Journal of Gerontology: MEDICAL SCIENCES
Cite journal as: J Gerontol A Biol Sci Med Sci. 2011 March;66A(3):320–325
doi:10.1093/gerona/glq207

Advance Access published on November 26, 2010

Obesity, Poor Muscle Strength, and Venous Thromboembolism in Older Persons: The InCHIANTI Study

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Background. Both obesity and the decline in muscle strength, which often occur with aging, are accompanied by functional and metabolic changes that may affect the risk of thrombosis. This study evaluated whether obesity and poor muscle strength are associated with venous thromboembolism (VTE).

Methods. Objectively confirmed VTEs were assessed at baseline and more than a 6-year follow-up in 1,045 participants more than or equal to 60 years enrolled in the InCHIANTI study.

Results. At baseline, 97 participants had a positive history of VTE. Obese participants were almost twice more likely (odds ratio 1.76; 95% confidence interval 1.03-3.01) and obese with poor muscle strength were threefold more likely (odds ratio 2.99; 95% confidence interval 1.56-5.73) to have VTE compared with lean participants with normal strength. Fifty-five VTEs occurred during follow-up. History of VTE, obesity, and/or poor strength independently predicted new VTE events. In participants with previous VTE, the odds ratio (95% confidence interval) for thrombosis was 6.64 (1.92-22.95) with poor strength, 9.69 (3.13-30.01) in the obese, and 14.57 (5.16-41.15) in the obese with poor strength as compared with lean participants with normal strength.

Conclusion. Obesity with or without poor muscle strength is a risk factor for VTE among older persons and significantly amplifies the risk of recurrent thrombosis.

Key Words: Venous thrombosis—Obesity—Poor muscle strength—Elderly.

Received July 15, 2010; Accepted October 11, 2010

Decision Editor: Darryl Wieland, PhD, MPH

STUDIES have consistently shown that the risk of venous thromboembolism (VTE) increases with age. The incidence of a first episode of VTE rises sharply with age with doubling of the risk for each decade after age 60 years. The cumulative incidence of VTE between 50 and 80 years is as high as 10% (1–3).

Notwithstanding the strong association between age and VTE, only few studies have assessed risk factors for VTE in older persons (4). Indeed, with the exception of major surgical procedures or stroke, the relevance of other variables that may predict VTE remains poorly understood (5). There are many reasons to hypothesize that obesity and the decline in lean body mass that often occur with aging may affect the risk of VTE. Obesity is characterized by high circulating prothrombotic factors and impaired fibrinolysis that determine a state of chronic hypercoagulability that may predispose to the development of venous thrombosis (6), which appears to be particularly important in older persons (6-8). In fact, data from a recent meta-analysis and a large registry study suggest that obese persons have higher risk of VTE (9,10). A progressive decline in lean body mass and increase in fat mass occur with aging in the large majority of individuals (11,12) and result in progressive weakness and impaired mobility. (11). Reduced strength and reduced mobility may slow down blood flow in the lower extremity venous district and contribute to the risk of VTE. In addition, the reduction in muscle strength is accompanied by metabolic and inflammatory changes that may contribute to a thrombophilic state (13). Prospective population-based studies have indeed reported an inverse relationship between muscle strength and inflammation (14-19). In a large investigation of 3,075 individuals aged 70–79 years, higher levels of inflammatory markers were found among participants with lower muscle mass and muscle strength after adjustment for age and chronic diseases (19). These findings have been subsequently confirmed by others (14,16-18). Interestingly, in a recent prospective population-based study, community-dwelling older adults with baseline frailty appeared to have a higher incidence rate of idiopathic VTE and a trend for higher total VTE, compared with those with no frailty (20).

The aim of the present analysis was to evaluate whether obesity and poor muscle strength independently and/or jointly are associated with higher prevalence of VTE and predict the development of VTE in the older population.

Methods

The study design of the InCHIANTI study has been described in details elsewhere (21). Briefly, the study was designed by the Laboratory of Clinical Epidemiology of the Italian National Institute of Research and Care on Aging (Florence, Italy) and performed in two small towns in Tuscany outside the urban area of Florence. The baseline data were collected in 1998–2000; the 3-year follow-up took place in 2001–2003 and the 6-year follow-up in 2004–2006.

