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Mild thyroid hormone excess is associated with a decreased physical function in elderly men

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Abstract

Introduction—In the adult, subclinical hyperthyroidism (Shyper) may alter skeletal muscle mass and strength. However, whether these effects are present in elderly subjects is not known. We explored the relationship between mild hyperthyroidism and physical function in a population-based sample of older persons.

Methods—In a cross-sectional analysis, calf muscle cross-sectional area (CMA), handgrip strength, nerve conduction velocity (NCV), and Short Physical Performance Battery (SPPB) scores were compared between 364 euthyroid (Eut) and 28 Shyper men as well as between 502 Eut and 39 Shyper women. In a longitudinal analysis, we evaluated the relationship between baseline plasma TSH, FT3 and FT4 and the 3-year change in SPPB score in 304 men and 409 women who were euthyroid at enrolment.

Results—At the cross-sectional analysis, Shyper men, but not women, had a significantly ($p = 0.02$) lower SPPB score than Eut controls, although with comparable CMA, grip strength and NCV, and were more likely to have poor physical performance (odds ratio = 2.97, $p < 0.05$).

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Longitudinal analysis showed that in Eut men higher baseline FT4 was significantly ($p=0.02$) predictive of a lower SPPB score at the 3-year follow-up.

Conclusion—Even a modest thyroid hormone excess is associated with a reduced physical function in elderly men.

Keywords

Subclinical hyperthyroidism; physical function; elderly male

Introduction

With the aging of the population, the number of individuals with functional impairments and disability has increased substantially with important consequences on health care resources utilization [1]. Mobility and functional autonomy require integrated functioning and anatomical integrity of many physiological systems, including central nervous system, peripheral nervous system and muscle. Impairments in these systems often emerge with aging and are considered by some as unavoidable consequences of aging. There is evidence that impairment in the physiological systems that are important for mobility may result from age-related changes in hormonal levels and the emergence of subclinical endocrine dysfunctions [2,3]. Altered thyroid function, especially subclinical, is perhaps the most frequent endocrine abnormality that occurs in older individuals [4,5]. In the adult, both overt and subclinical hyperthyroidism are associated with a decreased skeletal muscle mass and strength [6] a major determinant of frailty and disability in older individuals [7]. Thus, it is reasonable to hypothesize that elevated thyroid hormone concentrations may have a negative effect on physical performance, particularly in susceptible individuals such as older patients. However, whether a direct relationship exists between thyroid dysfunction and physical function in older persons is still a matter of debate. Using data from the Aging in the Chianti Area (InCHIANTI) study, an epidemiological study conducted on a population-based sample of persons living in the Chianti geographical area (Tuscany, Italy), we evaluated the hypothesis that subclinical hyperthyroidism is cross-sectionally associated with an impairment of physical function in older individuals, independent of potential confounders. In addition, based on literature reports demonstrating that within the normal range of thyroid parameters, persons with high-normal thyroid function are at an increased risk of adverse clinical outcome [8], we evaluated whether in euthyroid individuals, low-normal thyrotropin and/or high-normal free triiodothyronine and free thyroxine plasma concentrations were associated with high risk of accelerated decline of physical performance over a 3-year follow-up.

Methods

Study participants consisted of men and women, aged 65 and older, who participated in the Invecchiare in Chianti, “Aging in the Chianti Area” (InCHIANTI) study, conducted in two small towns in Tuscany, Italy. The main outcome of this longitudinal study is mobility disability and the rationale, design, and data collection have been described elsewhere [9]. Briefly, in August 1998, 1270 persons aged 65 years and older were randomly selected from the population registry of Greve in Chianti (population 11,709) and Bagno a Ripoli (pop.

4704), and of 1256 eligible subjects, 1155 (90.1%) agreed to participate. Participants received an extensive description of the study and participated after written, informed consent. Of the 1155 participants 65 years old seen at enrolment, 1055 (91.3%) consented to donate a blood sample. Thyroid hormones levels were assessed at baseline in all participants from fasting blood samples. In particular, there were 951 (82.4%) participants at enrolment who had complete data on circulating levels of free thyroxine (FT4), free triiodothyronine (FT3), and thyrotropin (TSH). In addition, most participants received a comprehensive assessment of lower extremity performance, which was repeated after three year of follow-up. Subjects who did not participate in the blood drawing were generally older and had greater comorbidity than those who participated in the blood drawing, as reported elsewhere [10]. We excluded from analyses subjects who were under treatment with dopaminergic agonists or antagonists (N.4 subjects), glucocorticoids (N. 5 subjects), lithium (N. 1 subject), amiodarone (N.4 subjects). Subjects with goitre at physical examination were included in the analyses. 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.

