



UNIVERSITÀ  
DEGLI STUDI  
FIRENZE

FLORE

## Repository istituzionale dell'Università degli Studi di Firenze

### **Subtle neurological abnormalities as risk factors for cognitive and functional decline, cerebrovascular events, and mortality in older**

Questa è la Versione finale referata (Post print/Accepted manuscript) della seguente pubblicazione:

*Original Citation:*

Subtle neurological abnormalities as risk factors for cognitive and functional decline, cerebrovascular events, and mortality in older community-dwelling adults / M.Inzitari; C.Pozzi; L.Ferrucci; D.Chiarantini; L.Rinaldi; M.Baccini;R.Pini;G.Masotti;N.Marchionni;M.Di Bari. - In: ARCHIVES OF INTERNAL MEDICINE. - ISSN 0003-9926. - STAMPA. - 168:(2008), pp. 1270-1276.

*Availability:*

This version is available at: 2158/316773 since: 2019-07-08T15:46:58Z

*Terms of use:*

Open Access

La pubblicazione è resa disponibile sotto le norme e i termini della licenza di deposito, secondo quanto stabilito dalla Policy per l'accesso aperto dell'Università degli Studi di Firenze (<https://www.sba.unifi.it/upload/policy-oa-2016-1.pdf>)

*Publisher copyright claim:*

(Article begins on next page)

# Subtle Neurological Abnormalities as Risk Factors for Cognitive and Functional Decline, Cerebrovascular Events, and Mortality in Older Community-Dwelling Adults

Marco Inzitari, MD; Claudia Pozzi, MD; Luigi Ferrucci, MD, PhD; Daniela Chiarantini, MD; Lucio A. Rinaldi, PT; Marco Baccini, PT; Riccardo Pini, MD; Giulio Masotti, MD; Niccolò Marchionni, MD; Mauro Di Bari, MD, PhD

**Background:** Subtle, but clinically detectable, neurological abnormalities (SNAs) are associated with impaired physical performance in elderly persons without overt neurological diseases. We investigated whether SNAs were prospectively associated with cognitive and functional status, death, and cerebrovascular events (CVEs) in older community-dwelling individuals.

**Methods:** In participants without history of stroke, parkinsonism and dementia, or cognitive impairment, a score ( $N_{\text{SNA}}$ ) was obtained by summing SNAs detected with a simple neurological examination. Cognitive status and disability were reassessed 4 years later, and deaths and CVEs were documented over 8 years.

**Results:** Of 506 participants free of neurological diseases (mean [SEM] age, 71.9 [0.3] years; 42% were men), 59% had an  $N_{\text{SNA}}$  of 1 or more (mean [SEM], 1.1 [0.06]; range, 0-8). At baseline, the  $N_{\text{SNA}}$  increased with age and with declining cognitive and physical performance, depressive symptoms, and disability, after adjusting for sev-

eral covariates, but did not increase with falls and urinary incontinence. The  $N_{\text{SNA}}$  prospectively predicted worsening cognitive status and disability, adjusting for demographics and for baseline comorbidity and cognitive and physical performance. The mortality rates were 22.6, 23.3, 23.9, 58.6, and 91.9 per 1000 person-years in participants with an  $N_{\text{SNA}}$  of 0, 1, 2, 3, and 4 or higher, respectively. Compared with an  $N_{\text{SNA}}$  of less than 3, having an  $N_{\text{SNA}}$  of 3 or higher was associated with an increased adjusted risk of death (hazard ratio, 1.77; 95% confidence interval [CI], 1.25-2.74) and of CVE (hazard ratio, 1.94; 95% CI, 1.07-3.54) over 8 years.

**Conclusion:** In this sample of older community-dwelling persons without overt neurological diseases, multiple SNAs were associated with cognitive and functional decline and independently predicted mortality and CVEs.

*Arch Intern Med.* 2008;168(12):1270-1276

## Author Affiliations:

Department of Critical Care Medicine and Surgery, Unit of Gerontology and Geriatrics, University of Florence and Azienda Ospedaliero-Universitaria Careggi, Florence, Italy (Drs Inzitari, Pozzi, Chiarantini, Pini, Masotti, Marchionni, and Di Bari and Mr Rinaldi); Longitudinal Studies Section, Clinical Research Branch, National Institute on Aging, Baltimore, Maryland (Dr Ferrucci); and Unit of Geriatric Rehabilitation, Azienda Sanitaria Locale, 10, Florence (Mr Baccini).

**S**TUDIES OF APPARENTLY healthy, older community-dwelling persons have shown that subclinical diseases of different organs are associated with poor physical performance<sup>1,2</sup> and frailty.<sup>3</sup> In the Cardiovascular Health Study (CHS),<sup>4</sup> a lower extent of subclinical cardiovascular disease predicted successful aging, defined as the years lived without physical and cognitive impairment, overt cardiovascular disease, cancer, and chronic obstructive pulmonary disease.

In further CHS analyses, the severity of neurological disease at neuroimaging predicted accelerated functional decline and onset of physical dependency.<sup>5</sup> Also subtle, but clinically detectable, neurological abnormalities (SNAs) seemed to be associated with poor physical performance and

falls in a cross-sectional investigation of 818 older community-dwelling persons without major neurological diseases.<sup>6</sup> However, to our knowledge, no study has ever investigated whether SNAs independently predict poor health outcomes in older persons.