Sample

A total of 1,270 persons aged 60 years or older were randomly selected from the population registry of Greve in Chianti (rural area) and Bagno a Ripoli (urban area near Florence). Of these, 152 participants did not receive an ultrasound Doppler examination of the lower extremity and 73 did not have one or more variables required for the analysis reported here. Therefore, the study population included 1,045 persons (640 women and 495 men), who had complete information. During the 6-year follow-up, 38 participants died, 2 refused to participate, and 14 were missing one or more variables of interest. Therefore, the sample considered for the longitudinal analysis included 991 participants.

Data Collection

Evaluations included an interview, the collection of a structured medical history, a physical examination, and blood sampling for hematology and clinical chemistry. Participants also underwent a peripheral quantitative computed tomography to assess the fat-lean distribution, a standard electrocardiogram, an ultrasound color Doppler examination of the carotids, vertebral arteries, and an assessment of the ankle-brachial index. Venous ultrasonography of the lower limbs was conducted during this visit with the deep venous system assessed from the groin to the ankle. All the tests mentioned were performed in the study clinic.

Within 2 weeks, the participants returned for a structured medical examination and an objective assessment of physical function performed by trained geriatricians and physical therapists. Examination was aimed at objectively assessing several aspects of physical function, with particular consideration given to muscle strength, joint range of motion, and walking.

Physical Performance

Several tests were performed in the InCHIANTI study (22) to evaluate physical function including the Short Physical Performance Battery and a modified version of the balance test used in the Frailty and Injuries: Cooperative Studies of Intervention Techniques (FICSIT) study (23,24). Lower extremity function was evaluated administering the Short Physical Performance Battery, which includes tests of walking speed, standing balance, and ability to rise from a chair. The results of each test were scored on a five-level categorical scale, with 0 representing inability to complete the test and 4 representing the highest level of performance. Adding the scores of the three performance tests produced a summary score ranging from 0 to 12. Balance was evaluated in different positions, characterized by a progressive reduction of the base of support (feet underneath inferior iliac spines, side by side, semi-tandem, tandem, one leg stand).

Physical Activity

Physical activity was assessed through an interviewer-administered questionnaire. participants were asked to indicate their average level of physical activity during the year preceding the enrolment in the study. One of the following seven response categories that incorporate duration, frequency, and intensity of physical activity could be chosen for each age period: (i) no physical activity, (ii) minimal physical activity, (iii) light physical activity performed 2 to 4 hours per week not accompanied by sweating (eg, walking), (iv) moderate physical activity performed 1–2 hours per week accompanied by sweating or light physical activity not accompanied by sweating for more than 4 hours per week, (v) moderate physical activity performed more than or equal to 3 hours per week accompanied by sweating, (vi) physical exercise performed regularly several times per week, and (vii) physical exercise that required maximal strength and endurance performed everyday.

The seven categories of self-reported physical activity were collapsed into four levels: Level I practically bedbound; Level II combined the first and the second categories reflecting insufficient physical activity; Level III was defined by the third and the fourth categories, reflecting high physical activity; and Level IV combined the last two categories.

Measurement of Muscle Strength

Maximal voluntary isometric strength of knee extensors was measured using a handheld dynamometer (Nicholas Muscle Tester; Sammon Preston, Inc., Chicago, IL) according to a standard assessment protocol (25). The test was repeated three times, and the best result of either side was used in the analyses. Strength was measured in kilograms (kg), and the lowest gender-specific tertile was used as a marker of low muscle strength. The cut-off points for gender-specific strength tertiles were 17.1 and 21.5 kg (range 3.9–41.7 kg) in men and 11.3 and 14.3 kg (range 3.5–31.2 kg) in women (11). Lower extremity muscle power was measured in a single leg extension movement using the power rig developed by Bassey and Short (26).

Measurement of Obesity

Body mass index (kg/m^2) was calculated using objectively measured height and weight. Weight was measured to the nearest 0.1 kg using a high-precision mechanical scale and standing height to the nearest 0.1 cm with a wall measure with participants wearing light indoor clothes and no shoes. Obesity was defined as body mass index more than or equal to 30 kg/m^2. Obesity with poor muscle strength was diagnosed in cases of isometric strength of knee extensors in the lowest sex-specific tertiles and a body mass index more than or equal to 30 kg/m^2 (11). Most of the assessment performed at baseline including the home interview, the standard medical visit, blood drowning, imaging tests, and the objective measurement of physical functionality were repeated at 3 and 6 years from baseline.