Measures of muscle status

After the home interview, participants received a full standardized medical and functional evaluation performed by, respectively, a geriatrician and an experienced physical therapist, both of whom had received special training on the assessment tools used in this study. The objective assessment of physical function was performed within 4 weeks after the interview in a dedicated laboratory. In particular, isometric grip strength was assessed by a hand-held dynamometer using a standard protocol [11]. We selected the handgrip as measure of strength for the present analysis because the assessment of handgrip is easy, reliable, and inexpensive. Furthermore, there is strong evidence in the literature that handgrip is a strong predictor of disability and mortality [12, 13]. A lower leg peripheral quantitative computerized tomography (pQCT) was performed in all participants by means of a recent generation device (XCT 2000, Stratec, Pforzheim, Germany) to evaluate calf muscle cross-sectional area. Data presented here were derived from standard 2.5-mm-thick transverse scans obtained at 66% of the tibia length, proximal to the anatomic marker. Previous studies demonstrated that this is the region with the largest outer calf diameter, with little variability across individuals [14]. The total dose of radiation administered to the participants was less than 1 mrem. The cross-sectional images obtained from the pQCT were analyzed by using the BonAlyse software (BonAlyse, Jyväskylä, Finland; <http://www.bonalyse.com>). Different tissues were separated according to different density thresholds: a density value of 35 mg/mm³ was used to separate fat from muscle tissue, and 180 mg/mm³ to separate muscle from bone tissue.

Measures of physical performance

Lower extremity function was assessed by the Summary Physical Performance Battery (SPPB) score which includes three simple tests: a measure of standing balance, the 4-m walking speed, and the ability to rise from a chair that have previously been described in detail 14. For each of these three physical performance tests, participants received a score from 0 to 4, with a value of 0 indicating the inability to complete the test and 4 the highest

level of performance [15]. The values were summed to create a total score ranging from 0 to 12 with higher scores representing better performance. Previous studies have demonstrated that older, nondisabled persons with a low score are at high risk of developing disability [15]. The validity of this scale has been demonstrated in analyses showing a gradient of risk of admission to a nursing home and mortality along the full range of the scale [14]. The subjects included in these analyses had summary scores ranging from 3 to 12 [14].

Standard surface electroneurographic (ENG) studies of the right peroneal nerve were conducted within 3 weeks of the home interview by a trained geriatrician. Details on the ENG technique used in InCHIANTI is referred elsewhere [16]. The parameter of nerve conduction studies considered in the analysis was the nerve conduction velocity (NCV [17]). Depressive symptoms were assessed with the 20-item Center for Epidemiologic Studies-Depression (CES-D) Scale [18].

Laboratory measures

Blood samples were collected in the morning after a 12-h fast. Aliquots of serum and plasma were obtained within three hours and stored at -80°C . Plasma concentrations of TSH, free triiodothyronine (FT3), and free thyroxine (FT4) were measured using a chemiluminescent immunoassay (Vitros Reagent, Ortho-Clinical Diagnostics, Johnson & Johnson Medical Section, Milan, Italy). Assay sensitivities were 0.003 mIU/L for TSH, 0.39 pg/mL for FT3, and 0.03 ng/dL for FT4. Intra-assay coefficient of variations (CVs) were 3.9–5.3% over the range 0.06–80.11 mIU/L for TSH, 4.4–5.1% over the range 2.86–11.90 pg/mL for FT3, and 4.5–5.3% over the range 0.61–3.90 ng/dL for FT4. Interassay CVs were less than 9% for all three hormones.