## For editorial comment see page 1252

We evaluated whether SNAs are associated, both cross-sectionally and longitudinally, with reduced cognitive and functional status and falls in older persons free of overt neurological diseases. We also tested the association between SNAs and urinary incontinence, which may be an early manifestation of subclinical neurological disease.<sup>7</sup> Finally, we verified whether SNAs in-

**Table 1. Prevalence of SNAs and Their Bivariate Associations With Physical Performance (SPPB Score) and Cognitive Function (MMSE) in 506 Older Community-Dwelling Persons**

Items of the Neurological Evaluation	Prevalence, %	P Value <sup>a</sup>	
		SPPB	MMSE
Muscle strength—physical examination			
Reduced shoulder elevation, detectable difference between the 2 sides while participant is shrugging against resistance	0.4	.02	.21
Reduced or absent foot extension, detectable difference between the 2 sides while participant is pushing against resistance (each foot is tested separately)	3.0	<.001	.11
Pronator drift or shift of 1 arm while both are extended frontally	0.6	.01	.42
Shift of 1 leg while both hips and knees are flexed at 90° in the supine position	0.0	NA	NA
Muscle strength—dynamometry (difference of >20% between the 2 sides)			
Handgrip	4.9	.11	.16
Hip flexion	11.3	.66	.49
Sensitivity—physical examination, reduced foot plant sensitivity (light touch) in at least 2 of 3 tests	4.3	<.001	.95
Deep tendon reflexes, absent or diminished (present but slightly detectable) muscle contraction in response to tendon stimulation with a reflex hammer using standard techniques			
Absent or reduced patellar reflexes	3.0	.03	.64
Absent or reduced Achilles reflexes	29.9	.002	.01
Plantar (Babinski) reflex, extension of the big toe or fanning of the other toes or contraction of the fascia lata while rubbing the lateral margin of the sole from heel to toe	3.6	.09	.83
Extrapyramidal signs			
Bradykinesia, slowness, reduction in amplitude or arrest during thumb-finger tapping, hand movements (opening-closing, pronosupination), heel tapping, or arising from a chair	0.2	.14	.01
Resting tremor while the participant is relaxed, with both hands resting in the lap	3.6	.02	.01
Muscle rigidity, steady resistance throughout the entire range of movement at passive rotation of the neck and flexion and extension of elbows and knees	2.4	<.001	.001
Postural instability—retropulsion at the pull test	20.0	.02	.01
Superior functions			
Frontal lobe function (Purdue Pegboard Test)—dominant hand	9.1	<.001	<.001

Abbreviations: MMSE, Mini-Mental State Examination; NA, not applicable; SNAs, subtle neurological abnormalities; SPPB, Short Physical Performance Battery. <sup>a</sup>P values indicate significant differences in mean SPPB and mean MMSE between participants with and without each specific subtle neurological abnormality.

independently predict mortality and incident cerebrovascular events (CVEs) over an extended follow-up.

## METHODS

### STUDY PROTOCOL AND SAMPLE SELECTION

The “Insufficienza Cardiaca negli Anziani Residenti a Dicomano” (ICARe Dicomano) study enrolled all the older (≥65 years) community-dwelling individuals living in Dicomano, a small rural town near Florence, Italy. The methods of the study, which followed the principles of the Declaration of Helsinki, have been detailed elsewhere.<sup>8</sup> Participants gave informed consent. Adherence rates ranged from 91.2% to 80.7% in different phases of the study. Participants and nonparticipants had similar sex and age distribution, although slightly fewer men (77.4%) than women (83.1%) underwent the final clinical assessment.<sup>8</sup> From the 1995 baseline study sample, we excluded participants with previous stroke, parkinsonism, dementia, or cognitive impairment. Participants were reinterviewed in 1999. Vital status and hospitalizations were followed up until December 2003.

### DATA COLLECTION

#### Diagnosis of Overt Neurological Disease

Neurological diseases were identified with standardized algorithms based on previous diagnoses, medical records, structured medical interviews, and clinical examinations.<sup>8</sup> The diagnosis of stroke was adjudicated when a previous diagnosis

or positive questionnaire items (deficit in strength in an upper and/or lower extremity, speech, or visual field) were confirmed by hospital discharge records, neuroimaging, or clinical examination. The diagnosis of Parkinson disease or parkinsonism was based on clinical examination or a previous physician’s diagnosis in current specific drug treatment. Participants who scored 26 or less on the Mini-Mental State Examination (MMSE)<sup>9</sup> received an extensive neuropsychological evaluation by an expert geriatrician, who adjudicated the final diagnosis of dementia. Conservatively, in the present study we also excluded participants with cognitive impairment (MMSE score <24) who refused or missed the complete neuropsychological evaluation necessary to diagnose dementia.

#### Neurological Clinical Evaluation

The neurological assessment, conducted by expert geriatricians and summarized in **Table 1**, required up to 15 minutes and included a traditional neurological examination plus 2 simple tests (ie, dynamometry and the Purdue Pegboard Test).<sup>8</sup> Handgrip and hip flexion strength were assessed on both the right and left sides with handheld dynamometers, according to a standard protocol.<sup>10</sup> Consistent with published criteria for lower extremity strength testing,<sup>10</sup> clinically relevant asymmetry for handgrip strength was defined as a difference of more than 20% between the 2 sides. In the Purdue Pegboard Test, participants are timed while putting 10 small sticks into an equal number of holes in a tablet. Originally introduced to evaluate manual dexterity,<sup>11</sup> this test also explores frontal lobe cognitive function because it requires integrity of attention, sequencing, planning, and motor coordination. We used the score obtained with the dominant hand.