Study Outcomes

Color-Doppler venous ultrasonography of the legs was performed at each visit by experienced physicians using an ultrasound machine (ESAOTE, Florence, Italy) equipped with a 7.5-MHz, dynamically focused, electronic probe. The venous system of the lower extremity was evaluated looking for venous insufficiency and thrombosis of the deep and superficial circulation.

All suspected episodes of deep venous thrombosis or pulmonary embolism that occurred during follow-up had to be objectively confirmed by means of ventilation perfusion–lung scintigraphy, spiral computed tomography, or pulmonary angiogram for pulmonary embolism and compression ultrasonography or venography for deep venous thrombosis. For patients with a positive history of deep venous thrombosis or pulmonary embolism at baseline, the thrombotic event had to be objectively confirmed as indicated by medical reports and ultrasound images.

Statistical Analysis

Baseline characteristics were compared between participants with and without evidence of VTE at baseline and at follow-up, using analysis of variance for continuous variables and $\chi 2$ test analyses for dichotomous or categorical variables. Univariate and multivariable analyses were conducted to assess the relationship between risk factors for thromboembolic events and VTE. The reported *p* values in the descriptive tables are adjusted for age and sex using, respectively, linear and logistic regression models. The association between VTE and age-specific body changes, that is obesity, poor muscle strength alone or jointly, was evaluated cross-sectionally and longitudinally by logistic regression models: Model 1 evaluated the crude association; Model 2 was adjusted for age and sex; Model 3 was adjusted for all variables significantly related to study outcome in univariate analysis, namely age, sex, cardiovascular disease or risk factors, hip fracture, hospitalization in the previous year, the Short Physical Performance Battery score, the modified balance score, and the self-reported physical activity. Analyses were performed with the SAS statistical software, version 8.2 (SAS Institute, Cary, NC). A *p* value of 0.05 was considered significant.

Table 1. Baseline Characteristics According to Presence and Absence of VTE

	VTE, (*n* = 95)	No VTE, (*n* = 950)	*p*	*p**
Age, years	74.6 (0.8)	74.0 (0.2)	.43	
Sex, females	69 (72.6)	514 (54.1)	.001	
Stroke	4 (4.2)	46 (4.8)	.78	.94
Diabetes	11 (11.6)	110 (10.4)	.72	.59
Congestive heart failure	8 (8.4)	42 (4.4)	.08	.09
Clearance creatinine, ml/min	72.6 (2.8)	77.4 (0.8)	.64	.59
Myocardial infarction	3 (3.2)	46 (4.8)	.61	.57
Cancer	7 (7.4)	59 (6.2)	.66	.68
History of hip/femur fracture	3 (3.2)	29 (3.1)	.95	.80
Non obese with normal strength	33 (34.7)	437 (46.0)	<.001†	<.001†
Obesity with normal strength	23 (24.2)	156 (16.4)		
Non obese with poor muscle strength	21 (22.1)	289 (30.4)		
Obesity with poor muscle strength	18 (19.0)	68 (7.2)		
Number of hospitalizations (previous year)	19 (20.0)	123 (13.0)	.06	.03
Short physical performance battery (0-12)	9.1 (0.3)	10.1 (0.1)	.001	.003
FICSIT balance score	19.4 (0.5)	20.8 (0.1)	<.001	.001
Muscle power (dominant) leg	84.0 (5.7)	105.6 (2.2)	.003	.35
Muscle strength knee extension, kg	14.4 (0.6)	16.2 (0.2)	.006	.35

Notes: Data are reported as frequencies (percentages) for dichotomous or categorical variables and as mean (*SE*) for continuous variables. **p* values adjusted for age and sex; †for trend *p* value. Poor muscle strength was defined according to sex-specific tertiles of muscle strength of knee flexor (kg) (*M*: 17.1, 21.5 kg; *F*: 11.3, 14.3 kg). Obesity is defined as a body mass index ≥30 kg/m^2. VTE = venous thromboembolism; FICSIT = Frailty and Injuries: Cooperative Studies of Intervention Techniques.