Definition of thyroid function

Thyroid function was classified in all participants, according to TSH and free thyroid hormone concentrations. Euthyroidism was defined by plasma TSH concentrations within the reference normal range (0.46–4.68 mIU/L). Subclinical hyperthyroidism was defined by plasma TSH concentrations <0.46 mIU/L with in-range concentrations of both FT3 (2.77–5.27 pg/mL) and FT4 (0.77–2.19 ng/dl). Subjects with low-T3 syndrome or non-thyroidal illness (FT3 <2.77 pg/mL with normal FT4 and TSH or FT3 <2.77 and FT4 <0.77 and normal TSH) (N. 4 subjects) were excluded from analyses.

Other covariates

Information on demographics, smoking and use of medication were collected by a standardized questionnaire. Average daily intake of energy (kcal) and type of nutrition were estimated using the European Prospective Investigation into Cancer and Nutrition food frequency questionnaire, validated in the InCHIANTI population [19]. Diseases were ascertained according to standard, pre-established criteria and algorithms that combine information from self-reported physician diagnoses, current pharmacological treatment, medical records, clinical examinations and blood tests [20]. Diseases included in the current analysis were congestive heart failure, stroke, diabetes, hypertension, and Parkinson's disease.

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). Based on self-report information, the level of physical activity in the year prior to the interview was coded as 1) hardly any physical activity; 2) mostly sitting (occasionally walks, easy gardening); 3) light exercise (no sweat) 2–4h/week; 4) moderate exercise (sweat) 1–2h/week (level 4); 5) moderate exercise >3h/week; 6) intense exercise (at the limits) >3 times/week. For analytical purposes, we grouped participants into three levels: (1–3) inactive or light physical activity; (4–5) moderate physical activity; and (6) intense activity. Smoking was coded in the analysis as “current smoking” versus “ever smoked” or “never smoked.” Education was recorded as years in school.

Statistical analysis

Variables are reported as means $\pm$ standard deviations for normally distributed parameters or as percentages. Median and Interquartile (IQ) (Q1–Q3) is reported for variables with a skewed distribution. Logistic regression analysis was used to examine the baseline cross-sectional association between subclinical hyperthyroidism and impaired mobility denoted as a SPPB score ≥ 9 [21], after adjusting for age, sex and multiple potential confounders. Selecting euthyroid participants at enrolment, linear regression models were used to examine the association between baseline circulating levels of FT4, FT3 and TSH and SPPB score at the 3-year follow-up, after adjusting for confounders including baseline SPPB score. All analyses were performed using SAS (version 8.2, SAS Institute, Inc., Cary, NC) with a statistical significance level set at $p = 0.05$.

Results

The general characteristics of the population at the enrolment are shown in Tables 1 and 2. Overall, 392 male and 541 female participants were eligible for the study. Of these, 28 males and 39 females had subclinical hyperthyroidism (Shyper). Among men, but not among women, participants with Shyper were significantly older than those who were euthyroid (Eut). Overall, N 163 (18.8%) of euthyroid and N. 16 (23.9%) of subclinically hyperthyroid subjects were under treatment with acetylsalicylic acid with no statistical difference ($p = 0.82$) between groups.

Cross-sectional relationship between subclinical hyperthyroidism and measures of physical performance.

Calf muscle cross-sectional area and grip strength were comparable, in both sexes, between Shyper and Eut subjects. In men, but not women, levels of physical activity were significantly ($p < 0.05$) higher in Eut than in Shyper subjects. No differences were demonstrated in NCV values between Eut and Shyper men while a slight, though significant lower NCV values were found in Shyper compared to Eut women. In men, the SPPB score was significantly ($p < 0.02$) reduced in Shyper as compared to Eut subjects whereas no significant differences were found in the SPPB score between Eut and Shyper women. There was no difference in CES-D score between Eut and Shyper subjects in either sexes. The proportion of subjects affected by major diseases, such as congestive heart failure, Parkinson's disease and stroke was also comparable between groups in both sexes.

Men affected by Shyper were almost three-fold more likely (OR = 2.97; 95% confidence interval 1.01–8.71) to have impaired mobility, than those who were euthyroid (Table 3) while no significant relationship between Shyper and lower extremity function was found in women.

Longitudinal evaluation of the relationship between plasma thyroid hormone concentrations and physical performance.