Failure to complete the task, or a time to complete above the 90th percentile of the study sample, indicated an altered performance. The reliability of the neurological examination had been previously evaluated in a small sample of older outpatients with characteristics similar to participants in the present survey. For the standard neurological examination, interrater agreement in the distinction between normal vs abnormal findings was very high ( $\kappa > 0.95$ ). Other items, based on continuous measures (eg, muscle strength) initially reported greater variability, which, after training and standardization, was contained to an interrater difference of 10% to 15%.

To obtain a final score of neurological damage, we calculated, for each participant, the number of SNAs ( $N_{SNA}$ ) detected with the neurological examination (defined as "subtle" because they neither related to definite neurological diseases nor were reported by the participants).

### Covariates

**Functional Status.** Functional status was measured as self-reported disability in the activities of daily living (ADLs) and, objectively, using the Short Physical Performance Battery (SPPB) for lower extremities<sup>12</sup> and the 6-minute walking test (6MWT).<sup>13</sup> According to a modified version of the World Health Organization questionnaire,<sup>8,14</sup> severity of disability was expressed as the number of basic and instrumental ADLs (BADLs and IADLs, respectively) in which the participant was dependent. The BADLs included 6 tasks: walking in the house, washing (hands and face), dressing oneself, toileting, transferring from bed to chair, and eating. The IADLs included 9 tasks: walking outside, walking 400 m without rest, climbing stairs, shopping, bathing or showering, cooking, housekeeping (both light and heavy tasks), and trimming nails.

The modified version of the SPPB used in this study<sup>15</sup> included 3 subtests, for balance (standing in 5 tasks of increasing difficulty), walking (4-m gait speed), and muscle strength (time to stand up 5 times from a chair). In the ICARE Dicomano study population, the SPPB summary score (range, 0-12, where 0 is worst performance and 12 is the best) predicted disability and death.<sup>16</sup>

Sustainable walking capacity was assessed with the 6MWT,<sup>13</sup> which measures the distance walked in 6 minutes at the preferred velocity and represents a valid and reliable indicator of physical performance in elderly persons.<sup>17,18</sup>

**Falls and Urinary Incontinence.** Specific questionnaires were used to evaluate the number of falls in the preceding 12 months (0, 1-2, and  $\geq 3$  falls) and urge urinary incontinence (never, rare, or persistent).<sup>8</sup>

**Cognitive and Emotional Status.** Cognitive status was assessed with the MMSE<sup>9</sup>; depressive symptoms, with the Geriatric Depression Scale.<sup>19</sup>

**Comorbidity.** Comorbidity was measured with the Index of Co-existent Diseases, calculated as the sum of individual severity scores assigned to 14 chronic conditions, which were identified with structured diagnostic algorithms.<sup>16,20</sup>

**Follow-up.** In 1999, cognitive status, ADL disability, and falls were assessed using the same instruments as in 1995. Vital status and hospital admissions for CVE through 2003 were ascertained using administrative databases of the Tuscany region of Italy.

### STATISTICAL ANALYSIS

Continuous variables are expressed as mean (SEM), and *t* tests were used to examine differences in MMSE and SPPB between

participants with and those without each SNA. Differences in baseline characteristics across increasing  $N_{SNA}$  were assessed with the  $\chi^2$  test for trend for categorical variables and with analysis of variance (ANOVA) (or analysis of covariance [ANCOVA], to adjust for age and sex) for continuous variables. Multivariable logistic regression was used to evaluate the association between  $N_{SNA}$ , taken as the independent variable in a cross-sectional design, and the prevalence of falls (0 vs  $\geq 1$ ) and urinary incontinence (never vs rare or persistent), adjusting for age and sex.

The ANOVA (or ANCOVA, when continuous variables were entered as covariates) was used to model the longitudinal associations between  $N_{SNA}$  and declines in functional status (difference in the number of limitations in BADL and IADL from 1995 to 1999), cognitive status (change in MMSE from 1995 to 1999), and falls in the 12 months preceding the follow-up evaluation. Age, sex, comorbidity, SPPB, MMSE, and disability were entered in the models as covariates. Polynomial contrasts were applied to test for linear trends between contiguous categories of the  $N_{SNA}$  (0, 1, 2, 3, and  $\geq 4$ ).

Cox proportional hazards regression models were used to evaluate  $N_{SNA}$  as a predictor of death and hospitalization for CVE, adjusting for age, sex, comorbidity, SPPB, MMSE, BADL, IADL, and, limited to the outcome of CVE, for previous transient ischemic attacks. Because mortality rates seemed to sharply increase for  $N_{SNA}$  values of 3 or higher, this was used as a cutoff point in survival analyses. Age and sex were forced in the model, whereas  $N_{SNA}$  ( $\geq 3$  vs  $< 3$ ) and the other baseline variables were entered at the first step and backward deleted thereafter ( $P = .05$ ). Additional Cox models were constructed to examine the effect of adding  $N_{SNA}$  to age, sex, comorbidity, and functional and cognitive status in the prediction of either death or CVE. For each outcome, the statistical significance of the difference between the  $-2 \log$  likelihood of 2 models, 1 without and the other with  $N_{SNA}$ , was tested against a  $\chi^2$  distribution ( $P < .05$ ) to determine the improvement of the models after the inclusion of  $N_{SNA}$ .