Results

The demographic characteristics of the study population according to prevalent VTE are reported in Table 1. Participants with versus those without prevalent VTE were not different for age, prevalence of cancer, cerebrovascular or cardiovascular disease, number of hospitalizations, traumas,

Table 2. Association Between Obesity, Poor Muscle Strength, and VTE in the InCHIANTI Study at Baseline

	Model 1		Model 2		Model 3	
	OR	95% CI	OR	95% CI	OR	95% CI
Obesity with poor muscle strength	3.21	1.76-5.86	2.90	1.57-5.36	2.99	1.56-5.73
Non obese with poor muscle strength	1.02	0.59-1.77	0.97	0.54-1.74	1.02	0.56-1.86
Obesity with normal muscle strength	1.76	1.03-3.01	1.65	0.96-2.86	1.72	0.97-3.06
Non obese with normal muscle strength	Reference group		Reference group		Reference group	

Notes: Model 1: crude values; Model 2: values adjusted by age and sex; Model 3: values adjusted by age, sex, hip femur fracture, congestive heart failure, hospitalization in the previous year, the Short Physical Performance Battery score, and modified FICSIT balance score. VTE = venous thromboembolism; OR = odds ratio; CI = confidence interval; FICSIT = Frailty and Injuries: Cooperative Studies of Intervention Techniques.

cardiovascular risk factors, renal function, muscle power, and muscle knee extension. Participants with a positive VTE history were more likely to be women (72% vs 54%, p =.001).

Overall, 24% of participants with VTE were obese compared with 16.4% of those without VTE (odds ratio [OR] 1.76; 95% confidence interval [CI] 1.03-3.01). Participants with VTE were also threefold more likely to have both obesity and poor muscle strength (18.6% vs 6.6%, OR 3.21; 95% CI 1.76-5.86) than those free of VTE. In multivariable analysis, the significant association between VTE and the combination obesity/poor muscle strength was maintained after adjustment for age, sex, cancer, congestive heart failure, hospitalization in the previous year, self-reported physical activity, balance score, and lower extremity performance (OR 2.99; 95% CI 1.56-5.73) (Table 2). Poor strength alone was not significantly related to VTE.

Table 3. Demographic and Clinical Characteristics According to the Occurrence or not VTE During Follow-up

	VTE (n = 55)	No VTE (n = 936)	p	p^*
Age, years	75.7 (0.9)	73.4 (0.2)	.02	
Sex, females	45 (81.8)	505 (54.0)	<.001	
Stroke	8 (14.6)	83 (8.9)	.16	.13
Diabetes	16 (29.1)	162 (17.3)	.03	.03
Congestive heart failure	25 (45.5)	363 (38.8)	.32	.60
Myocardial infarction	8 (14.6)	99 (10.6)	.36	.29
Cancer	7 (12.7)	101 (10.8)	.66	.84
History of hip/femur fracture	9 (16.4)	38 (4.1)	<.001	.003
History of VTE at baseline	27 (49.1)	63 (6.7)	<.001	<.001
Non obese with normal strength	16 (29.1)	374 (38.3)	.001†	.001†
Obesity with normal strength	14 (25.5)	140 (14.9)		
Non obese with poor muscle strength	13 (23.6)	348 (37.2)		
Obesity with poor muscle strength	12 (21.8)	90 (9.6)		
Hospitalization	31 (56.4)	350 (37.4)	.004	.003
Short physical performance battery (0-12)	9.1 (0.4)	10.4 (0.1)	<.001	.008
FICSIT balance score	19.2 (0.6)	21.1 (0.1)	<.001	.008
Muscle power (dominant) leg	79.1 (7.1)	106.3 (2.2)	.003	.80
Muscle strength knee extension, kg	14.1 (0.7)	16.4 (0.2)	.006	.83
Use of anticoagulants	11 (20.0)	36 (3.9)	<.001	<.001

Notes: Data are reported as frequencies (percentages) for dichotomous or categorical variables and as mean (*SE*) for continuous variables. $^*p$ values adjusted for age and sex; †for trend p value. VTE = venous thromboembolism; FICSIT = Frailty and Injuries: Cooperative Studies of Intervention Techniques.

Compared with those without VTE, participants with a positive VTE history had significantly worse lower extremity performance and balance (Table 1). Similarly, performance in most of other tests of physical function or walking ability was significantly worse in participants with VTE history. The relationship between VTE and lower extremity performance was maintained after adjusting for multiple confounders, including age, sex, cancer, hip femur fracture, congestive heart failure, hospitalization in the previous year, and balance score (data not shown).