In the longitudinal analysis we studied the relationships between circulating concentrations of TSH, FT3 and FT4 in subjects who were euthyroid at the enrolment and changes in lower extremity function over a 3-year follow-up. Among male participants, 38 died and 22 refused to participate at the 3-year follow-up, leaving 304 men for this analysis. Among female participants, 44 died and 49 refused to participate at the 3-year follow-up, leaving 409 women for this analysis.

In men, high plasma FT4 concentrations at the enrolment, although within the normal range, were associated with steeper decline of SPPB at the 3-year follow-up, after adjusting for SPPB at enrolment and other confounders (Table 4). Neither TSH nor FT3 plasma concentrations at the enrolment were predictive of differential changes in SPPB over the 3-year follow-up.

In women, we found no relationships between baseline circulating concentrations of either thyroid hormones or TSH and SPPB score at the 3-year follow-up (data not shown).

Discussion

The findings of this study suggests that subclinical hyperthyroidism is associated with a reduced physical function, as demonstrated by the poor lower extremity performance, in older community-dwelling men. In the adult, both overt and subclinical hyperthyroidism have been shown to cause a reduction of muscle mass and strength which improve after treatment [6]. Thus, it is reasonable to hypothesize that thyroid hormone excess may negatively affect physical function through its detrimental effects on muscle mass and/or strenght, especially in older persons who already tend to have reduced lean body mass. Gussekloo and co-workers did not find any relationship between circulating concentrations of thyrotropin and performance in elderly subjects, although low levels of T3 were associated with poor functional outcomes [22]. Other Authors demonstrated that higher FT4 and reverse T3 concentrations are associated with a lower physical function in elderly men [23].

Since subclinical hyperthyroidism has been associated with a reduction of muscle mass and strength in the adult [5] and since reduced strength is a strong predictor of accelerated decline of lower extremity performance, we expected that the subclinical hyperthyroidism-associated decline in physical performance observed in older men, would be associated with a reduction in muscle mass and strength. However, we did not find any difference between subclinical hyperthyroidism and euthyroidism of either muscle mass or muscle strength in our study sample. These findings suggest that the mechanism for the effect of subclinical hyperthyroidism on physical performance is not a direct effect on skeletal muscle. One

possible alternative explanation is that the effect of subclinical hyperthyroidism on physical performance may be mediated by damage in the central nervous system. There is some evidence that excess of thyroid hormone may damage neurons through an increase in oxidative stress and eventually lead to apoptosis and neuronal death [24,25]. Also, a hyperthyroidism-induced reduction in TRH secretion may lead to an impairment of brain acetylcholine metabolism, since TRH has been shown to increase local acetylcholine synthesis and release [26]. In agreement with this hypothesis, we and others recently demonstrated that subclinical hyperthyroidism affects cognitive decline [4,27].

It has been reported that high-normal thyroid function is associated with the risk of developing adverse clinical outcomes, such as atrial fibrillation, in euthyroid elderly subjects [8]. Therefore we evaluated whether euthyroid subjects with low TSH and/or high FT3 and/or FT4 at baseline had an increased risk of developing a decline of lower extremity performance at the 3-year follow-up. We found that among male participants with baseline euthyroidism, high baseline FT4 plasma concentrations were predictive of a steeper SPPB decline over the 3-year follow-up. Although we did not measure reverse T3 in our samples, we considered those subjects who, at the enrolment, had plasma FT3 concentrations below normal values and normal FT4 and TSH, as affected by low-T3 syndrome and excluded them from analyses. For this reason we believe that the association between high FT4 at the enrolment and the decline in SPPB score at 3 years, is unlikely to be due to a baseline low-T3 syndrome. Contrary to what we demonstrated for FT4, no relationship was found between baseline plasma TSH concentrations and 3-year SPPB. This phenomenon could be due, at least in part, to the well known age-related subtle abnormalities in TSH secretion [28] which may result in a variability of plasma TSH concentrations, especially for values within the normal reference range, in our sample size of euthyroid subjects. Moreover, the fact that in euthyroid subjects high FT4, but not TSH, may correlate with some clinical outcome is not a unique finding. For example, Gammage and co-workers demonstrated that atrial fibrillation is independently associated with circulating FT4 concentrations even in euthyroid subjects with normal serum TSH levels [29].