A 2-tailed  $P < .05$  was considered statistically significant. Analyses were performed using SPSS statistical software (version 12.0; SPSS Inc, Chicago, Illinois).

## RESULTS

### BASELINE EVALUATION

Of 864 eligible participants, 697 underwent baseline clinical evaluation.<sup>7</sup> Exclusion of 118 participants with history of stroke, parkinsonism, dementia, or cognitive impairment, and of another 73 with incomplete data led to a final sample of 506 participants (mean [SD] age, 72.5 [0.3] years; 57% were women). Participants excluded owing to incomplete data were older (77.5 [0.9] years;  $P < .001$ ) than those included but did not differ in sex, BADL disability, severity of comorbidity, or level of physical performance (data not shown).

Of the 15 neurological signs considered, 5 were associated only with the SPPB, 1 only with the MMSE, and 5 with both tests (Table 1). The 2 most prevalent SNAs were reduced Achilles reflexes and postural instability. The greatest observed  $N_{SNA}$  was 8 (mean [SD], 1.1 [0.06]), in a possible range of 0 to 19 (considering that 4 signs could be bilateral). The number of participants with an  $N_{SNA}$  of 0, 1, 2, 3, and 4 or more was 208, 131, 96, 38, and 33, respectively. The mean age increased across  $N_{SNA}$  levels, whereas the proportion of women was similar (Table 2). Comorbidity increased with higher  $N_{SNA}$  in

**Table 2. Demographic and Clinical Characteristics of 506 Older Participants, by N<sub>SNA</sub>**

Characteristic	N <sub>SNA</sub> , No. of Participants <sup>a</sup>					P Value
	0 (n = 208)	1 (n = 131)	2 (n = 96)	3 (n = 38)	≥4 (n = 33)	
Age, y <sup>b</sup>	71.2 ± 0.4	71.2 ± 0.4	73.7 ± 0.5	73.9 ± 1.1	78.1 ± 1.2	<.001
Women, No. (%)	113 (54.3)	77 (58.8)	54 (56.3)	26 (68.9)	17 (51.5)	.52
ICED <sup>c</sup>	6.5 ± 0.2	7.1 ± 0.3	7.5 ± 0.3	7.5 ± 0.5	7.6 ± 0.5	.08
MMSE score <sup>c</sup>	26.9 ± 0.1	26.8 ± 0.2	26.7 ± 0.2	26.4 ± 0.3	25.6 ± 0.4	.003
GDS score <sup>c</sup>	6.6 ± 0.4	8.6 ± 0.6	8.0 ± 0.6	8.9 ± 1.0	8.9 ± 1.0	.047
SPPB score <sup>c</sup>	9.8 ± 0.1	9.5 ± 0.1	9.5 ± 0.1	8.9 ± 0.1	7.4 ± 0.1	<.001
6-MWT <sup>c</sup>	344 ± 91	326 ± 79	311 ± 91	306 ± 90	253 ± 93	<.001
BADLs, No. with dependency <sup>b</sup>	0.02 ± 0.02	0.05 ± 0.03	0.07 ± 0.04	0.06 ± 0.05	0.06 ± 0.06	.50
IADLs, No. with dependency <sup>b</sup>	0.3 ± 0.08	0.4 ± 0.10	0.6 ± 0.11	0.6 ± 0.16	1.4 ± 0.21	<.001

Abbreviations: 6-MWT, walking distance during a 6-minute walking test; BADL, basic activity of daily living; IADL, instrumental activity of daily living; GDS, Geriatric Depression Scale; ICED, Index of Coexistent Diseases; MMSE, Mini-Mental State Examination; N<sub>SNA</sub>, number of subtle neurological abnormalities; SPPB, Short Physical Performance Battery score.

<sup>a</sup>Data are given as mean ± SEM except where noted.

<sup>b</sup>Unadjusted means from analysis of variance models.

<sup>c</sup>Means adjusted for age and sex from analysis of covariance models.

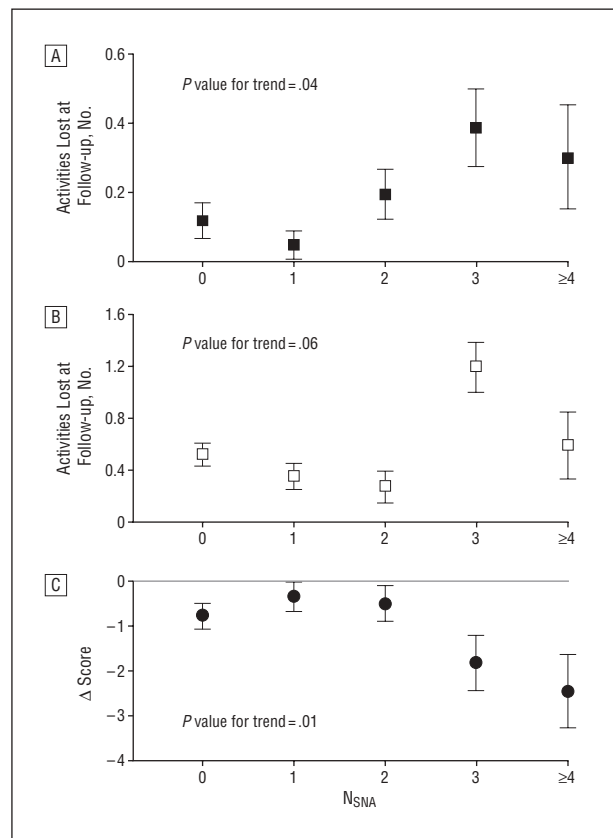
unadjusted comparisons ( $P < .001$ ; data not shown), although after adjusting for age and sex the linear trend was no longer significant ( $P = .08$ ) (Table 2). After controlling for age and sex, an increasing N<sub>SNA</sub> was associated with a greater severity of IADL disability, more depressive symptoms, and worse cognitive and functional status (Table 2).

