and it is likely that the same mechanisms that induce muscle metabolic dysregulation (probably catabolic imbalance) cause the reduction in myofibers intrinsic contractility and later lead to muscle apoptosis and true sarcopenia. Further, the decrease of muscle strength, which is the overall result of both the reduction in muscle mass and intrinsic contractility, is also the most important parameter impacting functional status and quality of life.

Future studies are needed to clarify the mechanism by which higher levels of ''antioxidant'' UA positively affect muscle function and to better understand to which extent we should reshape our attitude concerning treatment of patients with slightly elevated UA levels.

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Disclosures

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Statements

All authors have read and approved submission of the manuscript.

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