Our data are consistent with the absence of any significant relationships between CHF and the risk of having impaired mobility. One possible explanation for this phenomenon is that the presence of heart failure and diseases were ascertained according to standard, pre-established criteria and algorithms based upon those used in the Women's Health and Aging Study for coronary heart disease, congestive heart failure, peripheral artery diseases, diabetes mellitus, chronic obstructive pulmonary disease, and osteoarthritis recording [20]. This algorithm, however, does not take into account the heart ultrasound parameters and this might have led to a not complete evaluation of the heart failure.

Data on circulating antithyroid antibodies were not available in this study. Autoimmune thyroid disease maybe associated to CNS disorders [30,31] and this could have negative consequences on physical function. Therefore we can not address the question on whether thyroid autoimmunity or autoimmune-associated CNS disease may be involved in the loss of physical function we observed in our subclinically hyperthyroid subjects. However, because the population examined in this study resides in an area that is generally considered moderately iodine deficient [32,33], it can be speculated that a significant proportion of

subjects with subclinical hyperthyroidism in this population may have thyroid nodular disease and associated thyrotoxicosis, rather than autoimmune hyperthyroidism.

We did not observe any association between thyroid hormone excess and abnormalities of physical function in women. We have no direct explanation for this finding. However, in agreement with other literature reports [34], our data demonstrated that SPPB score was lower in women than in men. It could therefore be hypothesized that the negative effect of subclinical hyperthyroidism on physical performance is no longer detectable in the lower portion of the SPPB spectrum (at least, lower than that we observed in our euthyroid men). In this perspective, a SPPB cut-off lower than that we used in the present study might be more sensitive for defining, in cross-sectional analyses, the poor physical function in women. Furthermore, a sexual dimorphism has been shown for some hyperthyroidism-associated clinical pictures. For example, in a recent study on older hyperthyroid subjects Boalert and coworkers have demonstrated that women are less likely to have atrial fibrillation than men [35].

According to our data, diabetes seems to influence the development of impaired mobility in women, but not men. Our results do not provide a clear explanation for this phenomenon. However, the total number of subjects affected by diabetes, on the total number of 955 subjects, was 79 (40 men and 39 women). Because of this low number of subjects we believe that the statistical power for the association between diabetes and impaired mobility is low and this may be taken into consideration when explaining the sex-related difference in these data.

The absence of a second determination of circulating concentrations of TSH represents a limitation of this study, and we can not rule out the possibility that only transient changes in TSH levels might have occurred in some patients. Another important limitation of these study is represented by the absence of information on aetiology of sub clinical hyperthyroidism.

In conclusion, in our population of independently living elderly men, even a moderate thyroid hormone excess is associated with a reduced lower extremity function. Our subclinically hyperthyroid men had a reduced SPPB score but both muscle mass and strength were comparable with those of euthyroid subjects. These findings suggest that subclinical hyperthyroidism is linked to reduced physical function through a mechanism other than a detrimental effect on muscle strength. Future studies should address the question on whether subclinical hyperthyroidism produces the same adverse effect on physical function in both men and women and should test the hypothesis that excess thyroid hormone concentration causes damage in the central control of movement.

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Table I

General characteristics of male participants at enrolment (n=392).

Characteristic	Euthyroidism ((n = 364 (92.9%))	Subclinical hyperthyroidism ((n = 28 (7.1%))	P*
Age (years) ^I	74.43 (6.92)	73.95 (6.68)	<0.001
Physical activity			0.05
Sedentary/light n (%)	49 (13.6)	7 (25.7)	
Moderate n (%)	282 (77.8)	19 (68.6)	
High n (%)	33 (8.6)	2 (5.7)	
CSAM (mm ²)	6855.6 (1242.2)	6778.3 (992.2)	0.37
Grip strength (kg) ^I	37.30 (10.7)	40.6 (9.94)	0.17
SPPB score ^I	10.5 (2.7)	9.5 (4.3)	0.02
Nerve conduction velocity (m/sec) ^I	42.48 (3.72)	42.03 (3.98)	0.46
CES-D score ^I	8 [5–13]	8 [5–12]	0.73
Congestive heart failure n (%)	18(5)	2 (5.7)	0.78
Parkinson's disease n (%)	7 (1.9)	0	—
Stroke n (%)	24 (6.67)	2 (7.0)	0.91
Alcohol intake (g/day)	20 [10–31]	20 [10–31]	0.07
Diabetes n (%)	8 (2.2)	3(1.1)	0.78

^I Mean (SD) for continuous variables or median [interquartile range]; CSAM, cross-sectional muscle area.