In bivariate comparisons, increasing N<sub>SNA</sub> was also associated with more falls in the previous year ( $\chi^2 = 4.46$ ;  $P$  value for trend = .04) and with more frequent urge urinary incontinence ( $\chi^2 = 5.88$ ;  $P$  value for trend = .02). After adjusting for age and sex, these associations were no longer statistically significant ( $P$  value for trend = .12 for falls;  $P$  value for trend = .47 for urinary incontinence).

### LONGITUDINAL ANALYSIS

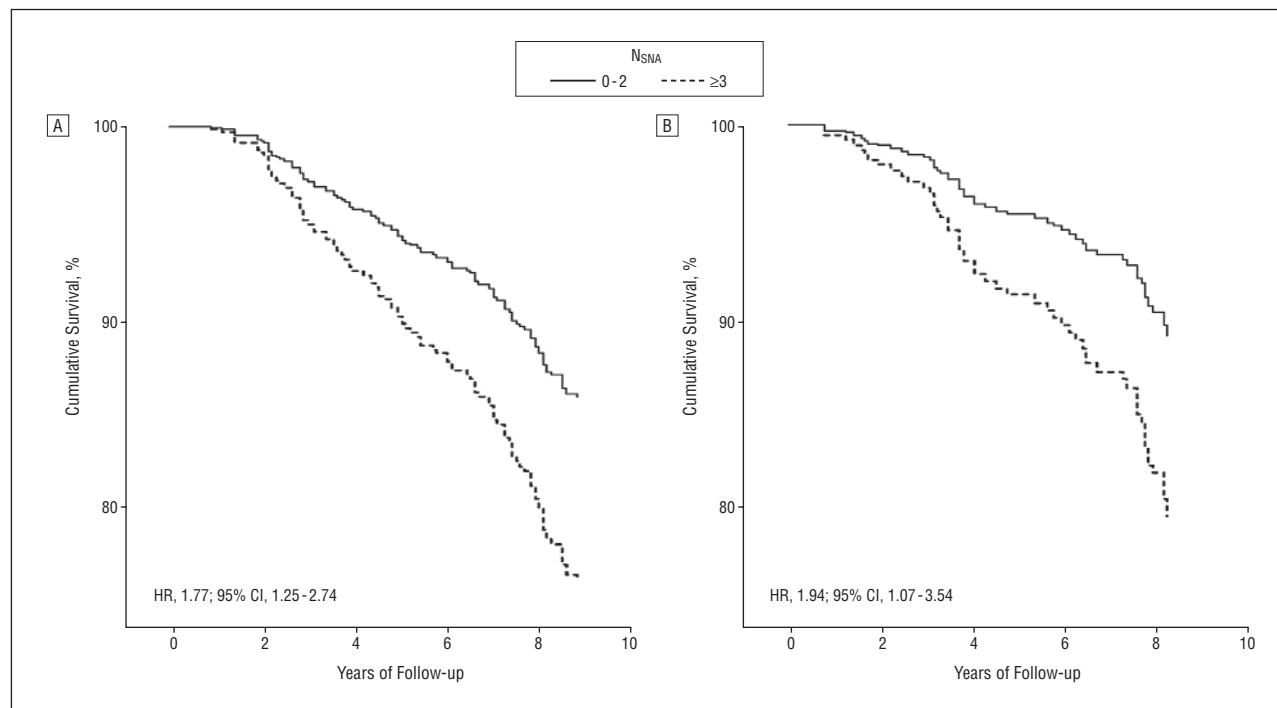
In 1999, 420 of the original 506 participants were reinterviewed. Increasing N<sub>SNA</sub> predicted 4-year functional and cognitive decline, expressed as the number of BADLs and IADLs lost, and the reduction in MMSE score between baseline and follow-up, respectively. The analyses were adjusted for age, sex, and baseline comorbidity, SPPB, MMSE, and BADL and IADL (Figure 1). In bivariate analysis, N<sub>SNA</sub> predicted the number of falls in the 12 months preceding the 1999 evaluation ( $P = .03$ ). This result was no longer significant after adjustment for demographics and comorbidity ( $P = .13$ ).