During the 3- and 6-year follow-up, a new (or recurrent) episode of VTE was diagnosed in 55 patients (5.6%). Older age, female sex, diabetes, history of hip fracture, number of hospitalizations from baseline, and history of VTE were significantly more frequent among participants who developed a new VTE event (Table 3). In analysis, obesity and poor muscle strength were associated with a threefold higher risk of VTE (relative risk 2.98; 95% CI 1.36-6.53) whereas obesity with normal strength doubled the risk (relative risk 2.24; 95% CI 1.06-4.71) compared with participants who were nonobese with normal strength. Poor muscle strength alone was not a significant predictor of venous thrombotic events (relative risk 0.84; 95% CI 0.40-1.76). Half of the thrombotic events were recurrent episodes that made the history of VTE the strongest predictor for new VTE (relative risk 11.02; 95% CI 5.89-20.64; p < .0001) independently of age, sex, diabetes, hospitalization in the previous year, balance, and lower extremity performance. The association between a positive history of VTE and recurrent events was significantly influenced by the presence of obesity and/or poor muscle strength. Among participants with a previous VTE, the OR (95% CI) for new VTE was 6.64 (1.92-22.95) in those with poor muscle strength, 9.69 (3.13-30.01) in the obese, and 14.57 (5.16-41.15) in obese participants with poor muscle strength (p for trend <.001) (Table 4). These results remained unchanged after adjustment for other confounders in multivariable analysis. In the absence of obesity and poor muscle strength, the risk of VTE was comparable between participants with and without history of previous VTE at baseline.

Participants who developed VTE had significantly worse baseline lower extremity and balance performance. Physical function tests at baseline including the Short Physical

Table 4. Association Between Obesity, Poor Muscle Strength, and VTE in the InCHIANTI Study at Follow-up

	Model 1		Model 2		Model 3	
	OR	95% CI	OR	95% CI	OR	95% CI
Nonobese with poor muscle strength and VTE at baseline	5.92	1.84-19.12	5.99	1.79-19.95	6.64	1.92-22.95
Obesity with normal muscle strength and VTE at baseline	11.42	3.98-32.82	10.78	3.59-32.40	9.69	3.13-30.01
Obesity and poor muscle strength and VTE at baseline	18.45	7.07-48.20	15.06	5.65-40.15	14.57	5.16-41.15
Nonobese with normal muscle strength and non-VTE at baseline	1.19	0.60-2.33	1.43	0.71-2.87	1.50	0.74-3.03
Nonobese with normal muscle strength and VTE at baseline	Reference group		Reference group		Reference group	

Notes: Model 1: crude values; Model 2: values adjusted by age and sex; Model 3: values adjusted by age, sex, hospitalization, hip femur fracture, FICSIT balance score, stroke, diabetes, and the Short Physical Performance Battery score. VTE = venous thromboembolism. OR = odds ratio; CI = confidence interval; FICSIT = Frailty and Injuries: Cooperative Studies of Intervention Techniques.

Performance Battery (9.1 ± 0.4 vs 10.4 ± 0.1, $p < .001$), the modified FICSIT balance score (19.2 ± 0.6 vs 21.1 ± 0.1, $p < .001$), and muscle power (79.1 ± 7.1 vs 106.3 ± 2.2 watts, $p = .003$) were significantly worse among participants with VTE (Table 3). Patients with multiple thrombotic events during follow-up were more frequently women than men (OR 5.4; 95% CI 1.9-15.7), more likely to have had hospitalizations in the year before the recurrence (OR 2.6; 95% CI 1.2-5.7), and to have a positive history of hip fracture (OR 6.7; 95% CI 2.6-17.7), and diabetes (OR: 2.3; 95% CI 1.1-5.1).

Discussion

The current study confirms that history of previous hospitalization, hip fracture, and previous VTE are risk factors for VTE development in older persons. Independently of confounders, obesity with or without poor muscle strength was also associated with the likelihood of having VTE at baseline and with a higher risk of developing VTE over the follow-up. By contrast, poor muscle strength alone was not associated with the risk of VTE. The coexistence of a previous VTE and obesity associated with poor muscle strength carried an extremely high risk of new (or recurrent) thrombotic events.