* From age-adjusted linear or logistic regression models, as appropriate.

Table II

General characteristics of female participants at enrolment (n = 541).

Characteristic	Euthyroidism (n = 502 (92.8%))	Subclinical hyperthyroidism (n = 39 (7.2%))	P*
Age (years) ^I	76.1 (7.6)	77.1 (8.7)	0.41
Physical activity			0.48
Sedentary/light n (%)	27.0%	31.2%	
Moderate n (%)	70.6%	66.7%	
High n (%)	2.4%	2.1%	
CSMA (mm ²)	5494.7 (956.6)	5451.4(1137.0)	0.86
Grip strength (kg) ^I	21.9 (7.5)	19.7 (8.3)	0.22
SPPB score ^I	9.2 (3.4)	8.6 (3.9)	0.21
Nerve conduction velocity (m/sec) ^I	45.0 (3.5)	43.7 (5.1)	0.03
CES-D Score ^I	13 [8–21]	12 [7–18.5]	0.16
Congestive heart failure n (%)	18.5%	22.9%	0.60
Parkinson's disease n (%)	0.9%	2.1%	0.79
Stroke n (%)	6.4%	6.2%	0.41
Alcohol intake (g/day)	8.5 [4.3–10.0]	5 [4.3–10.0]	0.43
Diabetes n (%)	62 (12.)	5 (11–4)	0.87

^I Mean (SD) for continuous variables or median [interquartile range]; CSMA, cross-sectional muscle area.

* From age-adjusted linear or logistic regression models, as appropriate.

Table III

Logistic regression analysis relating subclinical hyperthyroidism to the risk of having impaired mobility (defined by SPPB = 9).

Characteristic	HR	95% CI	P
Men			
Model 1			
Subclinical hyperthyroidism vs. euthyroidism	2.60	1.01–6.98	0.047
Age (years)	1.18	1.13–1.22	<0.001
Model 2			
Subclinical hyperthyroidism vs. euthyroidism	2.99	1.01–8.74	0.048
Age (years)	1.17	1.12–1.23	<0.001
Physical activity	0.01	0.05–0.21	<0.001
Nerve conduction velocity	0.95	0.87–1.03	0.22
Congestive heart failure	0.98	0.67–1.45	0.94
Diabetes	1.12	0.99–1.28	0.07
Stroke	1.80	1.01–3.23	0.04
Parkinson's disease	0.53	0.10–2.63	0.44
Alcohol intake	1.06	0.98–1.02	0.51
Women			
Model 1			
Subclinical Hyperthyroidism vs. euthyroidism	1.76	0.79–3.95	0.16
Age (years)	1.20	1.16–1.25	<0.0001
Model 2			
Subclinical Hyperthyroidism vs. euthyroidism	1.38	0.44–4.26	0.58
Age (years)	1.18	1.12–1.23	<0.0001
Physical activity	0.37	0.20–0.68	0.001
Nerve conduction velocity	0.96	0.89–1.04	0.37
Congestive heart failure	1.20	0.80–1.71	0.31
Diabetes	1.16	1.04–1.29	0.008
Stroke	1.50	0.83–2.74	0.18
Parkinson's disease	2.54	0.82–7.79	0.10
Alcohol intake	0.99	0.94–1.04	0.64

Table IV

Backward regression models* relating SPPB over 3-year follow-up and baseline FT4, after adjusting for baseline SPPB, in men who were euthyroid at enrolment.

FT4 (Over 3-year follow-up, <i>n</i> = 304)			
Characteristic	Beta	SE	<i>P</i>
Model 1			
FT4	−1.25	0.44	0.005
Model 2			
FT4	−1.01	0.43	0.02

* Model 1: adjusted for age and SPPB at enrolment; Model 2: adjusted for age, SPPB at enrolment, physical activity, nerve conduction velocity, stroke, Parkinson's disease, diabetes, and congestive heart failure.