From 1995 through 2003, 113 participants died and 62 were hospitalized for CVE. The mortality rates were 22.6, 23.3, 23.9, 58.6, and 91.9 per 1000 person-years in participants with an N<sub>SNA</sub> of 0, 1, 2, 3, and 4 or greater, respectively. Compared with a value of less than 3, having an N<sub>SNA</sub> of 3 or greater was associated with a 2-fold greater risk of death (hazard ratio [HR], 1.77; 95% confidence interval [CI], 1.25-2.74, adjusted for age, sex, baseline comorbidity, SPPB, MMSE, and BADL and IADL) and CVE (HR, 1.94; 95% CI, 1.07-3.54, adjusted also for history of transient ischemic attacks) (Figure 2). When added to age, sex, comorbidity, cognitive and physical



**Figure 1.** Prediction of functional and cognitive decline from 1995 to 1999 in 420 older community-dwelling persons free of overt neurological diseases at baseline. All analyses adjusted for age, sex, baseline comorbidity, physical performance, cognitive functioning, and basic and instrumental activities of daily living (BADLs and IADLs, respectively). N<sub>SNA</sub> indicates the number of subtle neurological abnormalities; the error bars indicate the mean ± SE. A, BADL analysis; B, IADL analysis; C, Mini-Mental State Examination (MMSE) analysis.

functions, and functional status in Cox models, N<sub>SNA</sub> improved the prediction of mortality ( $P = .006$  for the likelihood ratio test), whereas the improvement of the model



**Figure 2.** Cumulative survival and cumulative event-free survival during the follow-up period. Mortality (A) and incident hospitalization for cerebrovascular events (B) in 506 older community-dwelling persons free of overt neurological diseases, by number of subtle neurological abnormalities ( $N_{SNA}$ ) ( $<3$  vs  $\geq 3$ ). Cox proportional hazard models were adjusted for age, sex, baseline comorbidity, cognitive and physical performance, and functional status at baseline (A and B) and history of transient ischemic attacks (B). CI indicates confidence interval; HR, hazard ratio.

predicting CVE did not reach statistical significance ( $P = .08$  for the likelihood ratio test).

#### COMMENT

In our sample of older community-dwelling persons free of overt neurological diseases, a standardized examination disclosed at least 1 SNA in more than half of the participants, with a prevalence increasing with age. A strong and independent association was demonstrated cross-sectionally among the  $N_{SNA}$  and IADL disability, worse cognitive and physical performances, and more depressive symptoms. In longitudinal analyses, the  $N_{SNA}$  predicted functional and cognitive decline over 4 years and mortality and CVE over 8 years.

Despite some differences in the neurological examination, our baseline results reinforce those obtained in a similar population-based, cross-sectional study of older persons.<sup>6</sup> In both investigations, a mean number of approximately 1.1 SNAs was detected, with similar associations among the  $N_{SNA}$  and physical performance and falls. Compared with the previous report, the present analysis has a more accurate control for covariates. Moreover, the longitudinal design provides support to the hypothesis of a causal relationship among the  $N_{SNA}$  and functional and cognitive decline, death, and CVE. To our knowledge, this is the first study showing this association prospectively in a relatively large sample of unselected elderly persons. A previous report<sup>21</sup> was limited in terms of number of participants (only 59), setting (clinical selection), and signs tested (tendon reflexes and vibration sense).

Performance-based tests for cognitive and physical functions and depressive symptoms are relevant clinical markers of cardiorespiratory, skeletal, muscular, and nervous functions and predict subsequent disability, CVE, and mortality in apparently healthy older adults.<sup>12,22-25</sup> In the present study, SNA predicted cognitive and functional decline, CVE, and mortality independent of all these other measures of cognitive function, physical performance, and mood. Thus, a simple neurological examination seems to be an additional prognosticator of hard outcomes, particularly death, above and beyond other measures used in clinical practice. It is likely that the neurological examination might capture additional information about the integrity of the nervous system in apparently healthy older adults.

A previous study<sup>26</sup> documented the relationship between specific SNA and diffuse brain white matter lesions using computed tomographic scans in older adults without dementia. Similarly, in CHS participants without a history of stroke, the number of neurological findings was independently associated with silent infarctions at brain magnetic resonance imaging.<sup>27</sup> In turn, neuroimaging evidence of subclinical brain disease is associated with cognitive decline, executive dysfunction, depression, gait disorders, falls, urinary incontinence,<sup>7</sup> poor physical performance,<sup>5,28</sup> and incident ADL dependency.<sup>29</sup> Subclinical brain disease also predicts CVE<sup>30</sup> and mortality<sup>31</sup> in elderly individuals. Thus, we speculate that our findings reflect the presence of diffuse white matter lesions or brain infarcts. However, although most of the neurological signs included in the  $N_{SNA}$  could be an expression of damage in the central nervous system, some

of them may be caused by peripheral neuropathy, a condition that can indeed contribute to physical performance decline in elderly persons.<sup>32</sup>

Our results suggest a nonlinear relationship between  $N_{\text{SNA}}$  and the long-term hard outcomes of death and CVE, the risk of which dramatically increased in the presence of 3 or more SNAs. The absence of a dosage-response relationship does not exclude per se causation. Rather, a given level of neurological damage, up to a critical threshold, might be required before overt consequences become apparent. This threshold effect might reflect, for example, diffuse or confluent white matter hyperintensities rather than isolated lesions. Alternatively, it is possible that the associations we found were driven only by a limited number of specific neurological abnormalities, which more likely occurred when more SNAs were detected. Given the limited sample size, we could not discriminate between these alternatives; further studies are needed to confirm these findings and to highlight their pathogenesis and consequences.

Additional study limitations must be considered. First, our clinical summary score of neurological damage is probably less sensitive and specific than neuroimaging, and, therefore, it is of limited value in etiologic studies. Nevertheless, because of its low cost and ease of use, it might prove useful in clinical practice and in epidemiologic studies. Second, we were unable to prospectively investigate the association between SNAs and changes in physical performance because the SPPB and the 6MWT were not reassessed during the follow-up.