The role of obesity as risk factor for VTE is still debated. A recent meta-analysis evaluated the association between VTE and cardiovascular risk factors including obesity (9). Although a twofold higher rate of venous thrombosis was found for obese individuals, the wide heterogeneity between studies and the lack of adjustment for critical confounders limits the generalizability of these findings.

At baseline, we found that the combination of obesity and poor strength was strongly and significantly associated with VTE. Confirming the cross-sectional findings, we found that obesity with or without poor muscle strength was an independent risk factor for new VTE development over a 6-year follow-up. Although previous VTE was by far the strongest predictor of new events, this association was significantly modulated by the presence of obesity and poor muscle strength. The coexistence of obesity and poor strength with previous VTE increased the risk of developing new VTE up to 15 times. By contrast, previous VTE did not appear to predict new VTE among lean participants with normal strength. These findings strongly suggest that elderly patients affected by sarcopenic obesity should receive education for VTE prevention, and those with a previous VTE probably be considered for long-term prophylaxis (27).

The pathogenesis of VTE has been historically related to the Virchow's triad of stasis, changes in the vessel wall, and prothrombotic changes in the blood. The higher risk of developing VTE observed in individuals with obesity with poor muscle strength as well as in those with lower extremity performance could be, at least partly, accounted by a less efficient pumping function of lower extremity muscles on the venous system. Although the slowing down of the venous blood flow may be an important aspect, venous stasis alone is usually not considered a sufficient factor in the genesis of thrombosis but rather regarded as a permissive factor in thrombogenesis. Accordingly, poor strength alone was not predictive of thrombosis. The high circulating prothrombotic factors and impaired fibrinolysis (28) as well as the chronic, low-grade inflammation that accompanies obesity in particular when associated with poor strength may contribute to a prothrombotic state and trigger the development of venous thrombosis (28,29). In a recent prospective cohort study of 4,859 participants 65-year old and older, frailty was associated with an increased risk of idiopathic, not total, VTE after adjustment for confounders such as body mass index (21). Poor muscle strength was one of the elements considered in the definition of frailty that included also weight loss, feelings of exhaustion, walk time, and physical activity. Taken together, these data suggest that poor muscle strength is more a contributor than a determinant of thrombosis within a vulnerable subset of older adults.

Confirming previous observations, we found that hospitalization and trauma are independent risk factors for venous thromboembolic events (4). Surprisingly, cancer was not significantly associated with a higher risk of thrombosis, which may be due to the relative low number of cancer patients included in this study. We did not have enough data to fully characterize whether participants with missing information were more ill or disabled. It is likely that participants with overt cancer were unable to provide complete data that could explain the lack of association between cancer and VTE.

Some limitations of the present study need to be acknowledged. In the definition of poor muscle strength, we used the sex-specific knee extension strength that mainly reflects the strength of the quadriceps. However, the quadriceps may not be the critical muscles in the pathogenesis of VTE. In addition, the associations observed at baseline suffer from the inherent limitations of cross-sectional analyses. Although a causal pathway with VTE occurring time before the development of obesity with poor muscle strength cannot be completely excluded, the associations were confirmed in longitudinal analysis both for obesity, poor muscle strength, and physical functional tests.

Because of the limited size of the population investigated, we were unable to precisely identify cutoffs of physical function tests that best predict the risk of thrombosis, and further studies are needed to verify the level of physical impairment that may warrant thromboprophylaxis. Finally, the relevance of risk factors such as hospitalization or traumas remains difficult to establish because data on such events were recorded retrospectively and the adequateness of the prophylaxis could not be ascertained with precision in some cases. Therefore, the estimated risk for VTE has to be taken with caution.

In conclusion, obesity with or without poor muscle strength is a significant risk factor for VTE among older persons. These age-related features significantly amplify the risk associated with a positive history of VTE. VTE is a major cause of morbidity among the elderly, and the dramatic increase of the prevalence of obesity in Western countries and an increasingly obese elderly population will undoubtedly place a growing burden on the Health Care Systems (30). Additional studies are warranted to confirm these findings and consider the possibility of prophylaxis in these groups.

Funding

Italian Ministry of Health and in part by the U.S. National Institute on Aging (Contracts 263_MD_9164_13 and 263_MD_821336) to the InCHIANTI Study (ICS 110.1/RS97.71), Intramural Research Program, National Institute on Aging, National Institutes of Health, USA.

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