With these limitations in mind, our findings indicate that SNAs are frequent and must be systematically investigated in elderly persons. Subtle neurological abnormalities can be used to reveal otherwise undetected brain damage with relevant functional correlates and a clear prognostic value on survival and the development of CVE. Moreover, should the hypothesized association with cerebrovascular disease be demonstrated in future studies, the detection of multiple SNAs might prompt further cardiovascular investigation and eventually lead to a more intensive management of cardiovascular risk factors.

Our data support the hypothesis that SNAs in elderly individuals are a manifestation of early brain damage, a finding that may have important implications in research studies on the prevention of age-related cognitive and functional decline. Understanding the nature of dysfunctions underlying the decline in physical performance and disability contributes to planning specific preventive interventions. If our findings are confirmed by future research,  $N_{\text{SNA}}$  might be also considered as a surrogate outcome for such intervention studies.

**Accepted for Publication:** September 10, 2007.

**Correspondence:** Marco Inzitari, MD, Department of Critical Care Medicine and Surgery, Unit of Gerontology and Geriatrics, University of Florence, via delle Oblate, 4, 50141 Florence, Italy (marcoinzitari@gmail.com).

**Author Contributions:** Dr Inzitari had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the analysis. *Study*

*concept and design:* Inzitari, Ferrucci, and Di Bari. *Acquisition of data:* Ferrucci, Pini, Masotti, Marchionni, and Di Bari. *Analysis and interpretation of data:* Inzitari, Pozzi, Ferrucci, Chiarantini, Rinaldi, Baccini, Pini, Masotti, Marchionni, and Di Bari. *Drafting of the manuscript:* Inzitari, Pozzi, Chiarantini, Rinaldi, Baccini, and Di Bari. *Critical revision of the manuscript for important intellectual content:* Inzitari, Ferrucci, Pini, Masotti, Marchionni, and Di Bari. *Statistical analysis:* Inzitari, Ferrucci, and Di Bari. *Obtained funding:* Masotti, Marchionni, and Di Bari. *Administrative, technical, and material support:* Inzitari, Pozzi, Chiarantini, and Di Bari. *Study supervision:* Di Bari.

**Financial Disclosure:** None reported.

**Funding/Support:** This work was sponsored by the Italian Ministry of Scientific and Technological Research (National Special Project on Heart Failure), by the government of Tuscany, and by the Azienda Ospedaliero-Universitaria Careggi-Firenze, Italy.

**Role of the Sponsor:** The sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

**Additional Contributions:** Subashan Perera, PhD, and Mindi Spencer, PhD, from the University of Pittsburgh, Pittsburgh, Pennsylvania, provided advice in revising the manuscript.

## REFERENCES

1. Enright PL, McBurnie MA, Bittner V, et al. The 6-min walk test: a quick measure of functional status in elderly adults. *Chest*. 2003;123(2):387-398.
2. Newman AB, Haggerty CL, Kritchevsky SB, Nevitt MC, Simonsick EM. Walking performance and cardiovascular response: associations with age and morbidity: the Health, Aging and Body Composition Study. *J Gerontol A Biol Sci Med Sci*. 2003;58(8):715-720.
3. Newman AB, Gottdiener JS, Mcburnie MA, et al. Associations of subclinical cardiovascular disease with frailty. *J Gerontol A Biol Sci Med Sci*. 2001;56(3):M158-M166.
4. Newman AB, Arnold AM, Naydeck BL, et al. "Successful aging": effect of subclinical cardiovascular disease. *Arch Intern Med*. 2003;163(19):2315-2322.
5. Rosano C, Kuller LH, Chung H, Arnold AM, Longstreth WT Jr, Newman AB. Subclinical brain magnetic resonance imaging abnormalities predict physical functional decline in high-functioning older adults. *J Am Geriatr Soc*. 2005;53(4):649-654.
6. Ferrucci L, Bandinelli S, Cavazzini C, et al. Neurological examination findings to predict limitations in mobility and falls in older persons without a history of neurological disease. *Am J Med*. 2004;116(12):807-815.
7. Kuo HK, Lipsitz LA. Cerebral white matter changes and geriatric syndromes: is there a link? *J Gerontol A Biol Sci Med Sci*. 2004;59(8):818-826.
8. Di Bari M, Marchionni N, Ferrucci L, et al. Insufficienza Cardiaca negli Anziani Residenti a Dicomano. Heart failure in community-dwelling older persons: aims, design and adherence rate of the ICARE Dicomano project: an epidemiologic study. *J Am Geriatr Soc*. 1999;47(6):664-671.
9. Folstein MF, Robins LN, Helzer JE. The Mini-Mental State Examination. *Arch Gen Psychiatry*. 1983;40(7):812.
10. Bandinelli S, Benvenuti E, Del L, et al. Measuring muscular strength of the lower limbs by hand-held dynamometer: a standard protocol. *Aging (Milano)*. 1999;11(5):287-293.
11. Costa LD, Vaughan HG Jr, Levita E, Farber N. Purdue Pegboard as a predictor of the presence and laterality of cerebral lesions. *J Consult Psychol*. 1963;27:133-137.
12. Guralnik JM, Ferrucci L, Simonsick EM, Salive ME, Wallace RB. Lower extremity function in persons over the age of 70 years as a predictor of subsequent disability. *N Engl J Med*. 1995;332(9):556-561.
13. Guyatt GH, Sullivan MJ, Thompson PJ, et al. The 6-minute walk: a new measure of exercise capacity in patients with chronic heart failure. *Can Med Assoc J*. 1985;132:919-923.
14. Heikkinen E, Waters WE, Brzezinski ZJ. *The Elderly in Eleven Countries: A Socio-*

- medical Survey*. Copenhagen, Denmark: World Health Organization Regional Office for Europe; 1983. Public Health in Europe, No. 21.
15. Di Bari M, Pozzi C, Cavallini MC, et al. The diagnosis of heart failure in the community: comparative validation of four sets of criteria in unselected older adults: the ICARe Dicomano Study. *J Am Coll Cardiol*. 2004;44(8):1601-1608.
  16. Di Bari M, Virgilio A, Matteuzzi D, et al. Predictive validity of measures of comorbidity in older community dwellers: the Insufficienza Cardiaca negli Anziani Residenti a Dicomano Study. *J Am Geriatr Soc*. 2006;54(2):210-216.
  17. Bean JF, Kiely DK, Leveille SG, et al. The 6-minute walk test in mobility-limited elders: what is being measured? *J Gerontol A Biol Sci Med Sci*. 2002;57(11):M751-M756.
  18. Harada ND, Chiu V, Stewart AL. Mobility-related function in older adults: assessment with a 6-minute walk test. *Arch Phys Med Rehabil*. 1999;80(7):837-841.
  19. Yesavage JA, Brink TL, Rose TL, et al. Development and validation of a geriatric depression screening scale: a preliminary report. *J Psychiatr Res*. 1982;17(1):37-49.
  20. Greenfield S, Apolone G, McNeil BJ, Cleary PD. The importance of co-existent disease in the occurrence of postoperative complications and one-year recovery in patients undergoing total hip replacement: comorbidity and outcomes after hip replacement. *Med Care*. 1993;31(2):141-154.
  21. Baloh RW, Ying SH, Jacobson KM. A longitudinal study of gait and balance dysfunction in normal older people. *Arch Neurol*. 2003;60(6):835-839.
  22. Guralnik JM, Simonsick EM, Ferrucci L, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. *J Gerontol*. 1994;49(2):M85-M94.
  23. Inouye SK, Peduzzi PN, Robison JT, Hughes JS, Horwitz RJ, Concato J. Importance of functional measures in predicting mortality among older hospitalized patients. *JAMA*. 1998;279(15):1187-1193.
  24. Penninx BW, Guralnik JM, Ferrucci L, Simonsick EM, Deeg DJ, Wallace RB. Depressive symptoms and physical decline in community-dwelling older persons. *JAMA*. 1998;279(21):1720-1726.
  25. Whooley MA, Browner WS. Association between depressive symptoms and mortality in older women: study of Osteoporotic Fractures Research Group. *Arch Intern Med*. 1998;158(19):2129-2135.
  26. Steingart A, Hachinski VC, Lau C, et al. Cognitive and neurologic findings in demented patients with diffuse white matter lucencies on computed tomographic scan (leuko-araiosis). *Arch Neurol*. 1987;44(1):36-39.
  27. Price TR, Manolio TA, Kronmal RA, et al; Cardiovascular Health Study; CHS Collaborative Research Group. Silent brain infarction on magnetic resonance imaging and neurological abnormalities in community-dwelling older adults. *Stroke*. 1997;28(6):1158-1164.
  28. Wolfson L, Wei X, Hall CB, et al. Accrual of MRI white matter abnormalities in elderly with normal and impaired mobility. *J Neurol Sci*. 2005;232(1-2):23-27.
  29. Inzitari D, Simoni M, Pracucci G, et al. Risk of rapid global functional decline in elderly patients with severe cerebral age-related white matter changes: the LADIS study. *Arch Intern Med*. 2007;167(1):81-88.
  30. Inzitari D. Leukoaraiosis: an independent risk factor for stroke? *Stroke*. 2003;34(8):2067-2071.
  31. Kuller LH, Arnold AM, Longstreth WT Jr, et al. White matter grade and ventricular volume on brain MRI as markers of longevity in the cardiovascular health study. *Neurobiol Aging*. 2007;28(9):1307-1315.
  32. Inzitari M, Carlo A, Baldereschi M, et al. Risk and predictors of motor-performance decline in a normally functioning population-based sample of elderly subjects: the Italian Longitudinal Study on Aging. *J Am Geriatr Soc*. 2006;54(2):318-324.

### Correction

**Errors in Abstract and Text.** In the Original Investigation by Fung et al titled “Adherence to a DASH-Style Diet and Risk of Coronary Heart Disease and Stroke in Women,” published in the April 14, 2008, issue of the *Archives* (2008;168[7]:713-720), 2 errors occurred in the text. On page 713, in the first sentence of the “Results” section in the abstract, the number of cases of stroke is incorrect. The corrected sentence reads as follows: “We documented 2129 cases of incident nonfatal myocardial infarction, 976 CHD deaths, and 2317 cases of stroke.” On page 715, in the first sentence of the “Results” section, the number of cases of CHD is incorrect. The corrected sentence reads as follows: “During 24 years of follow-up, we documented 3105 cases of CHD, of which 2129 were nonfatal and 976 fatal, and 2317 cases of stroke, of which 1242 were ischemic and 400 hemorrhagic (the remainder could not be clearly classified).”